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Study of urinary level of kidney injury molecule-1 (KIM-1) in acute kidney injury

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Abstract

Introduction: Traditional methods of assessing renal function include serum blood urea nitrogen and serum creatinine measurements, which are insensitive and vague for detecting renal damage prior to considerable loss of renal function. It is also crucial to highlight that serum blood urea nitrogen and creatinine are not real 'injury indicators', but rather measures of 'functional alterations in filtration capacity'. Recently, there has been an urgent demand for AKI biomarkers to aid in the rapid diagnosis and prediction of the severity and prognosis of AKI.

Aim: The purpose of this cross-sectional and analytical study is to estimate urinary Kidney Injury Molecule-1 (KIM-1) levels in cases of acute kidney injury, compare urinary KIM-1 levels with serum creatinine and blood urea, and demonstrate the utility of urinary KIM-1 as an early biomarker of acute kidney injury.

Materials and Methods: The research was carried out at Katuri Medical College in Guntur and was a cross-sectional and analytical study that lasted from January 2021 to November 2022. There were a total of 100 topics chosen.

Males and females over the age of 18 were both included in the study, and all provided informed permission.

There were two groups in the research population. The first group consists of 50 patients admitted for snake bites, whereas the second group comprises of 50 patients treated for sepsis. Those who did not develop AKI were referred to as controls.

Results: When compared to serum creatinine and blood urea, the study results demonstrate that KIM-1 can be employed as a biomarker of AKI and for early detection of AKI.

There was no significant difference in urine KIM-1 levels between patients and controls in various age groups.

When males and females were examined in snake bite cases, urinary KIM-1 levels were found to be considerably higher in males, but there was no significant difference between males and females in controls. It was discovered that the levels of urinary KIM-1 rise with the severity of AKI in both snake bite and sepsis cases.

Limitations: The study's limitations were a limited sample size and the analysis of urine KIM-1 only on the first day of admission. It is unclear if KIM-1 levels in urine fluctuate over time.

Introduction

Acute kidney injury (AKI), also known as acute renal failure, is defined by a rapid impairment of kidney function that leads to the retention of nitrogenous waste products over a time span ranging from a few hours to several weeks. [1]

AKI is a collection of conditions defined by a rise in the Blood Urea Nitrogen (BUN) concentration and/or an increase in the Serum Creatinine concentration, which is frequently linked with a decrease in urine volume.[1]

AKI is a new consensus term that encompasses a spectrum of acute kidney disease that can range in severity from asymptomatic changes in glomerular filtration rate laboratory parameters to rapidly fatal changes in the regulation of effective circulating volume and plasma electrolyte and acid-base balance. [1] As a result, the term AKI has superseded the term acute renal failure (ARF), because AKI encompasses the complete spectrum of clinical characteristics ranging from moderate elevations in blood creatinine levels to overt renal failure. [2]

The burden of AKI is rapidly increasing, and it is associated with an elevated risk of death among hospitalised patients, particularly those admitted to the Intensive Care Unit. [1] The frequency of hospital-acquired AKI has been increasing in recent years, as proven in a single patient sample from 1996 to 2003. Despite breakthroughs in dialysis and intensive care, death rates remain high, ranging from 30 to 65%. AKI was linked to an increase in not just mortality but also in hospital stay duration and total cost. [2] Long-term effects of AKI include the possibility of progressing to CKD stages 4 and 5. Traditional methods of assessing renal function include serum blood urea nitrogen and serum creatinine measurements, which are insensitive and vague for detecting renal damage prior to considerable loss of renal function. [3] It is also crucial to highlight that serum blood urea nitrogen and creatinine are not real 'injury indicators', but rather measures of 'functional alterations in filtration capacity'.

Recently, there has been an urgent demand for AKI biomarkers to aid in the rapid diagnosis and prediction of the severity and prognosis of AKI.

