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A STUDY OF URINARY BETA 2 MICROGLOBULIN AS A NOVEL KIDNEY BIOMARKER TO PREDICT THE RISK OF PROGRESSION TO CHRONIC KIDNEY DISEASE FOLLOWING SNAKE BITE INDUCED ACUTE KIDNEY INJURY

Nephrology

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ABSTRACT

Introduction: Urine β2 microglobulin (β2m) is a validated marker to diagnose sepsis and toxin-related acute kidney injury (AKI). In our study, we used urinary β2m as a potential marker to identify persistent tubular dysfunction leading to chronic kidney disease following clinical recovery from snake bite induced AKI **Methods:** A total of 42 patients who developed AKI following hemotoxic envenomation were followed up for a period of 6 months. Urine albumin excretion, estimated glomerular filtration rate (eGFR), and urine β2m levels were measured at 2 weeks, 3 months, and 6 months following discharge. **Results:** At the end of 6 months of follow-up, 6 patients (14.3 %) progressed to chronic kidney disease (CKD) (eGFR < 60 ml and/or urine albumin excretion > 30 mg/d). The urine β2m levels were 1590 µg/l (interquartile range [IQR] 425–5260), 610 µg/l (IQR 210–1850), 850 µg/l (IQR 270–2780) at 2 weeks, 3 months, and 6 months, respectively (P = 0.020). The levels of urine β2m in the study population at the end of 6 months remained significantly higher compared with the levels in healthy control population (850 µg/l [IQR 270–2780] vs. 210 µg/l [IQR 150–480]; P = 0.001). Similar trends were noticed in a sensitivity analysis, after excluding patients with CKD. **Conclusion:** Urine β2m levels remain persistently elevated in approximately half of the individuals who recover from AKI due to snake envenomation.

KEYWORDS

acute kidney injury, beta 2 microglobulin, snake bite

INTRODUCTION

The epidemiology and etiology of Acute Kidney Injury(AKI) in the tropical low- and middle-income countries from Southern and eastern parts of Asia is dominated by tropical diseases which includes infections and envenomation, occurring in relatively comorbidity free healthy individuals(1). A maladaptive repair of the renal tubules following a snake bite induced AKI leads to acute kidney disease, which may either subsequently recover or progress to CKD(2)(3).

Young individuals who lack the basic risk factors for renal dysfunction constitute the main cohort of victims of snake bite induced AKI and suffer the risk of progressing to CKD in due course of time(4)(5). The current screening recommendations to identify the progression of AKI to CKD are not sensitive enough to detect subclinical persistent tubular dysfunction, necessitating the need for novel biomarkers to act as screening tools to detect it early.

β2m is a protein secreted by all nucleated cells at a constant rate, filtered by glomerulus, reabsorbed and catabolized by renal tubules, resulting in very low urine concentrations in healthy individuals(6). Urine β2m levels are reported to reflect renal tubular injury following exposure to toxins and drugs (7). Data from animal experiments have shown that urine β2m rapidly rises following exposure to nephrotoxins and returns to baseline following recovery (8).

In our study, we have used urinary beta 2 microglobulin as biomarker to assess persistent renal dysfunction in patients who had suffered from snake bite induced AKI.

Methodology

Screening the study population

The study period was from January 2023 to June 2024. All patients admitted to medical wards with AKI due to hemotoxic envenomation were screened. AKI was defined as per Kidney Disease: Improving Global Outcomes 2012 work group criteria. Patients with previous history of CKD were excluded. Patients with bipolar length of kidneys less than 9 cm, cysts, stones, or any other structural abnormalities of kidneys were also excluded. All patients who gave consent were enrolled at the time of discharge from the hospital. Demographic, clinical, and laboratory details were collected at the time of enrollment. The study protocol was approved by the institute ethics committee

Follow-up Visits

The follow-up period was 6 months. A total of 3 follow-up visits were scheduled at 2 weeks, 3 months, and 6 months following hospital discharge. Serum creatinine, urine albumin excretion, and urine β2m were checked during the follow-up visits. Fresh urine samples of 10 ml were collected for β2m during each follow-up visit. The estimation was done at a later date with enzyme-linked immunosorbent assay. The lower limit of detection of the β2m assay was 20 µg/l. Sample collection was deferred for 2 weeks in patients with history of any intercurrent urinary or systemic infections during the follow-up visits.

