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Is urinary kidney injury molecule-1 a noninvasive marker for renal injury in patients with ureteral stones?

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ABSTRACT

Objective: The objective of this study is to evaluate whether levels of urinary kidney injury molecule-1 (KIM-1) are increased in patients in different stages of hydronephrosis and to follow the course of the KIM-1 levels after ureterorenoscopy (URS).

Methods: The study included 39 ureteral stone patients who had planned to undergo URS and had various degrees of hydronephrosis, as well as 40 healthy control patients. The levels of urinary KIM-1 molecule were detected before URS (U1) and on the 30th day following the procedure (U2) in the study group and compared with the urinary KIM-1 levels of the control group.

Results: The levels of urinary KIM-1 were significantly higher in the study group as compared with the control group. Preoperative levels of KIM-1 were not found to depend on hydronephrosis level. Postoperative levels of KIM-1 were significantly higher, with higher degrees of hydronephrosis, as detected by ultrasonography, on postoperative day 30 as compared with lower degrees of hydronephrosis detected at the same time. The localization and the size of the ureteral stone showed no differences with respect to the levels of KIM-1 among patients in the study group.

Conclusions: Elevated urinary KIM-1 levels at the end of the first month after URS indicate continued renal injury due to ureteral stone. The degree of hydronephrosis was proportional to the level of urinary KIM-1. The degree of hydronephrosis at postoperative day 30 is the most important factor determining KIM-1 levels. Neither the localization of the ureteral stone nor the size of the stone are important in determining KIM-1 levels.

Key words: *Ureteral stone, hydronephrosis, kidney injury molecule-1 (KIM-1), renal injury*

Introduction

Hydronephrosis is the distention of the renal calyces and pelvis with urine as a result of the obstruction of the outflow of urine distal to the renal pelvis. The etiology of hydronephrosis is multifactorial, and urolithiasis is the major etiologic factor. Chronic urinary tract obstruction leads to renal injury, which may persist after surgical management [1]. Urologists have changed their strategies in past decade regarding the management of he absence of epithelial dysplasia. Open surgery had been performed in the past for ureteral stones, but now, ureterorenoscopy (URS) is the major technique used for the treatment of ureteral stones [2].

Many diagnostic imaging techniques, such as renal ultrasonography (US), sintigraphy, computerized tomography (CT), and laboratory tests such as plasma

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and urine creatinine and cystatin C levels, are widely used to demonstrate renal injury [3-5]. Although these methods are typically adequate for diagnostic evaluation, additional markers are required to determine the progress and the outcome of the disease. Recently, kidney injury molecule-1 (KIM-1) has been used as a biomarker of renal injury [1].

Kidney injury molecule-1 is a transmembrane glycoprotein that is a biomarker for renal tubular damage, and it is upregulated in proximal tubular cells following ischemic or nephrotoxic injury [6]. Its expression is absent in glomerulular, interstitial, and medullary cells [7-9]. Kidney injury molecule-1 is detectable in urine via a noninvasive test, and its rapid increase after renal injury makes it a valuable marker [10]. Several studies have shown that KIM-1 is secreted in patients with glomerulonephrosis, IgA nephropathy, glomerulosclerosis, and obstructive nephropathy [1,11,12].

In this study, we aimed to evaluate whether levels of urinary KIM-1 are increased in patients with hydronephrosis and to follow the course of KIM-1 levels after a URS procedure. We also compared the levels of KIM-1 in patients with various stages of hydronephrosis and various sizes of ureteral stones.

Materials and Methods

We performed this prospective, controlled clinical trial in a tertiary center between March 2014 and June 2014. Approval for the study was obtained from the local ethics committee, and all patients signed an informed consent form to participate in the study.

The study included 39 ureteral stone patients who planned to undergo URS with various degrees of hydronephrosis, as well as 40 healthy control patients. The demographic and clinical variables of the patients were recorded. All patients underwent urinary US to determine the degree of hydronephrosis. The staging was performed according to the Society for Fetal Urology (SFU) Hydronephrosis Grading System: There is no splitting of the renal pelvis in grade-0 hydronephrosis (G0); there is splitting in grade 1 (G1); splitting is confined to the sinus, but there is no calyceal dilatation in grade 2 (G2); there is dilatation of the renal pelvis beyond the sinus and uniform calyceal dilatation in grade 3 (G3); and the renal parenchyma is thinned to <50% of the contralateral side in grade 4 (G4) hydronephrosis. In this study, we categorised hydronephrosis into three groups: without hydronephrosis (G0), grade 1 hydronephrosis (G1), and grade 2 to 4 hydronephrosis (G2-4).

