# **Original Research Article**

DOI: http://dx.doi.org/10.18203/2349-2902.isj20181034

# Serum c-reactive protein as a predictive factor for spontaneous stone passage in patients with 4 to 8 mm distal ureteral stones

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Received: 07 March 2018 Accepted: 12 March 2018

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# **ABSTRACT**

**Background:** Ureteral stones are common problems in daily emergency department practice. Ureteric stone is responsible for 20%. Ureter obstruction caused by a ureteral stone triggers inflammatory changes in the proximal submucosal layer and prevents passage of the stone. C reactive protein (CRP) was found to be an indicator of ureteral stone outcome. The objective of this study was to measure serum CRP for patients with 4-8 mm distal ureteric stone and use its level as predictive factor for spontaneous stone passage.

**Methods:** A prospective study was designed on a total of 73 patients (M=34; F=39) who were in the age group (18-50) years, who presented with ureteral colic secondary to a solitary unilateral, 4 to 8 mm distal ureteral stone. Patients were grouped according to spontaneous stone passage. The patients were selected at the urology unit, in Ghazi AL Hariri Hospital for Specialized Surgery, Medical City Complex in Baghdad from October 2014 till October 2016. The follow up continued until the stone spontaneously passed, as reported by the patient, or for a maximum period of 4 weeks.

**Results:** Age, BMI, and gender did not show significant difference between the two groups ;30 have spontaneous stone passage (SSP), and 43 no spontaneous stone passage (no SSP). Stone size is significantly higher in the group without SSP their median is 6 mm compared to 4 mm for SSP group. CRP is significantly elevated in no SSP group compared to SSP. CRP, stone size and previous history of stone passage was the only significant and independent predictors of SSP (low CRP, low stone size, and positive history predict SSP).

**Conclusions:** Stone size, CRP, previous Hx of stone passage are independent predictors for SSP. Measuring serum CRP levels is useful for predicting whether spontaneous ureteral stone passage will be successful. More aggressive treatment methods such as URS should be considered when serum CRP levels is high.

Keywords: CRP, Passage, Stone, Ureter

# INTRODUCTION

Ureteral stones are a common problem in daily emergency department practice.<sup>1</sup> The annual incidence is about 1-2 cases of acute ureteric colic per 1,000 people and the average lifetime risk around 5-10%.<sup>2</sup> Ureteric

stone is responsible for 20% of all urinary tract stones, and 70% of these stones are located in the distal portion of the ureter.<sup>3</sup>

Stone recurrence is also a common medical condition and the recurrence rates are estimated to be up to 50% within

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5 to 10 years from the first episode of renal colic.<sup>4,5</sup> It is estimated that 12% of males and 6% of females will experience an episode of renal colic at some stage in their life with incidence peaking between age 40 and 60 years for males and in the late 20's for females.<sup>6</sup>

The majority of ureteral calculi can pass spontaneously, and intervention is usually not required.<sup>7</sup> If the stone diameter is less than 4 mm, spontaneous passage is generally possible), and for stones  $\leq$ 5 mm independent of their location within the ureter spontaneous passage rate 68%.<sup>8,9</sup>

Ureteral calculi >6 mm which are located in the proximal ureter at the onset of symptoms have a 5% or less chance of spontaneous passage Whereas Ureteral calculi located at the distal ureter have a 50% chance of spontaneous passage with only conservative observation.<sup>8</sup>

The composition of ureteral calculi varies, but most stones are composed of calcium salts such as calcium oxalate monohydrate, calcium oxalate dihydrate and calcium phosphate.

Less common materials include cystine, uric acid and struvite. A stone's composition is one of the factors together with location, size, degree of impaction, shape, surface contour and other considerations that may influence choice of treatment.<sup>10</sup>

Most of the urinary stones pass through the renalcalyces to the pelvis and subsequently to the ureter. Primary stone formation in the ureter requires an already existing obstructed urinary flow.

Despite an improved understanding of the mechanisms of stone formation it is obvious that ureteral stones are still a problem afflicting an increasing number of patients worldwide.<sup>11</sup>

Serum C-reactive protein (CRP) was so named because it was first discovered as a substance in the serum of patients with acute inflammation that reacted with the C-(capsular) polysaccharide of pneumococcus.<sup>12</sup>

Discovered by Tillett and Francis in 1930, it was initially thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer. 13,14

However, the discovery of hepatic synthesis demonstrated that it is a native protein. 15-17

CRP increase as a result of inflammatory responses and are clinically used as indexes ofthe degree of inflammation. Ureter obstruction caused by aureteral stone triggers inflammatory change in the proximal submucosal layer and prevents passage of the stone. 18

The objective of this study was to measure CRP for patients with 4-8 mm distal ureteric stone and use its level as predictive factor for spontaneous stone passage.

#### **METHODS**

A prospective study was designed on a total of 73 patients (M=34; F=39) who were in the age group (18-50) years, who presented with ureteral colic secondary to a solitary unilateral, uncomplicated 4 to 8 mm distal ureteral stone. Patients were grouped according to spontaneous stone passage.

