Role of Infection and Inflammation as Possible Causative Factors for Raised Serum Creatinine in Patients with Unilateral Ureteral Calculus Obstruction: A Prospective Case-Control Study

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Abstract

Introduction: Patients with the stone disease on many occasions present with obstructive uropathy. The reasons may be multi-factorial. One of the major postulated mechanisms is the role of infection and inflammation being the causative factors.

Purpose: With this aim in mind, we prospectively evaluated the role of infection and inflammation as possible causes of raised serum creatinine in patients with unilateral ureteral calculus disease.

Materials and Methods: A prospective case-control study of all patients who presented to the Urological Department with unilateral ureteric calculi was performed. 50 patients who presented with raised serum creatinine (>1.3 mg%), with structurally normal contralateral kidneys were included in the study group (SG), and another randomly selected 50 patients without raised serum creatinine were included in the control group (CG).

Results: Patients in SG had a mean age of 39.86 and those in the CG aged had a mean age of 38.26. Males clearly predominated, with the male:female overall ratio of 3:1. Of the co-morbid conditions, diabetes and hypertension were found to be more in the SG (16% and 22%, respectively), as compared to CG (8 and 10%, respectively). The mean serum creatinine levels at a presentation in the SG and CGs were 1.9 mg% and 1.0 mg%, respectively and the two-tailed P < 0.0001. The majority of patients in the SG had a glomerular filtration rate of <60 ml/min, while a majority of those in the CG were of more than 60 ml/min. Among the laboratory parameters, absolute leukocyte count, C-reactive protein, and erythrocyte sedimentation rate were found to be statistically significant difference between the study and CGs.

Conclusion: This study evaluates the factors that might cause an abnormal renal function in patients with unilateral ureteral obstruction. Further, well-designed studies are needed to substantiate the hypothesis drawn from this study.

Key words: C-reactive protein, Glomerular filtration rate, Obstructive uropathy, Serum creatinine, Ureteric calculus, Ureteral obstruction

INTRODUCTION

The lifetime prevalence of kidney stone disease is estimated at 10% in men and 6% in women, with the

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probability of having a stone varying according to age, gender, race, and geographic location.¹ Its overall prevalence is still on the rise.² Stone disease typically affects adult men more commonly than adult women. By a variety of indicators, including inpatient admissions, outpatient office visits, and emergency department visits, men are affected two to three times more frequently than women, but the ratio in the recent past has narrowed down considerably from 3.4 to 1.3 males per female.³ Most stones become symptomatic when they fall into the ureter causing pain or obstruction.

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Infected hydronephrosis is a common complication of ureteral obstruction produced by urolithiasis and can be lethal if it progresses to septicemia.⁴ Prompt and effective diagnosis and treatment are necessary to avoid urosepsis, a systemic inflammatory response syndrome whose diagnosis is based on physical examination (fever, increased heart rate, and tachypnea) and laboratory data (leukocytosis, leukopenia, and marked neutrophilia).⁵

The emergency intervention of the obstructed urinary tract is required together with antibiotic therapy and sometimes intensive management.⁶ Despite these measures, Stone formers had a significantly higher risk for all-cause mortality with a hazard ratio of 1.95.⁷

Bilateral ureteral calculus obstruction due to calculus disease causing elevated serum creatinine and a decline in renal function is well-established. Many time, we come across situations where, unilateral ureteral calculus obstruction causes a decline in renal function even though they have a structurally normal kidney on ultrasound and patients not having any preexisting disease. We have tried to study this group of patients to find out the reasons for raised serum creatinine. With this particular aim in mind, we prospectively evaluated the role of infection and inflammation as possible causes of raised serum creatinine in patients with unilateral ureteral calculus disease.

MATERIALS AND METHODS

A prospective case-control study of all patients who presented to the urology department in the period from January 2010 to March 2011 with a history of ureteric colic secondary to unilateral ureteric calculi were evaluated.

50 patients during the study who presented with raised serum creatinine (> 1.3 mg%), with structurally normal contralateral kidneys were included in the study group (SG) and another randomly selected 50 patients without raised serum creatinine were included in the control group (CG). Informed consent obtained from all the patients. All details regarding patient's demographics, clinical details, investigation findings, the outcome of management were entered in the Proforma.

Inclusion Criteria

All patients aged <60 years, with unilateral ureteral calculi obstruction and raised serum creatinine with apparently normal contralateral kidney were included in SG and those without raised creatinine as CG.