Kidney Injury Molecule-1 (KIM-1) is a transmembrane protein located in the renal tubules that is not detectable in normal kidneys but is significantly increased and produced [4]KIM-1 is a member of the vast family of

KIMs, also known as T-cell Immunoglobulin Mucin proteins (TIMS), which operate as a signal or receptor for adhesion or signalling.[5]

The protein is detected in urine significantly sooner than rises in serum blood urea nitrogen and creatinine due to fast cleavage of the protein from the apical membrane of the tubular epithelial cell enters the tubular lumen.[4]

The purpose of this study was to look at the levels of urine Kidney Injury Molecule - 1 in individuals with Acute Kidney Injury and to see whether it may be used as an early biomarker of AKI.

Aim of the Study

1. To calculate urine KIM-1 levels in patients with AKI.
2. To compare urine KIM-1 levels with serum creatinine and blood urea, and to demonstrate urinary KIM-1's value as an early biomarker of acute kidney damage.

Materials and Methods

After receiving consent from Katuri Medical College's Ethics Committee, the study was carried out at Katuri Medical College, Guntur. The research was a cross-sectional and analytical study that was carried out between January 2021 and November 2022. There were a total of 100 patients chosen. Males and females over the age of 18 were both included in the study, and all provided informed consent. There were two groups in the research population.

The first group consists of 50 patients admitted for snake bites, whereas the second group comprises of 50 patients treated for sepsis.

Those who did not develop AKI were referred to as controls.

Inclusion Criteria

- Patients hospitalised within 12 hours of being bitten by a snake
- Patients who got sepsis while having a septic focus.
- Age more than 18 years

Exclusion Criteria

- Chronic kidney disease
- Snake bite and sepsis patients with elevated serum creatinine on admission
- K/c/o hypertensive on treatment
- H/o diabetes mellitus
- H/o Polycystic Kidney Disease
- Nephrotic syndrome

Study Protocol

A detailed history was elicited for

- Co-morbid diseases and concomitant drug intake
- History of snake bite, time and site of bite, species of snake, native treatment, treatment before hospitalization.
- History of reduced urine output
- History of infections, fever.

Clinical examination

A comprehensive physical examination was performed to search for fang marks, cellulitis, bleeding from the site of bite, local necrosis, blistering, gangrene, regional lymph node enlargement, and symptoms of gum bleeding, epistaxis, and ecchymosis.

A thorough examination was performed to rule out illnesses of the respiratory, genitourinary, gastrointestinal, central nervous system, or musculoskeletal systems.

All vital indicators were examined.

The characteristics of uremic symptoms were sought.

Investigations

1. Urinary KIM-1
2. Serum creatinine
3. Serum urea
4. Haemogram
5. Clotting time

Statistical Analysis

- The Student's t-test was used for statistical data analysis.
- The data was reported as mean and standard deviation.
- A 'P' value of less than 0.05 was considered significant. Pearson's correlation coefficient was used to analyse the correlation between the measured parameters.

Results

A total of 100 people were chosen for the investigation. These comprised 50 patients who had been bitten by a snake and 50 individuals who had sepsis. Urine KIM-1 levels were assessed within 24 hours after admission. For all samples, serum creatinine and blood urea were measured on the day of admission and again on the third day. Patients who had AKI were labelled as cases, whereas those who did not develop AKI were labelled as controls. RIFLE criteria were used to determine the stage of AKI.

Table 1: Comparison of urine KIM-1 levels in snake bite patients and controls

KIM-1 values(ng/ml)	Control	Cases
Range	0.1 - 0.9	1.2 - 8.9
Mean	0.544	4.812
Standard deviation	0.24	2.53
'p' value	<0.001 Significant	

Table 2: Urinary KIM-1 levels in various age groups of snake bite victims and controls

Age group	Controls		Cases	
	Mean	**S.D.**	**Mean**	**S.D.**
<40 years	0.523	0.283	4.44	2.438
≥40 years	0.567	0.187	5.37	2.697
'p' value	0.652 Not significant		0.392 Not significant	

Table 3: Urinary KIM-1 levels in men and females in snake bite patients and controls

Sex	Controls		Cases	
	Mean	**S.D.**	**Mean**	**S.D.**
Males	0.538	0.272	5.81	2.37
Females	0.55	0.206	2.9	1.238
'p' value	0.906 Not significant		0.001 Significant	

