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Research Article

Association of NSAID Exposure, Stone Burden and Metabolic Abnormalities With Reduced Renal Function in Patients With Recurrent Urolithiasis: A Cross-Sectional Analytical Study

Irfan Elahi[1], Zainab Mustafa[2], Irfan Ahmad[3], Abdul Razaq[4], Hafsa Siddiqui[5], Fouzia Perveen[6]

1. Associate Professor, Nephrology, King Edward Medical University, Lahore, Pakistan.
2. Demonstrator, Pharmacology Department, King Edward Medical University, Lahore, Pakistan.
3. Associate Professor, Nephrology, Akhtar Saeed Medical and Dental College, Lahore, Pakistan.
4. Assistant Professor, Urology, M. Islam Medical and Dental College, Gujranwala, Pakistan.
5. Medical Officer, Renal Transplant Unit/Nephrology, Dow University of Health Sciences, Karachi, Pakistan.
6. Associate Professor, Pharmacology, Queen Medical College, Kasur, Pakistan

Irfan Elahi: Corresponding author

Abstract

Recurrent urolithiasis causes progressive renal parenchymal injury through obstructive uropathy, repeated surgical interventions, underlying metabolic derangements, and frequent exposure to non-steroidal anti-inflammatory drugs (NSAIDs) for acute renal colic management. The objective of this cross-sectional analytical study was to evaluate the relative associations and independent impacts of cumulative NSAID exposure, overall stone burden, and specific metabolic abnormalities on reduced renal function in patients with recurrent urolithiasis. A total of 450 adult patients presenting with a documented history of recurrent nephrolithiasis (2 stone episodes) were evaluated across tertiary urology centers. Renal function was classified according to estimated glomerular filtration rate (eGFR; CKD-EPI formula), with reduced renal function defined as eGFR < 60/mL/min/1.73 m^2 . Clinical data collected included cumulative lifetime NSAID exposure (quantified in standard dose-years), total stone burden (measured via non-contrast computed tomography [NCCT] maximum surface area in mm 2), and 24-hour urine metabolic profiles. Reduced renal function was identified in 28.4% (n = 128) of the cohort. Multivariable logistic regression revealed that high cumulative NSAID exposure (‘ 5 dose-years; aOR: 3.42, 95% CI: 1.95–6.01, p < 0.001), total stone burden > 300 mm ^2 (aOR: 2.85, 95% CI: 1.58–5.14, p = 0.001), persistent hyperoxaluria (aOR: 2.18, 95% CI: 1.22–3.89, p = 0.008), and

hyperuricemia/hyperuricosuria (aOR: 1.94, 95% CI: 1.08–3.48, p = 0.026) were significant independent risk factors for reduced eGFR. Chronic cumulative NSAID use and cumulative stone burden represent strong modifiable risk factors for loss of renal function in recurrent stone formers, emphasizing the urgent need for non-nephrotoxic analgesic strategies and metabolic stone prevention protocols.

Keywords: Urolithiasis, NSAID exposure, nephrotoxicity, chronic kidney disease, metabolic stone screening, hyperoxaluria, stone burden.

Introduction

Nephrolithiasis affects up to 12% of the global population, with recurrence rates exceeding 50% within ten years of the initial index episode. While urolithiasis was historically considered a benign condition following stone passage or surgical clearance, contemporary epidemiologic evidence links recurrent nephrolithiasis directly to an increased risk of chronic kidney disease (CKD) and end-stage renal disease (ESRD). [1–3]

The etiology of renal function decline in recurrent stone formers is multifactorial. Obstructive uropathy and high stone burden directly induce intrarenal backpressure, interstitial inflammation, tubular necrosis, and subsequent focal glomerulosclerosis. Concurrently, metabolic abnormalities—including hyperoxaluria, primary hyperparathyroidism, gouty diathesis, and renal tubular acidosis—cause persistent nephrocalcinosis and tubulointerstitial damage. [4–6]