The sizes of the stones in the study group were measured in all patients via US in two dimensions and classified as small size if the stone was <0.5 cm^2, medium size if it was between 0.5-1 cm^2, and large size if it was >1 cm^2. The localization of the stone was also determined via US, and the stones were classified as upper ureteral, mid ureteral, or lower ureteral stones.

We used a flexible fiber ureterorenoscope (Viper Flexible Ureteroscope 270°™, Richard Wolf, Knittlingen, Germany) and laser lithotriptor (MegaPulse Stone Laser Tower 30+™, Richard Wolf, Knittlingen, Germany) in all ureterorenoscopy procedures. Because we aimed to determine the effects of hydronephrosis, stone localization, and stone size on renal injury, we included only those patients who were not catheterized with a double J stent.

The levels of urinary KIM-1 molecule were detected before URS (U1) and postoperatively at day 30 (U2) in the study group and compared with the urinary KIM-1 levels of the control group (CG). The urinary KIM-1 levels were compared among patients with ureteral stones of different sizes, localizations, and degrees of hydronephrosis.

The urine samples taken from the patients for KIM-1 evaluation were centrifuged within the 20th minute for 10-20 minutes at 2,000-3,000 r.p.m. The supernatant part was stored at -20/-80 ^{0}C. The samples were analyzed via ELISA (SunRed Biological Technology®, Shanghai).

SPSS for Windows, Version 21.0 (IBM, Chicago, USA), was used for statistical analysis. The statistical methods employed were the Kolmogrov Smirnov z-test, t-test, Mann-Whitney U test, two-way ANOVA test, one-way ANOVA test, Kruskal-Wallis H test, Levene's test, and post-hoc Tukey HSD tests. The results are expressed as mean ± standard deviation (Sd). A p value < 0.05 was considered statistically significant.

Results

The demographic findings of the patients were similar between the groups (Table 1). There were no solitary kidneys, failures of renal functions, or urinary

infections in any patients who were included the study group or CG. We reached the renal pelvis during the URS procedure in all patients, and we did not confirm ureteropelvic junction obstruction or any other cause of obstruction (tumor, kidney stone, etc.).

We found that the mean values were different between the CG and U1 groups (p=0.000) and between the CG and U2 groups; these differences were statistically significant (p=0.000). In addition, we did not find any statistically significant difference when we compared the U1 and U2 groups (p=0.338) (Table 2).

First, we compared KIM-1 levels with the preoperative and 30-day postoperative US findings in terms of the hydronephrosis variable (G0, G1, and G2-4). Regarding the preoperative US findings, we did not identify any differences in KIM-1 levels between the degrees of hydronephrosis (G0, G1, and G2-4) in the U1 group (p=0.073) or in the U2 group (p=0.580). However, when we compared the degrees of hydronephrosis in terms of the postoperative day 30 ultrasound findings in the U2 group, we found a statistically significant difference in KIM-1 levels between those patients without hydronephrosis and G1 (p=0.01) and between those without hydronephrosis and G2-4 (p=0.019). Between G1 and G2-4, no difference was observed (p=1.0) (Table 3).

After regression analysis, no differences were detected between the U1 and U2 groups in terms of stone size or the localization of the uretheral stones.

Discussion

In this present study, we assessed urinary KIM-1 levels in patients with various degrees of hydronephrosis. We demonstrated that urinary KIM-1 levels were significantly higher in the patients as compared with the CG. Preoperative levels of KIM-1 were found not to depend on hydronephrosis level. Postoperative levels of KIM-1 are significantly higher with higher degrees of hydronephrosis, as detected by ultrasonography on postoperative day 30, as compared with lower degrees of hydronephrosis detected at the same time. Interest-

Table 1. Stone characteristics and demographic findings.

Variables	Patient Group	Control Group	P
N	39	40	
Age Median (Min.-Max)	43 (16-84)	39 (18-75)	0.893
Gender (Male/Female) n(%)	26/13 (66.6% / 23.4%)	28/12 (70.0% / 30.0%)	0.750
Mean Stone Size (cm)	0.53	-	
Lateralization of Stone (Right/Left)	19/20	-	
Mean Operation Time (minutes)	44.6	-	

Table 2. The statistical difference between control group, U1 and U2.

	U1	U2	CG	P
KIM-1	1.10 (0.40-2.26)*	1.18 (0.40-2.13)*	0.51 (0.23-0.77)**	p < 0.001

U1: Preoperative, **U2:** Postoperative 30th day, **CG:** Control Group

Table 3. The statistical differences between preoperative and day 30 postoperative U2 KIM-1 levels in terms of hydronephrosis values obtained via ultrasound.