The patients were selected at the urology unit, in Ghazi AL Hariri Hospital for Specialized Surgery, Medical City Complex in Baghdad. Starting from October 2014 till October 2016.

#### Exclusion criteria

- Patients who required early intervention:
  - i. Impaired renal function,
  - ii. solitary kidney,
  - iii. severe renal colic pain resistant to medical treatment, hydronephrosis grade 3 or greater and
  - iv. who preferred active stone removal.
- Urinary tract infection.
- Multiple ureteral stones.
- Chronic renal failure.
- Congenital urinary anomalies.
- Previous open or endoscopic ureteral surgery.
- Malignancy.
- Inflammatory disease.
- Liver failure.
- Pregnancy.

A total of 73 patients with distal ureteric stone 4-8 mm involved in the study and grouped according to spontaneous stone passage, group spontaneous stone passage (SSP) (30 patient) and group No spontaneous stone passage (no SSP) (43 patient).

Serum C-reactive protein was measured for all patients for its potential predictive value for spontaneous stone passage at a follow up of 4weeks. CRP values measured upon initial presentation (before use of NSAIDs) as these drugs reduce CRP. The reference range of CRP: 0-10mg/L Level, above 10 mg/L were considered as high.

Serum C-reactive protein measurement using NycoCard kit results in less than 3 minutes.

All patients were subjected to history taking KUB, urinary tract ultrasound, and Low - dose NCCT scan to diagnose stone site and size, and plasma CRP estimation, and re-evaluated weekly with plain abdominal radiography, ultrasonography and Low - dose NCCT whenever they were necessary.

The follow up continued until the stone spontaneously passed, as reported by the patient, or for a maximum period of 4 weeks.

Patient included in this study keep on Conservative treatment (diclofenac 100 mg or indomethacin suppositories on need as a non-steroidal anti-inflammatory drug for pain relief, Tamsulosin tab 0.4 mg and all patients were instructed to drink 2 L water daily).

Patients who failed to expel the ureteral stone spontaneously within 4 weeks of follow-up underwent ureteroscopy.

#### **RESULTS**

### Demographic data

Age, BMI, and gender did not show significant difference between the two groups (30 have stone passage, and 43

no stone passage) which mean demographic data are not confounder in this study as illustrated in Table 1.

Table 1: Demographic data by stone passage.

Variables		SSP	No SSP	P value	
Number		30	43	-	
Age		36.6±8.8	35.7±9.3	0.686 <sup>a</sup> [ns]	
BMI		28.1±4.4	30.2±4.4	0.051 <sup>a</sup> [ns]	
Gender	Female	17 (56.7%)	22 (51.2%)	0.643 <sup>b</sup>	
	Male	13 (43.3%)	21 (48.8%)	[ns]	

<sup>&</sup>lt;sup>a</sup>Independent T test, <sup>b</sup>Chi square test

#### Stone size

Stone size is significantly higher in the group without SSP their median is 6 mm compared to 4 mm for SSP group as illustrated in Table 2.

Table 2: Stone size from each group

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Variables		SSP	No SSP	P value
Number		30	43	-
Stone size (median, IQR)		4 (4 – 5)	6(5-7)	<0.001[Sig.]
Stone size groups	4 mm	19 (63.3%)	2 (4.7%)	
	5 mm	7 (23.3%)	9 (20.9%)	
	6 mm	3 (10%)	13 (30.2%)	<0.001[Sig.]
	7 mm	1 (3.3%)	10 (23.3%)	
	8 mm	0 (0%)	9 (20.9%)	
Mann Whitney U test,	IQR: interquartile	range (25% - 75%)		

Table 3: CRP from each group.

Variables	SSP	No SSP	P value
Number	30	43	-
CRP (mean±sd)	16.8±4.8	27.5±8.9	<0.001[sig.]

#### **CRP**

CRP is significantly elevated in no SSP group compared to SSP as illustrated in Table 3.

### Predictors of SSP

CRP, stone size and previous history of stone passage was the only significant and independent predictors of SSP (low CRP, low stone size, and positive history predict SSP) as illustrated in Table 4.

# DISCUSSION

Urinary stones are the third most common affliction of the urinary tract, exceeded only by urinary tract infections and pathologic conditions of the prostate (BPH and prostate cancer).<sup>11</sup> The majority of ureteralstones cause pain that is intense and rapid in onsetcausing patients to seek care acutely. 19

Urolithiasis is a common problem encountered by the surgeon and its incidence rising day by day. Ureteral stones are formed in the renal collecting system and then progress down the ureter. They then tend to lodge at sites where the ureter narrows. The three most common entrapment sites are at the ureteropelvic junction, over the iliac vessels and at the ureteral meatus.<sup>20</sup>

CRP increase as a result of inflammatory responses and are clinically used as indexes of the degree of inflammation.<sup>18</sup>

In this study, serum CRP level is measured in patients with ureteric stone as a new parameter to assist in making a decision concerning intervention versus observation.

All patients were followed for 4 weeks for spontaneous stone passage, However, the conservative management in some cases is associated with discomfort and can result in complications such as urinary tract infection, hydronephrosis, and renal function deterioration.