Table 4: Serum creatinine levels on day 1 and day 3 in snake bite patients and controls

Creatinine values on	Controls		Cases		'p' value
	Mean	**S.D.**	**Mean**	**S.D.**	
Day 1	0.808	0.191	0.864	0.175	0.3557 Not significant
Day 3	1.03	0.232	3.152	2.24	0.0001 Significant

Table 5: Blood urea levels on day 1 and day 3 in snake bite patients and controls

Urea values on	Controls		Cases		'p' value
	Mean	**S.D.**	**Mean**	**S.D.**	
Day 1	32.52	6.66	33.64	7.28	0.607 Not significant
Day 3	40.06	9.87	86.68	40.40	<0.001 Significant

Table 6: On the first day after a snake bite, urinary KIM-1 was compared to serum creatinine and blood urea.

Day -1		Mean	S.D.	'p' value
KIM-1	Cases	4.812	2.53	<0.001 Significant
	Controls	0.544	0.24	
Serum creatinine	Cases	0.864	0.175	0.356 Not significant
	Controls	0.808	0.191	
Blood urea	Cases	33.64	7.28	0.607 Not significant
	Controls	32.52	6.66	

Table 7: Pearson's correlation coefficient for urine KIM-1, serum creatinine, and blood urea in snake bite patients bite

Correlation between	Correlation coefficient	Correlation
KIM-1 and creatinine on day 1	0.094	Not correlated
KIM-1 and creatinine on day 3	0.882	**Correlated**
KIM-1 and urea on day 1	0.380	Not correlated
KIM-1 and urea on day 3	0.864	**Correlated**

Table 8: Urinary KIM-1 levels in patients and controls with sepsis were compared.

KIM-1 values	Control	Cases
Range	0.2 - 0.9	1.2 - 7.9
Mean	0.56	4.544
Standard deviation	0.216	2.268
'p' value	<0.001 Significant	

Figure 1

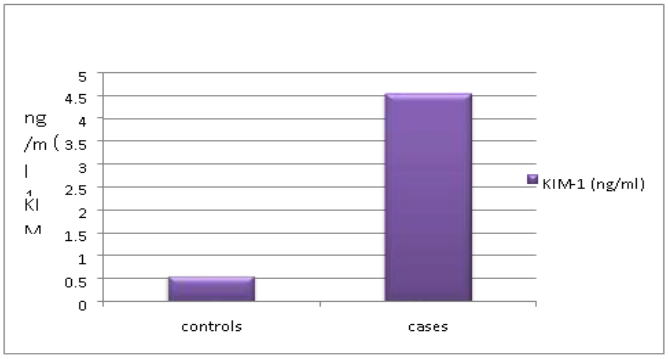


Table 9: Urinary KIM-1 levels in various age groups in sepsis patients and controls

Age group	Controls		Cases	
	Mean	S.D.	Mean	S.D.
<40 years	0.538	0.256	4.042	2.4217
≥40 years	0.571	0.202	5.008	2.1057
'p' value	0.754 Not significant		0.30 Not significant	

Figure 2

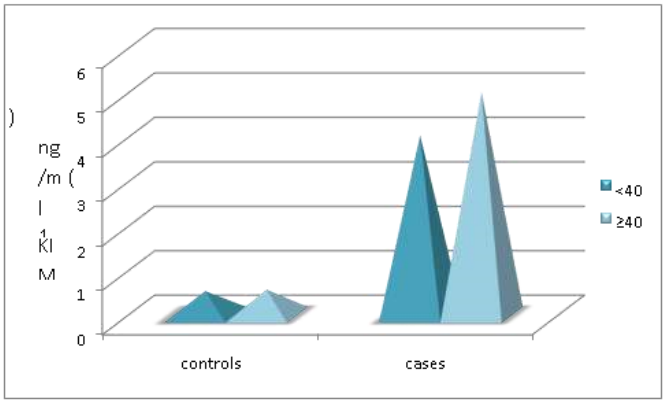


Table 10: Urinary KIM-1 levels in men and females in sepsis patients and controls

Sex	Controls		Cases	
	Mean	S.D.	Mean	S.D.
Males	0.557	0.199	4.306	2.33
Females	0.564	0.246	5.05	2.18
'p' value	**0.944** Not significant		**0.449** Not significant	

Table 11: Serum creatinine levels in sepsis patients and controls were compared.