		Preoperative Ultrasound Findings			Postoperative Day 30 Ultrasound Findings
Hydronephrosis	N	U1 Median (min-max)	U2 Median (min-max)	N	U1 Median (min-max)
G0	7	0.97 (0.40-2.26)	1.17 (0.40-1.78)	19	1.08 (0.40-1.31)[a]
G1	26	1.19 (0.96-1.30)	1.18 (0.83-2.13)	14	1.28 (1.06-2.13)[b]
G2-4	7	1.19 (0.96-1.30)	1.19 (0.83-1.54)	6	1.30 (1.17-1.78)[b]
P Values		0.073	0.580		0.002

ingly, the elevated KIM-1 levels persisted for at least 30 days after URS in patients with a high degree of hydronephrosis. This shows that the renal injury caused by hydronephrosis lasted more than a month. Additional long-duration progressive studies are needed to show the exact timing of the regression of renal injury due to ureteral stones.

Because KIM-1 is a glycoprotein that is secreted from the proximal tubule cells after ischemic and nephrotoxic injury, the fact that it is present at higher levels with higher degrees of hydronephrosis indicates increased renal injury. This point may be important in planning the timing of surgical intervention; higher KIM-1 levels indicate increased renal injury, and urgent treatment may be needed to prevent further injury. Wasilewska et al. [1] have evaluated the usefulness of urinary KIM-1 levels as biomarkers of obstructive nephropathy in children and showed similar results to those found in our study: KIM-1 levels were significantly elevated in patients who developed an obstructed kidney.

In the case of renal injury, the region that is most affected is the apical membrane of the proximal tubules, and KIM-1 is a protein that is secreted from that area after renal injury [13]. KIM-1 expression is important in the phagocytosis of necrotic cells in the tubules, which assists in remodelling after the injury [14]. In one investigation, KIM-1 expression was shown to persist until the damaged cells had completely recovered [10]. We suggest that the increased levels of KIM-1 seen in patients with hydronephrosis in our study indicate increased renal injury. Toker et al. [15] found similar results in children with vesicoureteral reflux (VUR): higher levels of VUR were associated with increased levels of urinary KIM-1, suggesting increased renal injury.

Furthermore, although some have suggested that the water pressure involved in the URS procedure increases instantaneous KIM-1 levels, insufficient studies have been performed to confirm this. In addition, in 2013, Fahmy et al. [16] detected no significant difference in KIM-1 levels before and after URS. Even if we accept that the water pressure increases instant KIM-1 levels, this would not explain the persistence of elevated KIM-1 levels after one month (U2 group).

The localization of the stone had no relation to urinary KIM-1 levels in our study. We suggest that it is not the localization of the stone, but the degree of hydronephrosis, that is important in cases of renal injury. The size of the stone is important in terms of the degree of hydronephrosis, but we did not find any difference in KIM-1 levels based on the size of the stone between the U1 and U2 groups. Also, we did not find any differences due to the various localizations of the stones.

This study has certain limitations. Firstly, we should discuss the timing of the KIM-1 evaluation, which was conducted before URS (U1) and on postoperative day 30 (U2) in the study group. Perhaps, we could add another group, such as patients evaluated at the second month or later, to understand how long KIM-1 levels persist. However, this was already an expensive study, and we did not want to increase the cost further. In addition, we had apprehensions that the study results would become incomprehensible if we did so. Secondly, we might include another CG composed of patients with non-obstructive small renal stones. For the reasons mentioned above, we omitted this group, as well.

We could obtain urine from both of the two ureters using different ureteral catheters intraoperatively to determine whether the high levels of KIM-1 were the result of a stone or hydronephrosis. Also, we might evaluate whether there was an obstruction of the ureter, a tumor, or another problem. However, we did not want to perform this procedure because this would necessitate a more invasive technique, and the cost would be high.

In conclusion, elevated urinary KIM-1 levels at the end of the first month after URS indicate continued renal injury due to hydronephrosis. The degree of hydronephrosis is proportional to the level of urinary KIM-1 on postoperative day 30. The most interesting finding of this study is that the localization of the ureteral stone and the size of the stone are not important, and that the degree of the hydronephrosis is the most important factor in renal injury. We suggest that early interventions should be performed in patients with higher degrees of hydronephrosis to prevent further renal injury. Further studies with more patients and longer follow-up periods, and without the limitations mentioned above, are required to show the course of KIM-1 levels in the case of renal injury.

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Conflict of interest

We received financial support from Samsun Training and Research Hospital's Training and Research Foundation to conduct this study to analyse the KIM-1 levels.

No conflict of interest is declared by the authors.

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