In present study the mean stone size was range 4-8 mm greatest dimension. Options for managing ureteral stones include conservative treatment and active stone removal with minimal invasive techniques, including ESWL and ureteroscopy. 21,22

Compared with ESWL, ureteroscopic lithotripsy achieves a greater stone-free state. Despite high success rates ureteroscopy is not complication free and it is more expensive than conservative management.<sup>23-25</sup>

Table 4: Predictors of no SSP.

	Univariate analysis			Multivariate analysis		
Predictors	OR	95%CI	P value	Adjusted OR	95%CI	P value
Age	0.991	0.946-1.039	0.71	-	-	-
Gender	1.048	0.412-2.662	0.922	-	-	-
BMI	1.114	0.998-1.243	0.054	-	-	-
Stone size	5.218	2.516-10.823	< 0.001	7.464	2.454-22.7	0.001
CRP	2.579	1.514-4.393	< 0.001	2.418	1.334-4.381	0.004
No Hx of stone passage	2.887	1.054-7.908	0.039	2.216	1.645-6.342	0.013
Logistic regression	OR: odd ratio, CI: confidence interval					

The proability of spontaneous stone passage, the effects of unrelived obstruction and the patient's wishes should be considered when electing for conservative management.

The choice between watchful waiting and active management until spontaneous passage is the main problem for the urologist when managing patients with ureteric stones.<sup>24</sup>

In our study upper limit of the patients age 50 year because many of the elderly patient taking other medication for chronic disease which affect the level of the CRP.

Age, BMI, gender did not show significant difference between two groups (SSP and no SSP). Distribution of stone passage in the study reveal SSP in 30 patients (41%) and no SSP in 43 patients (59%). In the present study the likelihood of a distal ureteral stone passage is dependent on several factors CRP, stone size and history of previous stone passage. Several studies showed high rates of spontaneous passage for distal ureteral stones smaller than 5 mm.<sup>26,27</sup>

In our series all patients had distal ureteral stones, stone size was a significant predictor of SSP on univariate analysis, which was confirmed by multivariate analysis median stone size for SSP 4mm and for non SSP 6mm which is explained in Mann Whitney U test. Serum CRP is another marker that has been investigated in some recent series as a potential predictive factor for SSP in patients with ureteralstones.<sup>28</sup>

In our study univariate analysis showed that serum CRP was significantly higher in patients who did not expel the ureteral stone spontaneously. CRP was also a significant

predictive factor forspontaneous passage on multivariate analysis.

In a recent retrospective study Park et al examined the relationship of the spontaneous passage rate of ureteral stones smaller than 8 mm with the CRP level and the neutrophil count.<sup>24</sup> A total of 187 patients who were diagnosed with ureteral stones less than 8 mm in size and were managed consecutively at Keimyung University Dongsan Medical Center from January 2001 to January 2011 were retrospectively analyzed. Ureteral stone removal was defined as no ureteral stone shown in an imaging test without any treatment for 8 weeks after diagnosis. The patients were divided into three groups according to the levels of serum CRP and into two groups according to neutrophil percentage. The associations between these factors and ureteral stone passage rates were then examined. The ureteral stone passage rates of the low serum CRP level group, the medium serum CRP level group, and the high serum CRP level group were 94.1% (159/169), 70% (7/10), and 50.0% (4/8), respectively. The passage rates of ureteral stones in the group with a normal neutrophil percentage and in the group with a higher neutrophil percentage were 94.5% (121/128) and 83.1% (49/59), respectively (p=0.011). Measuring serum CRP levels and neutrophil percentages in patients with small ureteral stones of less than 8 mm is useful in predicting whether the stone will be spontaneously passed. When the serum CRP level and neutrophil percentage of a patient are high, aggressive treatment should be considered.

Aldaqadossi studied 235 patients receiving MET. Stone expulsion within 4 weeks was recorded in 129 patients (54.9%), while 106 patients (45.1%) underwent ureteroscopy for stone extraction. C-reactive protein (CRP) was significantly different in the two groups; stone

expulsion was significant when low serum CRP levels (16.45+2.58) compared to those who failed (39.67+6.30).

In a study which measured CRP in patients with ureteral colic due to urolithiasis concluded that there is no defined cutoff level of CRP to predicts spontaneous passage of a ureteric stone, but A cut-off point for CRP of 28 mg/L achieved optimum sensitivity (75.8%) and specificity (88.9%) for determining the decision for drainage.<sup>29</sup>

### **CONCLUSION**

Stone size, CRP, previous history of stone passage are independent predictors for SSP. Measuring serum CRP levels is useful for predicting whether spontaneous ureteral stone passage will be successful. More aggressive treatment methods such as URS should be considered when serum CRP levels is high.

Funding: No funding sources Conflict of interest: None declared

Ethical approval: The study was approved by the

Institutional Ethics Committee

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Cite this article as: Mohammad EJ, Abbas KM, Hassan AF, Abdulrazaq AA. Serum c-reactive protein as a predictive factor for spontaneous stone passage in patients with 4 to 8 mm distal ureteral stones. Int Surg J 2018;5:1195-200.