Creatinine values on	Controls		Cases		'p' value
	Mean	S.D.	Mean	S.D.	
Day 1	0.86	0.191	1.072	0.499	0.056 Not significant
Day 3	1.034	0.195	3.656	2.585	<0.001 Significant

Table 12: Serum urea levels in sepsis patients and controls were compared.

Urea values on	Controls		Cases		'p' value
	Mean	S.D.	Mean	S.D.	
Day 1	32	7.836	36.44	8.347	0.0667 Not significant
Day 3	38.52	6.982	102.76	55.074	<0.001 Significant

Table 13: During the first day of sepsis, urinary KIM-1 was compared to serum creatinine and blood urea.

Day -1		Mean	S.D.	'p' value
KIM-1	Cases	4.544	2.268	<0.001 Significant
	Controls	0.56	0.216	
Serum creatinine	Cases	1.072	0.499	0.056 Not significant
	Controls	0.86	0.191	
Blood urea	Cases	36.44	8.347	0.0667 Not significant
	Controls	32	7.836	

Table 14: Pearson's correlation coefficient for urine KIM-1, serum creatinine, and blood urea in sepsis patients

Correlation between	Correlation coefficient	Correlation
KIM-1 and creatinine on day 1	0.439	Not correlated
KIM-1 and creatinine on day 3	0.888	**Correlated**
KIM-1 and urea on day 1	0.688	Correlated
KIM-1 and urea on day 3	0.871	**Correlated**

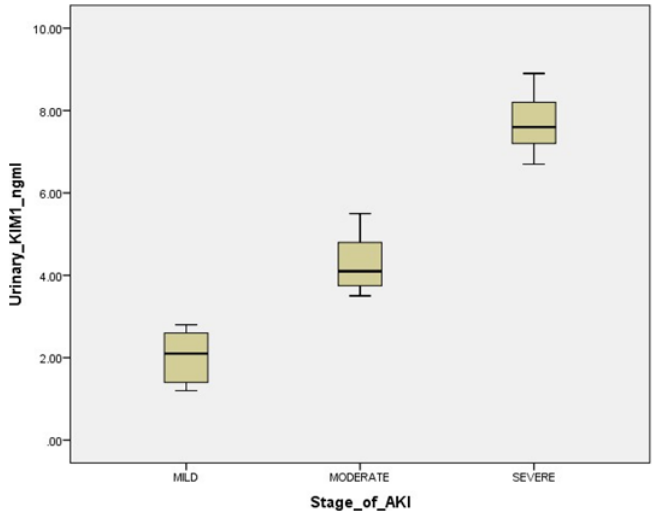
Table 15: The distribution of snake bite cases with AKI according to KDIGO stage and urine KIM-1 values

Stages ofAKI	N	MeanKIM-1 level	Standard deviation	Standarderror
Stage 1	8	2.025	0.656	0.232
Stage 2	8	4.2875	0.710	0.251
Stage 3	9	7.755	0.792	0.264

Table 16: ANOVA was used to compare the mean KIM-1 levels in groups with varying degrees of AKI after a snake bite.

P value	**<0.001**
F statistic	**135.356**
Degree of freedom	**2**

Figure 3



Discussion

In hospitalised patients, Acute Kidney Injury is a common cause of morbidity and death. As a result, reliable biological indicators for renal tubular damage are required to detect early kidney impairment and permit timely therapy initiation. Until recently, the usual diagnostic for detecting AKI was serum creatinine. Nevertheless, serum creatinine has several limitations as a marker for detecting AKI, which impacts both early diagnosis and prognosis.

Only until 50% of the renal cells have died can serum creatinine be discovered.

It does not correctly describe renal function until it reaches a stable level.

Serum creatinine levels are relatively insensitive to modest changes in GFR and may be several days behind

changes in GFR. Injury to the renal tubules is insufficient to cause a change in serum creatinine.

As a result, it is not possible to diagnose acute renal damage early.

