COMPARISON OF URINARY KIDNEY INJURY MOLECULE-1/CREATININE RATIO IN PATIENTS WITH RENAL STONE SIZE 5 MM - 20 MM

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ABSTRACT

Introduction:- Urolithiasis (stone formation in urine) is a common disease that affects the excretory system of urine in all age groups. Urolithiasis may be associated with complications such as infection, obstructive uropathy leading to acute renal failure, chronic kidney damage and in the worst scenario, to the loss of a kidney.

Methodology:- In this study, KIM-1 was measured in patients who were divided into three groups - A comprising controls(without renal stone), B contained patients each of whom having been suffering from renal stone size 5 to 10.9mm, C composed of patients having renal stone size 11 to 20mm. Each group contained 28 subjects with age ranging from 20 to 40years. Urinary KIM-1 levels was normalized by urinary creatinine in spot urine. KIM-1/Creatinine ratio in urine was expressed as (ng/mg).KIM-1/Creatinine ratio. It is a cross sectional, comparative study. Creatinine was estimated by jaffes method. Urine KIM-1 was determined in urine sample by ELISA method on semi-automated ELISA instrument .

Results:- Our results showed that urinary KIM-1 creatinine ratio was significantly raised in patients suffering from renal stone than control group.

Conclusion:- Our results proposes that urinary KIM-1is likely to become a useful biomarker for kidney injury associated with smallest renal stones. The significance relies not only in the possibility of identifying a urinary marker of injury, but also in the ability to measure the grade of renal injury allowing for modification of treatment paradigm.

Key words:- KIM-1, Urolithiasis, Renal injury, Creatinine

INTRODUCTION

Kidney stone is a common disease that affects all age groups.(Mehmet and Ender, 2015). It is a global disease that affect kidneys and cause morbidity. Its incidence has increased during the 20th century. In Pakistan, there are deserts where the climate is hot and dry. Both factors may have contribution to endemic urolithogenesis(various stages of stone formation) (Abbas et al., 2003, Ablett et al., 1995).

Formation of urine stones is a complex process; it involves nidus formation, aggregation, precipitation and crystal growth. Imbalance in renal stone forming factors and inhibiting factors plays a role. Biochemical abnormalities like, hypocitraturia, hypercalciuria, hyperoxaluria, hyperuricosuria, alteration in urine pH may also play a role Urolithiasis is a multifactorial disease, that is caused from interactions between hypercalciuria, environmental and genetic factors (Wagner and Mohebbi, 2010).

The most prominent clinical symptom in kidney stones is renal colic. Urolithiasis may be associated with complications such as infection, obstructive uropathy leading to acute renal failure, chronic kidney damage and in the worst scenario, to the loss of a kidney. However the extent of complication is dependent upon the site and size of the stone and this might be prevented if significant stones could be detected before the onset of symptoms with appropriate treatment. (Noshad et al., 2014) (Abbas etal,2003).

Serum creatinine, is used as a benchmark for assessment of renal function and consequently quantifying complications of the presence of stone. Serum creatinine concentrations do not change until a significant amount of kidney function has already been lost, with a reduction of at least 30% in GFR - which means that the kidney injury was present before serum creatinine rose.(Urbschat et al., 2011, Endre et al., 2011). There is a need for early detection of renal injury. Kidney injury molecule-1 (KIM-1), has been assigned more than one names according to its chemical nature by researcher like, T-cell immunoglobulin mucin 1, hepatitis A virus cellular receptor 1 and is a transmembrane glycoprotein the originally revealed name. KIM-1 is a sensitive and specific urinary

biomarker of renal injury.(Sutton, 2009) In this study, KIM-1 is a substance expressed in renal injury caused by the stone. The region of nephron that is most affected is the apical membrane of the proximal tubules. The kidney epithelium is prone to injury due to its blood supply and its ability to produce many toxins. In this study, KIM-1 was measured in patients with renal stone size 5 mm to 10.9mm and 11mm to 20 mm. Urinary KIM-1 levels was normalized by urinary creatinine in spot urine and KIM-1/Creatinine ratio in urine will be expressed as (ng/mg).KIM-1/Creatinine ratio will be used to estimate the extent of damage caused by the stone. This study will be helpful to determine the smallest size of kidney stone at which kidney injury can occur and to prevent further complication of urolithiasis. In cases where it involves both the kidneys patient can present with symptoms and signs of renal failure