In addition to intrinsic metabolic and obstructive factors, symptom management for acute renal colic relies heavily on non-steroidal anti-inflammatory drugs (NSAIDs) like diclofenac, ketorolac, and ibuprofen. NSAIDs inhibit cyclooxygenase-2 (COX-2), suppressing renal prostaglandin synthesis (PGE_2 and PGI_2) and inducing afferent arteriolar vasoconstriction. In the setting of acute ureteral obstruction or volume depletion, repeated or cumulative high-dose NSAID administration compromises renal perfusion, causing acute kidney injury (AKI) and accelerating tubulointerstitial fibrosis. [7–10]

Despite the widespread clinical reliance on NSAIDs for analgesia in renal colic, the long-term cumulative impact of repeated NSAID exposure relative to metabolic derangements and stone burden on renal parenchymal function remains inadequately quantified.

This cross-sectional analytical study aimed to determine the independent associations between cumulative NSAID exposure, stone burden parameters, metabolic derangements, and reduced renal function in patients with recurrent urolithiasis.

Methodology

A cross-sectional analytical study was conducted over an 18-month period, evaluating 450 adult patients (aged 18 to 70 years) with a confirmed history of recurrent urolithiasis (2 radiologically confirmed stone episodes) at King Edward Medical University, Lahore, Pakistan. The study protocol was approved by the institutional ethics committee, and written informed consent was obtained from all participants prior to enrollment.

Inclusion criteria comprised patients with active or recurrent kidney/ureteral stones evaluated at outpatient urology and nephrology clinics who had complete radiological, laboratory, and medication history records. Exclusion criteria included known pre-existing congenital solitary kidney, primary glomerulonephritis, active diabetic nephropathy, severe decompensated heart failure, or prior bilateral nephrectomy/renal transplantation.

Clinical parameters collected included age, gender, body mass index (BMI), hypertension status, total number of symptomatic stone episodes, and history of surgical stone interventions (shock wave lithotripsy [SWL], ureteroscopy [URS], percutaneous nephrolithotomy [PCNL]).

Cumulative NSAID exposure was calculated using a structured medication recall tool validated by pharmacy records, quantified as "NSAID dose-years" (defined as taking the standard daily therapeutic dose of an NSAID continuously for one year, e.g., diclofenac 150 mg/day or ibuprofen 1200 mg/day). High cumulative exposure was defined as 5.0 dose-years.

Stone burden was quantified using non-contrast computed tomography (NCCT), calculating total surface area (mm 2) by multiplying maximum cross-sectional diameters 0.7854) across all visible calculi. Metabolic evaluation included 24-hour urine collection analyzing calcium, oxalate, uric acid, citrate, sodium, and volume, along with serum chemistry (creatinine, uric acid, calcium, parathyroid hormone [PTH]).

Renal function was categorized using the CKD-EPI 2021 serum creatinine-based estimated glomerular filtration rate (eGFR). Reduced renal function was defined as eGFR < 60{ mL/min/1.73 m}^2 (CKD Stage 3a or higher).

Statistical analysis was conducted using SPSS version 26. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range [IQR]), and compared using Student's t-test or Mann-Whitney U test. Categorical variables were evaluated using Chi-square tests. Multivariable logistic regression analysis was performed to identify independent predictors of reduced renal function, controlling for age, gender, hypertension, and surgical history.