Exclusion Criteria

Those patients with long-standing diabetes mellitus and hypertension of more than 5 years, elderly age of more

than 60 years, bilateral calculus ureteral obstruction, stone obstruction in a solitary functioning kidney, patients with pre-existing chronic kidney disease and those who required external diversion at the initial presentation (percutaneous nephrostomy) were all excluded from the study. The primary endpoint of the study was the time of reaching nadir value of serum creatinine after the intervention.

Initial Evaluation

All patients who presented with history suggestive of ureteric colic were evaluated with the following protocol:

- 1. History and physical examination.
- 2. Laboratory investigations
 - a) Absolute leukocyte count
 - b) Serum creatinine: The raised serum creatinine at presentation was confirmed by a repeat analysis prior to inclusion into the study
 - c) Estimated glomerular filtration rate (GFR)
 - d) Erythrocyte sedimentation rate (ESR)
 - e) C-reactive protein (CRP)
 - f) Urinalysis and urine culture sensitivity.
- 3. Radiological imaging

Ultrasonography abdomen: To look for cortical thickness, dilatation of pelvicalyceal system, and presence of echogenic debris. Non-contrast computed tomography of kidney, ureter, bladder; to look for stone size, stone site, degree of dilatation, perinephric stranding if any, forniceal rupture and other evidence of stone impaction like

- ureteral wall edema and tortuosity of the ureter.
- 4. Intraoperative findings
 - a. Degree of stone impaction such as presence of mucosal edema/congestion at the site of stone impaction
 - b. Ease of negotiability of ureteric guide wire or catheter, beyond the site of stone impaction
 - c. Evidence of infection/inflammation in the system, proximal to the stone such as turbid urine
 - d. Urine specimen from the corresponding kidney was sent for culture, after relief of obstruction.
- 5. Follow-up: All patients were subjected to a daily serum creatinine monitoring until a nadir level was reached. Those who did not reach normal serum creatinine levels by 2 weeks were considered as having associated nephropathy. Apart from serum creatinine, the other parameters considered and compared with CG were CRP, ESR, estimated creatinine clearance, and urine culture.

All patients were started on parenteral antibiotics Cefaperazone - Sulbactum combination preoperatively and then switched over to culture-specific antibiotic. Those who had sterile urine were continued with the same antibiotics postoperatively. All patients underwent ureteroscopy and had a double J stent placed, which was removed in 2 weeks' time, once nadir creatinine levels were reached.

The Definition of Abnormal Lab Parameters Included the Following

- 1. Serum creatinine more than 1.3 mg/dl is defined as elevated
- 2. Absolute leukocyte count more than 12000 cells/cumm is defined as leukocytosis
- 3. An ESR of more than 20 mm (Wintrobe's method) in one hour is defined as elevated ESR
- 4. Quantitative estimation of CRP was done by enzymelinked immuno-assay. A value of >0.6 mg/dl is abnormal
- 5. GFR is calculated by Cockcroft-Gault formula
- 6. Estimated creatinine clearance, or GFR
 - a. ([140-age] × mass [in kg])\(72 × Serum creatinine [in mg/dL])
 - b. If the patient is female, multiply the above by 0.85
 - c. The value of GFR <90 ml/min is considered as abnormal.
- 7. Statistical analysis was performed using the SPSS v.16 package (SPSS Inc. Chicago, IL). A P < 0.05 was considered as statistically significant.

RESULTS

A total of 100 patients were recruited in the present study. It was a prospective case-control study, with two groups, each containing 50 patients. Table 1 gives the

Table 1: Summary of the demographic data and	
characteristics in study and control groups	

Characteristics	SG	CG	P value
Number	50	50	
Mean age	39.86	38.26	
Gender			
Male	42	33	<0.0001
Female	8	17	
Co-morbidities			
Diabetes	8	4	0.105
Hypertension	11	5	
Constitutional symptoms			
Fever	20	7	<0.0004
Vomiting	27	8	
Loin pain	50	50	
Duration of loin pain (in days)	6.3	2.64	
Clinical findings			
Loin tenderness	32	8	<0.001
Palpable tender kidney	42	1	<0.001
Blood parameters			
Leukocytosis (>17,000)	13	0	<0.0005
Elevated CRP	46	10	<0.0001
ESR	50	6	<0.0001
Urine culture			
Pre-operative urine culture positivity	1	0	
Intra operative urine culture positivity	3	2	1.000

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, SG: Study group, CG: Control group summary of the demographic data, patient characteristics, patients' symptomatology and constitutional symptoms at presentation, blood biochemistry values, pre- and intra- operative urine culture, and associated co-morbid illnesses.