MATERIAL AND METHODS

This is a Cross sectional, comparative study. Urine specimen from all the subjects were collected .Convenient sampling was done from the subjects.
Calculated Sample size in each group = 28
Study individuals will be divided into three groups.
Group 1 comprise of 28 individual in control group.
Group 2 comprise of 28 individuals with stone size 5mm – 10.9mm.
Group 3 comprise of 28 individuals with stone size 11mm -20mm.
The stone sizes were calculated by Ultrasonography.
Midstream random urine sample was collected from all the study individuals between 20-40years of age in a (20 ml) sterile container.
Urine creatinine was estimated by jaffes method (Rapoport, 1968)
Urine KIM-1 was determined in urine sample by ELISA method on semi-automated ELISA instrument of (Bio-Rad Diagnostics ELISA instrument,Model#680)

EXCLUSION CRITERIA

On the basis of history and investigations.

1. Renal stones with obstruction.2.Interstitial renal disease.3.Polycystic kidney disease.4.Renal carcinoma.5.Patients with, diabetes mellitus, hypercholesterolemia, hypertention and chronic kidney disease

RESULTS

This study consisted of measuring and comparing, KIM-1/ Creatinine ratio in control subjects and patients with renal stones. Total number of subjects was 84 with 28 subjects in each group. Group 1 comprised of control subjects. Group 2 comprised of subjects with non-obstructing renal stones, size 5-10.9 mm and Group 3 comprised of subjects with non-obstructing renal stone size 11-20 mm. The study subjects were selected from outdoor department of Lahore General Hospital Lahore on the basis of mentioned criteria that consisted of control subjects without renal stone and patients with non-obstructing renal stones of size 5mm – 20 mm. Samples were analyzed for determination of urine creatinine and KIM-1 in Chemical Pathology Department Laboratory at University of Health Sciences Lahore. The results are as follows ;

Table 1: Urine Creatinine Values Among Groups.

Variables		**Group 1 n=(28)**	**Group 2 n=(28)**	**Group 3 n=(28)**	**p- value**
Urine Creatinine(mg/dl)	Median	243	124	118	<0.001*
	IQR(Q1-Q3)	114 – 327	22 - 219	82 – 203	

* Statistically significant .

Table 2: KIM-1/Creatinine Ratio Among Groups:

Variable		**Group 1 n=(28)**	**Group 2 n=(28)**	**Group 3 n=(28)**	**p- value**
KIM-1 Creatinine Ratio (ng/mg)	Median	1.12	4.20	6.00	
	IQR(Q1-Q3)	0.70 - 1.70	3.30 - 7.20	4.50 - 7.60	<0.001*

* Statistically significant .

Table 3: Comparison of KIM-1/Creatinine Ratio between three Groups.

Variables		Group-1 (n=28)	Group-2 (n=28)	Group-3 (n=28)	p- value
KIM-1 Creatinine ratio (mg/g)	Median IQR (Q1-Q3)	1.12 0.70 - 1.70	4.20 3.30 - 7.20	6.00 4.50 - 7.60	<0.001* a <0.001* b <0.001* c 0.736 d

* Statistically significant $p \leq 0.05$, a Comparison among the three groups, b Comparison between group-1 and group-2, c Comparison between group-1 and group-3, d Comparison between group-2 and group-3.