Results

Table 1: Baseline Demographic, Clinical, and Metabolic Characteristics Stratified by Renal Function

Parameter	Total Cohort (N=450)	Normal eGFR (≥60) (n=322)	Reduced eGFR (<60) (n=128)	p-value
Age (Years ± SD)	46.8 ± 12.4	44.2 ± 11.5	53.3 ± 12.1	< 0.001
Gender (Male / Female %)	288 / 162 (64.0% / 36.0%)	202 / 120 (62.7% / 37.3%)	86 / 42 (67.2% / 32.8%)	0.375

Parameter	Total Cohort (N=450)	Normal eGFR (≥60) (n=322)	Reduced eGFR (<60) (n=128)	p-value
Hypertension (%)	158 (35.1%)	92 (28.6%)	66 (51.6%)	< 0.001
Body Mass Index	27.4 ± 4.2	26.8 ± 3.9	28.9 ± 4.6	< 0.001
NSAID Exposure & Stone Metrics				
Cumulative NSAID Exposure (Dose-Years, Median [IQR])	2.5 [1.0–5.5]	1.8 [0.5–3.5]	5.2 [2.5–8.5]	< 0.001
High Cumulative NSAID Exposure (5 Dose-Years) (%)	126 (28.0%)	62 (19.3%)	64 (50.0%)	< 0.001
Total NCCT Stone Burden (>300 mm}^2) (%)	135 (30.0%)	75 (23.3%)	60 (46.9%)	< 0.001
Mean Recurrent Stone Episodes (Count ± SD)	4.2 ± 2.1	3.6 ± 1.6	5.7 ± 2.5	< 0.001
Prior Surgical Stone Interventions(3 Procedures)	142 (31.6%)	82 (25.5%)	60 (46.9%)	< 0.001

Note: Patients with reduced renal function exhibited significantly higher age, rate of hypertension, cumulative NSAID intake, total stone burden, and frequency of stone-related surgical procedures.

Table 2: 24-Hour Urinary Metabolic Profile Comparison

Metabolic Parameter	Normal eGFR (≥60) (n=322)	Reduced eGFR (<60) (n=128)	Normal Reference Range	p-value
Hypercalciuria (%)	125 (38.8%)	32 (25.0%)	< 250mg/24h	0.006
Hyperoxaluria(%)	78 (24.2%)	52 (40.6%)	< 45 mg/24h	0.001
Hyperuricosuria (%)	68 (21.1%)	44 (34.4%)	< 750 mg/24h	0.004
Hypocitraturia (%)	142 (44.1%)	78 (60.9%)	> 320 mg/24h	0.002
Low 24-Hour Urine Volume (< 2.0 L/24h) (%)	185 (57.5%)	88 (68.8%)	> 2.0 L/24h	0.028

Note: Hyperoxaluria, hyperuricosuria, hypocitraturia, and low urine volume were significantly more prevalent among patients with reduced eGFR, whereas hypercalciuria was less frequent due to impaired filtration.

Table 3: Bivariate Correlation Matrix Between Clinical Factors and Mean eGFR

Clinical / Radiological Variable	Pearson Correlation (r)	Spearman Rho (ρ)	p-value
Cumulative NSAID Exposure (Dose-Years)	r = -0.482	\rho = -0.512	< 0.001
Total NCCT Stone Burden ({mm}^2)	r = -0.415	\rho = -0.438	< 0.001

Clinical / Radiological Variable	Pearson Correlation (r)	Spearman Rho (ρ)	p-value
Number of Recurrent Stone Episodes	r = -0.388	\rho = -0.402	< 0.001
24-Hour Urinary Oxalate Excretion	r = -0.312	\rho = -0.335	< 0.001
Serum Uric Acid Level	r = -0.365	\rho = -0.381	< 0.001

Note: Cumulative NSAID exposure demonstrated the strongest inverse correlation with estimated glomerular filtration rate across the cohort.

Table 4: Multivariable Logistic Regression Analysis of Independent Factors Associated with Reduced Renal Function (eGFR < 60 mL/min/1.73 m}^2)

Independent Risk Factor	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (aOR) (95% CI)*	p-value
High Cumulative NSAID Exposure (‘ 5 Dose-Years)	4.19 (2.68–6.55)	3.42 (1.95–6.01)	< 0.001
Total Stone Burden > 300 mm ^2	2.91 (1.88–4.50)	2.85 (1.58–5.14)	0.001
Persistent Hyperoxaluria	2.14 (1.38–3.31)	2.18 (1.22–3.89)	0.008
Serum Hyperuricemia / Hyperuricosuria	1.96 (1.24–3.10)	1.94 (1.08–3.48)	0.026

