Original Article

Diagnostic role of urine C-reactive protein levels on ureteral stone disease

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Abstract

Objective: To investigate the importance of serum and urine CRP levels in patients with ureteral stones.

Material and Method: Seventy-six patients were included in this study. Forty-nine patients in Group 1 had ureteral stones while 27 healthy volunteers in Group 2 were included as controls. Demographic data, preoperative radiologic imaging and perioperative findings of the patients (including stone size, presence of stone impaction etc.) were recorded. Serum and urine CRP levels were measured on the morning of surgery. Urine CRP was measured by quantitive sandwich enzyme immunoassay technique with Immunodiagnostic brand ELISA kit (BensheimR,Germany).

Result: Twelve stones (24.5%) were found to be obstructive. The mean serum and urine CRP values of participants were: 12.1 mg/L and 10.5ng/dL in Group 1, and 1.5 mg/L and 6.1 ng/dL in Group 2, respectively (pserumCRP=0.002, purineCRP=0.001). The serum and urine CRP levels were found to be 20.2 mg/L and 12.8 ng/dL for obstructive stones and 9.1 mg/L and 9.8 ng/dL for non-obstructive stones, respectively (pserum CRP =0.133) (purine CRP =0.492). According to the ROC analysis, the best cut-off values of serum and urine CRP were 2.4 mg/L and 6.7 ng/dL, respectively. The sensitivity and specificity values of the serum and urine CRP measurement were 78.0%, 85.2% and 63.5%, 85.1%, respectively.

Conclusion: Serum and urine CRP measurements are candidates to be new markers for ureteral stones. The usage of serum and urine CRP levels may support the presence and impaction of ureteral stones. We believe further studies involving larger series are necessary before more definite conclusions can be drawn.

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Introduction

Urolithiasis is a significant problem in terms of its increasing prevalence and morbidity, which are both related to urological health and overall health in general. Urolithiasis has a lifetime prevalence of 10%, which increases the importance of ureteroscopy and stone removal procedures[1]. Among the urinary tract stones, ureteral stones are the most significant with a prevalence of 3-5%. It has been reported that the number of ureteroscopy procedures increased by 127% in the last decade[2].

The most frequently used tool for diagnosing urinary stones is a full urine test. Urine is an ideal sample because it easy to collect for the diagnosis of various diseases. This test is an indispensable tool in the diagnosis and follow-up of urinary stone disease. It consists of many parameters, such as erythrocyte, presence of stone crystalloid, and leukocyte and leukocyte esterase, to identify urinary stones and infection[3]. However, in several diseases, such as renal colic and stone disease, the results of the urine test are relatively delayed and non-specific, which has led researchers to seek non-invasive biomarkers that are easy to implement. The importance of the imaging methods is undisputed for urinary system stone disease. In particular, non-contrast computed tomography is considered the gold standard method for the diagnosis of ureteral stone disease. But, this method does not provide sufficient information about impaction status because it does not use contrast agents. Therefore, it is necessary to use some biomarkers in conjunction with imaging techniques.

C-reactive protein (CRP) is a serum acute-phase reactant that tends to increase in many diseases and in particular in infections. There is a known association between serum CRP levels and urinary stones[4,5].

In this pilot study, we investigated the importance of serum CRP and the measurement of CRP in urine samples to identify and predict the presence and impaction of ureteral stones.

Material and method

The participants of this study were 49 patients who underwent an endoscopic procedure for the removal of ureteral stones (Group 1) and 27 healthy individuals (Group 2). The patients' demographic data, preoperative radiological findings and perioperative findings such as the presence of obstruction were recorded. It was noted that the urinary cultures of all the patients were sterile before the operation. In the preoperative radiological assessment, obstructed patients were identified as those with ureteral stones that prevented contrast from passing through or with a dilated collecting system proximal to the stone and/or patients whose ureter was completely obstructed by the stone leading not advancing a guide proximal to the stone.

The CRP levels were measured in the serum and urine samples collected in the morning. The urine samples were collected in sterile disposable containers using the midstream urine collection technique. Urine samples were centrifuged at 2000 rpm for 5 minutes and the supernatant were separated and stored at -80°C until analysis. The C-reactive Protein (CRP) was measured by quantitative sandwich enzyme immunoassay technique with the Immunodiagnostic ELISA kit (Bensheim, Germany). After 1:5 dilution, the urine samples were analyzed. The detection limit of the assay was 0.921 ng/mL. The intra and inter-assay precision of the assay were 6% and 11.6%, respectively.