Patients in SG aged between 19 and 60 years, with the mean age of 39.86 and those in the CG aged between 24 and 60 years, with a mean age of 38.26. There was not much of a difference between the two groups as far as age at presentation is concerned.

The two genders showed striking differences. Males clearly predominated, with the male:female overall ratio of 3:1. There was a statistically significant difference in gender between these two groups ($P \le 0.0001$).

The duration of pain ranged from 1 to 21 days in the SG, with a mean of 6.73, whereas the mean duration of pain was only 2.64 in the CG.

Of the co-morbid conditions, diabetes and hypertension were found to be more in the SG (16% and 22%, respectively), as compared to CG (8 and 10%, respectively). However, because in none of these patients, the co-morbid conditions were present for more than 2 years, it is unlikely that these co-morbid conditions would have had any effect on baseline renal function.

Among the constitutional symptoms, only fever, vomiting, and loin tenderness were found to be significantly different between the study and CGs. In the SG, 40% presented with fever, whereas 14% of them had the fever, in CG. This data were found to be statistically significant. 54% from the SG (n = 27) and 16% from the CG had vomiting as the principal bothersome constitutional symptom. Two patients each from both the groups had hematuria. Even though all patients had loin pain, tenderness was elicited in 64% of patients in the SG, but in only 16% in the other group ($P \le 0.001$). On the other hand, a palpable tender kidney was found in 60% of patients SG and only in 2% of patients in CG. This difference was also statistically significant (P < 0.001).

Figure 1 presents the serum creatinine levels on admission in the both the groups. The majority of them in SG (72%) had a serum creatinine of <2 mg%. Two patients had a serum creatinine of more than 3.1 mg%. The mean serum creatinine levels in the SG and CGs were 1.91 mg% and 1.07 mg% with standard deviation (SD) of 0.169 and 0.563 and standard error of means (SEM) of 0.024 and 0.080, respectively. The two-tailed *P* value by Fischer's exact test was <0.0001.

Figure 2 depicts the overall GFR in both the groups. From the above data, one could observe that a majority of patients

in the SG had a GFR of <60 ml/min, while a majority of those in the CG were of more than 60 ml/min. It was also observed that only 11 patients (22%) in the SG and none in the SG had a GFR of more than 100 ml/min. The two-tailed P value by Fischer's exact test equals 0.0001; Mean GFR in the SG and CGs were 53.9 ml/min and 90.9 ml/min with an SD of 19.8 and 53.9 and SEM of 2.80 and 2.15, respectively.

Figure 3 gives an overview of the types of ureteric calculi encountered in our study. Figure 3a and c shows the ureteric stones in the SG and CG respectively. Figure 3b and d shows the radiological imaging that is suggestive of stone impaction and consequent upper urinary tract infection

Among the laboratory parameters, absolute leukocyte count, CRP, and ESR were found to be statistically significant difference between the two groups.

Tables 1 and 2 depict the details of absolute leukocyte count in both the groups. In the present study, the raised absolute count was classified as mild (12001-17000), moderate (17001-22000), and severe (>22000). From this study, it was observed about 16% in the SG had normal leukocyte levels. Moreover, moderate to severe leukocytosis was observed only in the SG ($P \le 0.0005$).



Figure 1: Serum creatinine levels at initial presentation in both the groups



Figure 2: Glomerular filtration rate levels at initial presentation in both the groups

From Table 1, it was observed that 92% of patients (n = 46) in the SG had elevated CRP, whereas 80% of patients in CG had normal CRP levels ($P \le 0.0001$). It was also observed that none from the SG had normal ESR. 12% of patients in CG had elevated ESR ($P \le 0.0001$).

There was no statistically significant difference in the urine culture between study and CG. From the above table, it was observed that only one patient in the SG had a positive culture. This very low presence of culture positivity may be



Figure 3: (a) Ureteroscopic image showing turbid infected urine after dislodging the stone, (b) Plain computed tomography kidneys, ureters, and bladder showing perinephric stranding with dilatation of right ureter with distal ureteric stone impaction, (c) Ureteroscopic image showing dislodged stone in the control group, and (d) Floating debris on ultrasonography

Table 2: Leukocyte count in SG and CG							
Group	Absolute leukocyte count (%)				P value		
	Normal	Mild	Moderate	Severe			
SG	8 (16)	30 (60)	11 (22)	2 (4)	<0.005		
CG	25 (50)	25 (50)	0 (0)	0 (0)			