Independent Risk Factor	Unadjusted Odds Ratio (95% CI)	Adjusted Odds Ratio (aOR) (95% CI)*	p-value
Prior Surgical Interventions (‘ 3 Procedures)	2.58 (1.65–4.03)	1.82 (0.98–3.38)	0.058
Hypertension	2.67 (1.73–4.12)	1.92 (1.12–3.28)	0.018

Note: *Multivariable model adjusted for age, gender, hypertension, BMI, diabetes, cumulative surgical procedures, and baseline metabolic parameters.

Discussion

This cross-sectional analytical study highlights the multifactorial drivers of renal function loss in patients with recurrent urolithiasis. High cumulative NSAID exposure, large total stone burden, persistent hyperoxaluria, and hyperuricemia were identified as major independent factors associated with reduced renal function (eGFR < 60 mL/min/1.73 m^2).

Cumulative NSAID exposure emerged as the strongest independent modifiable risk factor for reduced eGFR (aOR: 3.42, 95% CI: 1.95–6.01). While short-term NSAID therapy remains a guideline-recommended first-line analgesic option for acute renal colic, recurrent stone formers frequently ingest OTC and prescription NSAIDs over extended periods. In the setting of acute ureteral obstruction or volume depletion, NSAID-induced inhibition of renal prostaglandins (PGE_2 and PGI_2) causes uncompensated afferent arteriolar constriction, decreasing renal plasma flow and glomerular filtration pressure. Repeated episodes of subclinical ischemic AKI culminate in chronic tubulointerstitial nephritis and interstitial fibrosis. [11–14]

Total stone burden (> 300\mm^2) was independently associated with a nearly 3-fold increase in the odds of reduced renal function (aOR: 2.85). Large stone volumes cause persistent partial intrarenal obstruction, chronic backpressure, bacterial colonization, and localized inflammatory tissue destruction. Additionally, managing large stone burdens requires multiple endourological procedures (SWL, URS, PCNL). Although modern minimally invasive techniques preserve

parenchymal volume, repeated access sheath placement, high-pressure irrigation, thermal laser injury, and PCNL tract dilation introduce localized parenchymal scarring that reduces functional nephron mass over time. [15–17]

Metabolic abnormalities played a central role in parenchymal damage. Persistent hyperoxaluria was independently associated with reduced renal function (aOR: 2.18). Calcium oxalate crystal deposition within renal tubular lumens and interstitial tissue triggers localized inflammasome activation (NLRP3 pathway), inducing tubular necrosis and nephrocalcinosis. Conversely, hypercalciuria was less frequent in the reduced eGFR subgroup, reflecting impaired filtration fraction and tubular reabsorption changes associated with advancing renal insufficiency. [18–20]

Limitations of this study include its cross-sectional design, which precludes establishing absolute temporal causality, and potential recall bias regarding lifetime over-the-counter NSAID consumption.

Clinicians managing recurrent urolithiasis must implement rigorous nephroprotective strategies. Limiting chronic NSAID use by utilizing alternative non-nephrotoxic analgesics (such as acetaminophen, alpha-blockers, or short-acting opioids during acute colic), performing timely surgical decompression of obstructive stones, and executing targeted 24-hour urine metabolic prophylaxis are critical to preventing progressive renal function decline in recurrent stone formers.

Conclusion

Reduced renal function in recurrent urolithiasis is driven by a combination of pharmacologic, structural, and metabolic factors. High cumulative NSAID exposure (5 dose-years) and large NCCT stone burden (> 300 mm ^2) are strong independent factors associated with reduced eGFR, alongside hyperoxaluria and hyperuricemia. Urologists and nephrologists must adopt non-nephrotoxic pain management strategies and early metabolic interventions to preserve long-term renal function in recurrent stone formers.

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