The urinary creatinine values were analyzed by Kruskal Willis Test. As the data was not normally distributed the normal values of urinary creatinine in group 1 subjects was 243mg/dl which was greater than median values of group 2 and 3 subjects in which the median value was 124 mg/dl and 118 mg/dl respectively as shown in Table 1.statistically significant difference was seen among groups as p-value was <0.001. This was statistically significant as in Table: 1.

Urinary Kidney injury molecule-1 values were analyzed by Kruskal Willis Test. The urine KIM-1 values were expressed as KIM-1/Creatinine ratio which was calculated by dividing urinary KIM-1 values by urine creatinine values.Kim-1/creatinine ratio was highest in Group 3 with a median value of 6.00 ng/mg as compared to group 2 and group 1 with a median value of 4.20 ng/mg and 1.12 ng/mg respectively. Statistically significant difference was observed as p-value was <0.001 which was statistically significant shown in table 2

Pairwise comparisons of median values of KIM-1/Creatinine ratio with Dunn-Bonferroni test, showed that there was a statistically significant difference between median levels of KIM-1 Creatinine ratio in group 1 and 2 with a p-value of <0.001. Statistically significant difference was also observed in group 1 and group 3 as p-value was <0.001which was statistically significant. The difference observed, when we compared median values of KIM-1 Creatinine ratio between group 2 and group 3 was statistically insignificant as p- value was 0.73 shown in table 3.

DISCUSSION

Kidney injury molecule (KIM-1) is a substance expressed in renal injury(Ichimura et al., 2008).

Most affected area is the proximal tubules (Sutton, 2009). Since its detection, Kim-1 has developed as a sensitive and specific urinary biomarker of kidney injury.(Sutton, 2009) .

In this study, Kim-1 was measured in patients with renal stone sizes 5 mm to 10.9mm and 11mm to 20 mm. Urinary Kim-1 and creatinine were measured in spot urine and was expressed as Kim-1/Creatinine ratio in urine in ng/mg.Kim-1/Creatinine ratio was used to estimate the extent of damage caused by the stone..

Number of studies have been carried out which measured Kim-1 in obstructive uropathy.
(Wasilewska et al, 2011) (Xue et al., 2014, Xie et al., 2014). A study carried out by Zhou et al. showed that Kim-1 significantly elevated in patients with renal injury (Huo et al., 2010). In one of the investigation carried out by Chaturvedi et al. showed that Kim-1 persisted until the damaged cells had completely recovered (Chaturvedi et al., 2009).

Current study was planned to see the role of Kim-1 in different sizes of nonbstructing renal stones in three groups. The purpose of this study was to compare Kim-1/Creatinine ratio in nonobstructing renal stone in patients having stone size from 5mm to10.9mm(Group 2) and from11mm to 20mm(Group 3) with control group(Group 1).

Kidney stones were detected and measured by ultrasonography in 56 subjects.

It was found that the Kim-1/ Creatinine ratio was significantly higher in subjects with stones as compared with subjects who did not have stones.

The elevated ratio of Kim-1/ Creatinine ratio found in second group and third group subjects with renal stones which showed that the renal injury occurred by the formation of the stone. (Sabbisetti et al, (2014)

The dimension of the stone is significant in terms of the level of Kim-1, but no statistical difference was found in Kim-1 levels based on the size of the stone between group 2 and group 3. Also, no difference was found due to the various localizations of the stones.

CONCLUSION

Our results proposes that urinary KIM-1is likely to become a useful biomarker for kidney injury associated with smallest renal stones. The significance relies not only in the possibility of identifying a urinary marker of injury, but also in the ability to measure the grade of renal injury allowing for modification of treatment paradigm.

This study will be helpful to determine the small size of kidney stone at which kidney injury can occur and to prevent further complication . In cases where it involves both the kidneys, patient can end up with symptoms and signs of renal failure.

RECOMMENDATION

Stone causes renal injury and therefore early intervention will prevent further damage of nephrons.

Studies with long duration period are required to show the exact timing of the regression of renal injury after stone removal.

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