SG: Study group, CG: Control group

Table 3: Summary of imaging techniques and intraoperative findings

Characteristics	SG	CG	P value
Imaging techniques			
Debris in ultrasound	31	8	< 0.002
Perinephric stranding in computed tomography	31	8	< 0.002
Intra operative ureteroscopic finding			
Stone impaction**	39	1	< 0.0001
Ureteral edema and congestion at stone	41	18	<0.020
impaction site			
Purulent urine on disimpaction	37	1	< 0.0001
Post-operative return of serum creatinine	47	50	
levels to <1.3 mg %			
Ability to negotiate the guidewire across the	6	29	0.0007
site of stone impaction			

**Stone impaction: Defined as either contrast not visualizing the ureter proximal to site of stone impaction or the guide wire not negotiable beyond the stone and returning back at impacted site, SG: Study group, CG: Control group

a true state of affairs or it may be a falsely negative culture secondary to impacted stone preventing urine from the obstructed site coming into the bladder.

Table 3 gives the summary of the findings of pre-operative imaging and intra operative ureteroscopic findings. Among the radiological findings, the presence of debris on ultrasound as internal echogenicity and perinephric stranding on computed tomography (CT) kidneys, ureters, bladder (KUB) were found to be significantly different between the two groups. Ultrasound screening of the kidneys showed evidence of floating debris in 62% of patients in SG, whereas 16% in the CG demonstrated debris in collecting system. The presence of debris within the collecting system is an indirect evidence of infection or inflammation in the system secondary to calculus obstruction. A statistically significant correlation $(P \le 0.001)$, further suggests that presence of debris within the pelvicalyceal system does have a significant impact on the ultimate renal function.

Non-contrast CT KUB was done in all patients in both groups. Perinephric stranding was seen in 62% of patients in the SG when compared this with CG it was only 16%. Perinephric stranding can be a feature of infection or inflammation, which may be directly or indirectly causal to raised serum creatinine. Two patients in the SG also had forniceal rupture. A 0.032 inches guide Terumo guide wire could be negotiated across the stone in only 12% in the SG, while in the CG the guide wire was negotiable in 58%, with a two-tailed P value that equals 0.0007. This data suggested that impaction at the stone site, strongly correlates with deterioration in renal function.

On the other hand, when urine from the kidney after disimpaction of the stone was analyzed, it was found that 2 patients from the CG and three from the SG had a positive urine culture. The low incidence of culture positivity may be a true state of affairs or it may be a falsely negative culture, because of antibiotics, received in previous 24 h.

DISCUSSION

Urinary tract obstruction is a common cause of acute and chronic renal failure. The clinical features of a kidney that is obstructed may range from being totally asymptomatic to severe acute pain. The diagnosis of an obstructed kidney is not very difficult these days, especially with the availability of high-resolution ultrasonography and computed tomography and digital intravenous urogram.⁸

During the first few hours, following acute unilateral ureteral obstruction (UUO), renal blood flow in the obstructed kidney increases secondary to preglomerular vasodilatation

of renal blood vessels, which increases GFR. As the GFR increases, increased urine formation begins to gradually increase ureteral pressure.9 After 4 h of obstruction, renal blood flow declines while ureteral pressure continues to increase along with post-glomerular vaso constriction. The increased intrarenal pressure activates the reninangiotensin system leading to rise in the vasoconstrictors such as thromboxane A2, which results in decreased renal blood flow and a decrease in ureteral pressure associated with preglomerular vasoconstriction.¹⁰ The pathological changes that occur during bilateral ureteral obstruction (BUO) differ from UUO. While during UUO, the kidney passes through these three phases, in BUO the kidney passes through a phase of preglomerular vasodilatation and then a postglomerular vasoconstriction without subsequent preglomerular vasoconstriction.^{11,12}

The readily available lab parameters such as absolute leukocyte count, ESR, and CRP are indirect indicators of the severity of inflammation/infection in the unilaterally obstructed renal system.¹³ In our SG, these lab parameters along with few imaging parameters such as the presence of debris in the pelvicalyceal system as well as certain clinical parameters, such as fever and loin tenderness, reflecting inflammation/infection, were significantly raised.

From the present study, there is no statistical difference in age between the CG and the SGs. However, there was a statistical difference in gender. Overall, 75% of the patients, when both groups were combined, were males.