The change in serum creatinine does not differentiate between the timing and kind of renal insult, as well as the location and amount of glomerular or tubular damage.

- To address these difficulties, stronger biological indicators of AKI are required, which must satisfy a number of criteria, including
- Enable early identification of kidney damage
- Determine the degree of kidney damage
- Establish risk stratification parameters and identify patients at risk for AKI.
- Direct treatment time • Reflect kidney damage improvement and worsening.This study compares urine Kidney Injury Molecule-1 (KIM-1) to serum creatinine and blood urea as a biomarker of AKI and for early detection of AKI.

In the current investigation, the mean value of urinary KIM-1 in patients hospitalized for snake bite was substantially greater in those who had AKI (cases) than in those who did not develop AKI (control group). Similarly, among sepsis patients, the mean value of urine KIM-1 was found to be considerably greater than that of the control group. Urinary KIM-1 levels were compared between 40-year-olds and 40-year-olds. There was no significant difference in urine KIM-1 levels between cases and controls in different age groups among patients with snake bite and sepsis.

This demonstrates that ageing has no effect on urine KIM-1 levels.

Furthermore, when urine KIM-1 levels were measured and compared between males and females in snake bite cases, it was shown that urinary KIM-1 levels significantly higher in males.

Males had much higher rates than females, although there was no significant difference between men and females among controls.

There was no significant difference in urine KIM-1 levels between males and females among sepsis patients, nor between control males and control females. This means that gender has no effect on urine KIM-1 levels in sepsis patients.

On day 1, serum creatinine levels were evaluated between patients and controls in this investigation.

There was no significant difference between individuals with snake bites and those with sepsis.

On day 3, serum creatinine levels in patients with snake envenomation are considerably higher than in controls, as well as in patients with sepsis.

On day 1, blood urea levels were examined between patients and controls.

Blood urea levels were not substantially higher on day 1 in patients with snake bites and sepsis compared to controls.

On day 3, blood urea levels are higher in both snake bite and sepsis patients than in controls.

According to this study, an increase in serum creatinine and blood urea levels is found only on the third day following nephrotoxic insult in patients with acute renal damage.

When urine KIM-1 levels were compared to serum creatinine and blood urea on day 1, it was discovered that there was a substantial increase in urinary KIM-1 levels among cases than controls, with a 'p' value of 0.001.

On day 1, however, there was no significant difference in serum creatinine ('p' value 0.356) or blood urea ('p' value 0.607) levels between patients and controls.

On day 1, there was a substantial increase in urine KIM-1 levels among patients with sepsis compared to controls, with a 'p' value of 0.001.

On day 1, however, there was no significant difference in serum creatinine ('p' value 0.56) or blood urea ('p' value 0.667) levels between patients and controls.

This demonstrates that urine KIM-1 levels rise far sooner than established indicators like serum creatinine and blood urea.

Pearson's correlation was used to examine the connection of urine KIM-1 with conventional indicators, serum creatinine and blood urea on day 1 and day 3. There was no significant link seen between the rise in urine KIM-1 and serum creatinine as well as blood urea on the day of admission in individuals who had AKI following snake envenomation.

On day 3, urine KIM-1 and serum creatinine, blood urea show a substantial positive connection.

There was no significant connection between urine KIM-1 and serum creatinine on day 1 among individuals with sepsis who developed AKI. Yet, on day 3, there was a strong positive association. Although there was a strong positive connection between urine KIM-1 and blood urea on day 1, on day 3 urinary KIM-1 was more substantially connected with blood urea.

On the basis of KDIGO staging for AKI, patients with snake bite and sepsis who developed AKI were divided into three groups, stage 1, 2, and 3.

The descriptive statistics of urine KIM-1 were established for each stage of AKI.

Moreover, the ANOVA test was used to determine the difference in means between the three groups.

There was a significant difference in the mean of stage 1 AKI (2.025ng/ml) among snake bite cases. AKI stage 2 (4.287ng/ml) and AKI stage 3 (7.755ng/ml), with a 'p' value of 0.001. Similarly, there was a significant difference in the mean of stage 1 AKI (1.8ng/ml) among sepsis patients. AKI in stage 2 (4.475ng/ml) and AKI at stage 3 (7.044ng/ml), with a 'p' value of <0.001. Consequently, in both snake bite and sepsis patients, urine KIM-1 levels were observed to rise with the severity of AKI.