The Statistical Package for Social Sciences (SPSS, Chicago, IL, USA) Version 13.0 program was used for the statistical analysis. For the comparison of ureteral stone presence and serum, urine CRP levels in an independent sample test were used. For the comparison of obstruction and serum of urine CRP levels, the Mann-Whitney U test was used. $P<0.05$ values were assumed to be statistically significant.

Result

Average patient age was 37.9±14.5 (15-85) years: 41.6±14.9 (17-85) in Group 1 and 31.3±11.0 (15-60) in Group 2 (P<0.05). Of the patients in Group 1, 37 were male (75.5%) and 12 were female (24.5%), and the control group (Group 2) consisted of 14 men (51.8%) and 13 women (48.2%). The average stone size was 11.06±4.6mm (4-21 mm) with 26 stones being located in the left ureter and 20 in the right ureter, and 2 patients had bilateral ureteric stones. Furthermore, the stones were located in the lower segment of the ureter in 24 patients, in the medium segment in 9 patients and the upper segment in 15 patients. Twelve stones (24.5%) were found to be obstructive and 37 (75.5%) were non-obstructive. The mean serum and urine CRP values of the participants were: 12.1 mg/L and 10.5 ng/dL in Group 1, and 1.5 mg/L and 6.1 ng/dL in Group 2, respectively. A comparison of the serum and urine CRP levels revealed a statistically significant difference between Group 1 and Group 2 (pserum CRP=0.001 and purine CRP=0.001). According to the Receiver Operating Characteristic (ROC) analysis, the best cut-off value of serum and urine CRP levels were 2.4 mg/L and 6.7 ng/dL, respectively. The sensitivity and specificity values of the serum and urine CRP measurement were 78.0%, 85.2% and 63.5%, 85.1%, respectively.

The presence of any degree of hydronephrosis was found to be 87.8% in all of the patients. Presence of hydronephrosis was found to be 100% (12/12) for the obstructive stones and 83.8% (43/49) for the non-obstructive stones. There was no statistically significant difference between the patients with obstructive and non-obstructive stones in terms of the presence of any degree of hydronephrosis (p=0.314). Preoperative nephrostomy was installed for 2 patients who had obstructive stones.

The serum and urine CRP levels were found to be 20.2 mg/L and 12.8 ng/dL for obstructive stones and 9.1 mg/L and 9.8 ng/dL for non-obstructive stones, respectively (Table 1). Thus, there was no statistically significant difference between the patients with obstructive and non-obstructive stones in terms of the serum and urine CRP levels (p serum CRP=0.133) (purine CRP=0.492).

Discussion

The association between CRP and inflammation has been reported in several system diseases. CRP is released from the liver into the bloodstream in response to inflammation, malignancies and cardiovascular system diseases[6,7]. Significant biological characteristics of CRP include a rapid increase in acute phase response, which can be a thousand-fold within

Table 1. Descriptive statistics of the study populations

	Group 1 (n=49)	Group 2 (n=27)	p	Obstructive ureteral stone (n=12)	Nonobstructive ureteral stone (n=37)	p
Serum CRP (mg/L) Min-Max	12.1 ± 16.2 (0.4-69)	1.5 ± 1.7 (0.2-7)	0.002	20.2 ± 23.6 (1-69)	9.1 ± 12.3 (4-61)	0.133
Urine CRP (ng/dL) Min-Max	10.5 + 6.4 (4.6-31.8)	6.1 + 1.7 (2.2-12.9)	0.001	12.8 + 9 (5.1-31.8)	9.8 + 5.2 (4.6-26.8)	0.492

24-48 hours, a rapid decrease to the original level, not exhibiting diurnal variation, and not differing according to age or gender[8]. In acute inflammation or tissue damage, the increase in the CRP level up to 1000-fold is temporary, while in chronic inflammation, the increased CRP level is maintained. The CRP level is measured to identify the disease activity in many clinical cases, such as rheumatoid arthritis, ankylosing spondylitis, systemic lupus and infective endocarditis. In healthy individuals, the CRP level in the serum is low and does not change during the daytime[9,10]. It is easy and inexpensive to measure the CRP levels on fresh or frozen plasma using biochemical methods[11].

As in other biological systems, there is an association between the genitourinary system diseases and serum CRP levels. This protein is used as a biomarker in patients with lower urinary tract symptoms of renal pathophysiology, and the genitourinary system[12] is used in those with renal cell carcinoma and upper urinary tract urothelial carcinoma,[13,14] as well as to predict inflammation and obstruction in patients with renal colic[15].