With the regard to the clinical symptoms, the presence of fever, loin tenderness, and vomiting was statistically different between both the groups. Fever is a factor, which can reflect underlying infection or inflammation. In the presence of infection, inflammatory markers such as interleukin-1, interleukin-6, should be elevated and are responsible for fever, although these markers, were not in the preview of the study. The significant difference in the presence of fever between these two groups indirectly reflects the severity and degree of infection or inflammatory process. Out of 20 patients with fever, 19 (95%) patients had elevated infective or inflammatory parameters. Out of 32 patients with loin tenderness 22 (68.75%), had elevated infective or inflammatory markers. Similarly, in the present study, there has been a strong correlation between loin tenderness and degree of obstruction ($P \leq 0.001$) Out of 32 patients with loin tenderness in the SG, 23 (74.2%) patients had perinephric stranding on CT KUB.

Rising levels of plasma creatinine in the setting of acute UUO (AUUO) often reflects acute renal failure, mandating immediate kidney drainage. It is hypothesized that reabsorption of perirenal urine extravasation, a common result of UUO, contributes significantly to the elevation in plasma creatinine, rendering the latter an inaccurate benchmark for renal function.¹⁴

There has also been strong correlation between inflammatory parameters, CRP, absolute leukocyte count, ESR, and vomiting.¹⁵⁻¹⁷ Out of 27 patients, who had vomiting in the SG, 23 (88.5%) patients had elevated infective or inflammatory parameters ($P \le 0.001$). This would suggest that the presence of these factors would be an indirect evidence of inflammation and obstruction.

All the patients with perinephric stranding on CT KUB and debris on ultrasonography had elevated infective or inflammatory parameters.^{18,19} Similarly, there has been a stronger correlation and statistically significant difference between these groups on radiological evidence of stone impaction and inflammation, like perinephric stranding and debris in the system.

Per-operative findings of mucosal edema or congestion at the stone site will also suggest ongoing inflammation and obstruction. Moreover, as such, in 80% of SG patients, there have been raised inflammatory or infective markers ($P \le 0.001$). Interestingly, once the obstruction is released, the serum creatinine came down to near normal, immediately after the procedure, which reached progressively to the nadir value, within a week.

This suggests that once the obstruction is relieved, the inflammatory mediators responsible for the decrease in the renal plasma flow have improved regaining the near normal baseline GFR. This fact is once again proved by near normal return of inflammatory markers, together with this event. The mean CRP level, in the SG was 0.8 mg/dl, whereas it was 0.4 mg/dl, in CG.

This would suggest a direct or indirect correlation between inflammation/infection and rise in serum creatinine. As in 49 out of 50 patients in the SG, the raised serum creatinine came back to normal relatively rapidly after relief of obstruction and relief of possible infection. Pathological event giving rise to raised serum creatinine must be an easily and rapidly reversible process. This event most likely must be vasospasm of the afferent glomerular arteries.

In any acute unilateral ureteric obstruction, the ipsilateral afferent glomerular arteries finally undergo vasoconstriction secondary to release of thromboxane A_2 . However, this normally does not lead to elevation of serum creatinine, if the contralateral kidney is normal. However, it can be hypothesized that the presence of associated inflammation/infection on top of acute obstruction, either the amount of thromboxane A_2 is secreted in larger

amount or other vasoactive cytokines such as interleukin 1 and interleukin 2 are also released which then instead of acting only locally on the ipsilateral kidney by autocrine or paracrine mechanism may also affect to contralateral renal vessel by endocrine mechanism, ultimately leading to bilateral afferent renal vasoconstriction, reduction of overall GFR and eventually rise in serum creatinine.

CONCLUSION

A clinical situation of unilateral calculus ureteral obstruction with raised creatinine, in patients with structurally normal contralateral kidney, does exist. This condition is hardly ever mentioned or discussed in the urological literature. There is no ready or easy answer to explain the rise in serum creatinine in the presence of only unilateral obstruction.

This abnormal surge would probably enable the vasoactive cytokines to extend their action on the contralateral renal vessel, as well as by an endocrine mechanism and their by leading to bilateral renal vasoconstriction and reduction of GFR and thereby rise in serum creatinine. The obstructing ureteric stones in such situations are likely to be impacted and hence are not likely to respond to conservative measures. Ureteroscopic removal of stone will rapidly remove the obstruction and reverse the infective/inflammatory process on renal failure. Further, well-designed studies are needed to substantiate the hypothesis drawn from this study.

LIMITATIONS

The numbers taken for this case-control study could have been much higher. The premorbid GFR values of patients in SG are not known. The roles of vasoactive inflammatory cytokines were only hypothesized in the present study and actually were not studied. A Doppler study to document resistive index of the renal vessels, could have probably given more insight into vasospasm.

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