As compared to established indicators such as serum creatinine and blood urea, our data suggest that urine KIM-1 is sensitive to small abnormalities in renal function, specific, and a noninvasive tool for the early detection and evaluation of acute kidney damage.[14] Urinary KIM-1 levels are related to the severity of tubular damage. KIM-1 is an effective marker for diagnosing ischemic acute tubular necrosis within 24 hours of kidney damage.[6, 7]

Dedifferentiation of proximal tubular epithelial cells occurs in response to an acute injury to the renal tubules. Kidney Damage Molecule-1 expression is much higher in these dedifferentiated cells. When epithelial cells are stressed, the Mitogen Activated Protein Kinase (MAPK) pathway is activated, and the highly glycosylated KIM-1 ectodomain is shed from the cellular surface into the tubular lumen via Matrix Metalloproteinases (MMPs). This results in the release of a soluble form of 90kDa, which is eliminated in urine. KIM-1 has the following characteristics that make it a suitable biomarker:

- It is exclusively found in damaged proximal tubular cells of the kidney and is nearly nonexistent in normal healthy kidneys. It lasts until the wounded cells have fully healed.

- It is identifiable in urine because to the quickly cleaved ectodomain that sheds into the tubular lumen.
- Urinary KIM-1 is linked to tissue KIM-1 and the degree of kidney injury.
- Urinary KIM-1 is now recognised as a non-invasive, sensitive, fast, and repeatable technique for assessing renal damage.[8,9]
- Urinary KIM-1, regardless of renal disease, acts as a prognostic indication of the pace of loss of renal function.
- As compared to established biomarkers such as blood urea nitrogen and serum creatinine, the identification of KIM-1 in urine within 12 hours of ischemia or toxic damage makes it an early diagnostic signal.[10]
- The emergence of KIM-1 prior to the diagnosis of fatal injury to proximal tubular epithelial cells enables for the reversal and treatment of kidney injury to occur on time.[16] Since KIM-1 is proven to be stable in urine even after repeated freeze-thaw cycles, there is no need for a stabilising buffer or protease inhibitor to prevent its destruction when collecting urine samples.15,11
- KIM-1 identified by ELISA is unaffected by physicochemical changes in urine and is linked with low interference from other urinary components of the ill patient.[17]
- KIM-1 is also used in immunohistochemical approaches to assess renal damage in biopsy specimens, and its over expression has been linked to inflammation and tubule-interstitial fibrosis.
- The behaviour of KIM-1 in humans is similar to that of animals.
- As a result, it is a "real translational biomarker" that may be employed in drug development, toxicity evaluation of novel candidate therapies, and kidney safety monitoring.[3,18]
- The Food and Drug Administration of the United States (FDA) and the European Medicines Agency (EMEA) have approved KIM-1 for the preclinical assessment of nephrotoxicity in order to enhance kidney safety monitoring.[12]
- The utility of KIM-1 has also been found in several other conditions such as
    1. Chronic kidney disease
    2. Diabetic glomerulopathy .[9]
    3. Acute or chronic renal transplant dysfunction.[14]
    4. Biomarker for renal cell carcinoma[15]
    5. Kidney injury in chidren undergoing cardiac surgery[3]
    6. IgA nephropathy associated with tubule-interstitial injury[13]

Conclusion

As compared to established biomarkers such as serum creatinine and blood urea, this study on snake envenomation and sepsis patients demonstrates that urine Kidney Injury Molecule-1 is a potential early predictive bio-marker of acute kidney injury.

This unique biomarker might help with early detection of acute kidney damage and management decisions, such as the provision of certain preventative and therapeutic methods, perhaps leading to less morbidity and death.

Limitations

The following drawbacks were found in this study:

1. There was a tiny sample size.
2. Urinary KIM-1 was only tested on the first day of hospitalisation.

3. It is unclear if KIM-1 levels in urine fluctuate over time.

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