Urinary stone disease is a commonly experienced problem throughout the world. The most frequently used diagnostic tools for this disease are a full urinary test and imaging techniques. It has been reported that inflammatory events, in particular urinary stones, increase renal glomerulosclerosis and as a result elevate CRP levels. Glomerulosclerosis can develop due to acute or chronic events in the kidney and is considered to be the equivalent of atherosclerosis in the cardiovascular system[16]. Therefore, despite the increasing number of studies that report the association between early period renal disease and CRP levels and decreased kidney functions, there is not yet sufficient evidence[17-19].

In a recent study investigating the role of serum CRP levels in upper urinary system infections, 58 patients with a urinary system infection and 28 individuals in the control group were evaluated. Patients were further divided into 2 groups comprising those with upper and lower urinary system infections. The serum CRP levels were found to be 127.33 mg/L in the upper urinary system infection group and 12.37 mg/L in the control group ($p<0.01$). It was concluded that serum CRP has a good diagnostic value in the differentiation between upper and lower urinary system infections[20-21].

Urinary stone disease is one of the most common reasons for patients to visit a urology practice. Treatment modalities are: pain relief is the first therapeutic step in patients with an acute stone episode, medical expulsive treatment (MET), extracorporeal shock wave lithotripsy (ESWL) and minimally invasive surgical procedures, such as ureteroscopy and retrograde intrarenal surgery. The most common finding is hydronephrosis based on imaging methods[22]. Infectious hydronephrosis is a common complication resulting from an obstruction caused by urinary stones. This can sometimes result in severe morbidity and mortality secondary to bacteremia and septicemia[23]. Studies investigating the early diagnosis of obstruction have reported that high serum CRP levels can be a useful marker. Wolff KM et al. found that the serum CRP levels of patients who developed hydronephrosis after ESWL secondary to symptomatic ureteral stones were 18 times higher than the normal population, while there was no significant difference in terms of white blood cell count, erythrocyte sedimentation rate (ESR) and temperature[24]. Similarly, Wu TT et al., who conducted a study with 38 patients with hydronephrotic kidneys, reported that renal ultrasonography can detect pyonephrosis with a specificity of 96% and a sensitivity of 38%. However, when the serum CRP cut-off value was taken as 100 mm, the specificity and sensitivity increased to 89 and 100%, respectively[25]. A study by El-Assmy A investigated the differences among the 4 groups in terms of stone size and treatment outcome, and determined they were not significant. However, the presence of hydronephrosis was highly associated with repeat treatment (2.4 vs 1.7 treatments; $p<0.001$)

and prolonged stone clearance time (16.2 vs 11.6 days; p<0.001). The authors reported that the degree of hydronephrosis caused by the stone does not affect the overall treatment success with ESWL. However, stones in obstructed systems are associated with a tendency for repeat treatment and a prolonged time for stone clearance[26]. Again, in a meta-analysis including 570 patients receiving emergency ESWL treatment for ureteral stones, emergency ESWL was reported to be safe and to have a high success rate[27].

In a review about MET, it is emphasized that MET is effective in the treatment of ureteral stones. However, it also made clear that the side effects of alpha blockers need to be taken into consideration. Therefore, we think that serum and urine measurements of CRP can help to avoid those side effects while addressing early definitive treatment. Today, valid treatment options for ureteral stones have some disadvantages of their own. There is not enough data on the appropriate selection of patients for MET. Data on the usage of ESWL in the presence of an obstruction and its timing are also insufficient. Although the success of URS treatment is higher than other methods, its high cost can be seen as a disadvantage[28]. Therefore, elevation of serum or urine CRP levels may be used as a sign of the need for early URS treatment, and may also serve as a factor in avoiding the side effects of non-appropriate MET or ESWL treatments.

In our study, the urine CRP levels in impacted ureteral stones were similar to those found in non-impacted stones while the serum CRP levels were higher 20.2 mg/L, 9.1 mg/L (pserum crp level=0.133) vs 12.8 ng/dL, 9.8 ng/dL (purine crp level=0.492). This statistically insignificant finding may be due to the low number of cases. This finding can guide doctors to opt for early endoscopic surgery rather than conservative, MET or ESWL treatment options.

Chuang YC et al. evaluated the association between urine and serum CRP levels and lower urinary system symptoms. The authors measured the serum CRP levels in a total of 97 patients, 20 of whom additionally provided a urine sample for CPR measurement. When compared with the asymptomatic control group, the serum CRP levels were found to be significantly higher in patients with an overactive bladder, chronic prostatitis, benign prostate hyperplasia and acute febrile bacterial infection. Of the patients with an overactive bladder, only those who had incontinence had a significantly higher serum CRP level while no significant difference was observed in continent patients. The urine CRP level was found to be significantly higher in only 1 male patient who had an acute bacterial prostate infection. Based on these results, Chuang YC et al. concluded that serum CRP levels are elevated in various, different diseases and accompanied by lower urinary system symptoms which can be used in clinical practice; however, the authors also reported that the urine CRP level cannot be used as a biomarker for lower urinary tract symptoms (LUTS)[29]. In another study exploring the association between urinary system infection and urine CRP levels, a total of 50 patients and 20 healthy individuals under the age of 15 were evaluated. No significant difference was found between the patient and control group in terms of the urine CRP levels. Furthermore, when the patients were divided into 3 groups according to the severity of renal damage based on their dimercaptosuccinic acid renal scintigraphy (DMSA) results, there was no significant difference between the groups in terms of their urine CRP levels. The authors concluded that the urine CRP level cannot predict the presence of urinary tract infection and renal damage[30]. However, because the serum CRP is an acute phase reactant, it may not show the long-term effects such as renal damage.

Despite several studies investigating the association between urinary system stones and serum CRP levels, there are only few that have focused on the urine CRP levels. Although serum CRP level can be used as a biomarker in patients with ureteral stones, particularly those accompanied by inflammatory processes, this measurement does not provide specific

results and is affected by several inflammatory events[6]. Therefore, in the current pilot study that was conducted to predict the presence of ureteral stones and the obstruction caused by these stones, the urine CRP level was found to be 6.1 ng/mL in the patient group and 1.5 ng/mL in the control group. However, there was no difference between the patients with impacted and non-impacted stones in terms of the urine CRP levels.

The current study has certain limitations. Complete obstruction was not clearly defined and thus it was difficult to establish a final diagnosis using imaging techniques before the operation. This may have resulted in a lower number of patients being diagnosed with obstructed systems. Furthermore, in these patients, due to the obstructed system, the urine CRP level may have been found to be lower. For patients with complete obstruction, CRP levels may have been determined in urine samples obtained from a previously placed percutaneous nephrostomy catheter. As a result, patients with ureteral stone disease had higher urine CRP levels. Further studies should be conducted on patients with impacted urinary stones.

Conclusion

The measurement of CRP in urine can be accepted as a new biomarker to predict the presence of ureteral stones. The measurement of serum and urine CRP seems to act as a marker that assists in the detection of ureteral stones and is easy to assess.

Conflict of interest

The authors declare that they have no conflict of interest.

References

1. Parmar MS. Kidney stones. BMJ 2004;328: 1420-1424.
2. Turney BW, Reynard JM, Noble JG, Keoghane SR. Trends in urological stone disease. BJU Int 2012;109:1082-1087.
3. Stamey T. Pathogenesis and Treatment of Urinary Tract Infections. In: Williams & Wilkins, Baltimore 1980, pp 239-241.
4. Dai J, Tang K, Xiao W, Yu G, Zeng J, Li Wet al. Prognostic significance of C-reactive protein in urological cancers: a systematic review and meta-analysis. Asian Pac J Cancer Prev 2014; 15:3369-3375.
5. Shoag J, Eisner BH. Relationship between C-reactive protein and kidney stone prevalence. J Urol 2014;191:372-375.
6. Ansar W and Ghosh S. C-reactive protein and the biology of disease. Immunol Res 2013;56:131.
7. Moutzouri E, Tsimihodimos V and Tselepis AD. Inflammatory biomarkers and cardiovascular risk assessment. Current knowledge and future perspectives. Curr Pharm Des 2013;19: 3827.
8. Meier-Ewert HK, Ridker PM, Rifai N, Price N, Dinges DF, Mullington JM. Absence of diurnal variation of C-reactive protein concentrations in healthy human subjects. Clin Chem 2001; 47:426-430.
9. Volanakis JE. Human C-reactive protein: expression, structure, and function. Mol Immunol 2001; 38:189.
10. St Sauver JL, Sarma AV, Jacobson DJ, et al. Association between C-reactive protein and benign prostatic hyperplasia/lower urinary tract symptom outcomes in population-based cohort. Am J Epidemiol 2009;169:1281-1290.
11. Khuseyinova N, Imhof A, Trischler G, Rothenbacher D, Hutchinson WL, Pepys MB, et al. Determination of C-reactive protein: comparison of three high-sensitivity immunoassays. Clin Chem 2003;49:1691-1695.
12. Cho KJ and Kim JC. Biomarkers for lower urinary tract dysfunction. Int J Urol 2013;20:13.
13. Tanaka N, Kikuchi E, Shirotake S, Kanao K, Matsumoto K, Kobayashi H, et al. The predictive

value of C-reactive protein for prognosis in patients with upper tract urothelial carcinoma treated with radical nephroureterectomy: a multi-institutional study. Eur Urol 2014;65:227-234.

14. Steffens S, Köhler A, Rudolph R, Eggers H, Seidel C, Janssen M, et al. Validation of CRP as prognostic marker for renal cell carcinoma in a large series of patients. BMC Cancer 2012; 12:399.
15. Angulo JC, Gaspar MJ, Rodríguez N, García-Tello A, Torres G, Núñez C. The value of C-reactive protein determination in patients with renal colic to decide urgent urinary diversion. Urology 2010;76:301-306.
16. Stuveling EM, Bakker SJ, Hillege HL, de Jong PE, Gans RO, de Zeeuw D. Biochemical risk markers: a novel area for better predictionof renal risk? Nephrol Dial Transplant 2005;20:497-508.
17. Ross R. Atherosclerosis - an inflammatory disease. N Engl J Med 1999;340:115-126.
18. Lu XL, Xiao ZH, Yang MY, Zhu YM. Diagnostic value of serum procalcitonin in patients with chronic renal insufficiency: a systematic review and meta-analysis. Nephrol Dial Transplant 2013;28:122-129.
19. Park CH, Ha JY, Park CH, Kim CI, Kim KS, Kim BH. Relationship Between Spontaneous Passage Rates of Ureteral Stones Less Than 8 mm and Serum C-Reactive Protein Levels and Neutrophil Percentages. Korean J Urol 2013;54:615-618.
20. Agrawal P, Pandey A, Sompura S, Pursnani ML. Role of blood C - reactive protein levels in upper urinary tract infection and lower urinary tract infection in adult patients (>16 years). J Assoc Physicians India 2013;61:462-463.
21. Swerkersson S, Jodal U, Sixt R, Stokland E, Hansson S. Relationship among vesicoureteral reflux, urinary tract infection and renal damage in children. J Urol 2007;178:647-651.
22. Türk C, Petřík A, Sarica K, Seitz C, Skolarikos A, Straub M et al. EAU Guidelines on Interventional Treatment for Urolithiasis. Eur Urol 2016;69:475-482.
23. Yoshimura K, Utsunomiya N, Ichioka K, Ueda N, Matsui Y, Terai A. Emergency drainage for urosepsis associated with upper urinary tract calculi. J Urol 2005;173:458-462.
24. Wolff JM, Boeckmann W, Mattelaer P, Krämer U, Jakse G. Early detection of infected ureteral obstruction after SWL employing C-reactive protein. J Endourol 1996;10:523-526.
25. Wu TT, Lee YH, Tzeng WS, Chen WC, Yu CC, Huang JK. The role of C-reactive protein and erythrocyte sedimentation rate in the diagnosis of infected hydronephrosis and pyonephrosis. J Urol 1994;152:26-28.
26. El-Assmy A, El-Nahas AR, Youssef RF, El-Hefnawy AS, Sheir KZ. Impact of the degree of hydronephrosis on the efficacy of in situ extracorporeal shock-wave lithotripsy for proximal ureteral calculi. Scand J Urol Nephrol 2007;41:208-213.
27. Picozzi SC, Ricci C, Gaeta M, Casellato S, Stubinski R, Ratti D, et al. Urgent shock wave lithotripsy as first-line treatment for ureteral stones: a meta-analysis of 570 patients. Urol Res 2012; 40:725-731.
28. Campschroer T, Zhu Y, Duijvesz D, Grobbee DE, Lock MT. Alpha-blockers as medical expulsive therapy for ureteral stones. Cochrane Database Syst Rev 2014;4:CD008509.
29. Chuang YC, Tyagi V, Liu RT, Chancellor MB, Tyagi P. Urine and Serum C-Reactive Protein Levels as Potential Biomarkers of Lower Urinary Tract Symptoms. Urol Sci 2010;21:132-136.
30. Nikibakhsh AA , Mahmoodzadeh H, Hejazi S, Noroozi M, Shfiei H, Gaibi S et al. Evaluation of Quantitative Urinary C-Reactive Protein Levels in Children with Urinary Tract Infection. J Ped Nephrology 2013;1:70-73.