Statistical Methods

All categorical variables were expressed as frequencies and percentages and continuous variables were expressed as means with confidence intervals or median with IQR wherever appropriate. The changes in eGFR, urine β2m, creatinine and urine albumin in the AKI cohort over 6 months of follow-up were compared using repeated measures analysis of variance with a Bonferroni correction. The analysis was done with IBM SPSS Statistics, V 19.

RESULTS

A total of 70 patients were recruited; 42 patients attended all 3 scheduled follow-up visits. The median duration of first follow-up was 29 days (IQR 23–35 days) from diagnosis of AKI. The clinical characteristics of the cohort at the time of hospitalization is given in Table 1.

Table 1. Demographic and clinical characteristics of study population (n = 42)

Parameter	Value

Age (yr), mean (CI)	41.83 (38.31–45.36)
Male gender, *n* (%)	27 (64.3)
Renal replacement therapy, *n* (%)	32 (76.2)
Haemoglobin, g/dl	10.99 (10.14–11.89)
Platelet count (ml), median (IQR)	40.5×10^3 (21.0–56.2)
Quantity of ASV received in ml, median (IQR)a	150 (80–240)
Serum creatinine at admission (mg/dl), median (IQR)	3.00 (1.29–4.71)
Peak creatinine (mg/dl), median (IQR)	8.30 (4.8–11.4)
Serum creatinine at discharge (mg/dl), median (IQR)	3.8 (2.1–5)
Proteinuria ≥ 1+, *n* (%)	28 (66.6)
AKI stage at admission, *n* (%)	
AKI 1	05 (11.9)
AKI2	02 (04.7)
AKI 3	35 (83.3)

Among 42 patients, 1 patient did not recover from AKI and remained dialysis dependent. A renal biopsy from the patient showed thrombotic microangiopathy. Kidney biopsy was done in another 2 patients with low GFR. The biopsies revealed chronic thrombotic microangiopathy and persistent acute tubular necrosis. Three other patients who progressed to CKD by 6 months did not give consent for kidney biopsy. The serum creatinine, GFR and urine β2m levels during follow-up are given in Table 2. The creatinine, eGFR improved, and urine β2m levels declined significantly between 2 weeks and 3 months, whereas the changes between 3 months and 6 months were not significant. The proportion of patients with urine β2m levels exceeding the 95th percentile for controls (> 644 µg/l) during the 3 follow-up visits are given in Table 2

Table 2. Renal function and urine β2 microglobulin levels on follow-up

Parameter	2wk	3mo	6mo	p-value
eGFR (ml/min per 1.73 m^2), mean (CI)	70.56 (63.18–77.93)	85.87 (80.67–91.27)	87.27 (80.02–92.53)	<0.001
Creatinine (mg/dl), mean (CI)	1.25 (1.11–1.39)	1 (0.94–1.06)	0.99 (0.96–1.03)	<0.001
Urine β2 microglobulin (µg/l), median (IQR)a	1235 (417–5355)	575 (172–1677)	565 (250–1607)	0.012
Urine β2 microglobulin >644 µg/l	25 (69.4%)	16 (44.4%)	17 (47.2%)	0.036

n = 36 (Excluding patients with CKD at 6 months)

The levels of urine β2m in the study population at the end of 6 months remained significantly higher compared with the levels in controls. The patients who had elevated urine β2m levels (>644 µg/l) at 6 months had marginally lower GFR throughout the follow-up period. The urine β2m levels at first visit strongly correlated with serum creatinine at 6 months.

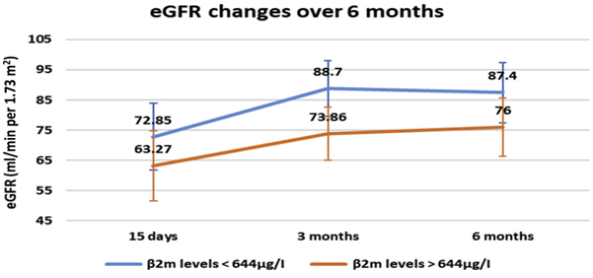

Figure 1: EGFR changes over 6 months

DISCUSSION

Even though snake bite is an important cause of AKI in the tropics, there is only limited information on the renal recovery patterns following envenomation. There are only 2 longitudinal studies that looked into the long-term recovery patterns following snake bite–related AKI namely Waikom et al(9) and other study from Sri lanka(10).

In the current study, we used urine β2m as a potential marker to identify persistent tubular dysfunction (11) following AKI resulting from snake envenomation. We observed that 15% of patients had low GFR or albuminuria at the end of 6 months of follow-up. However, approximately 50% of the subjects had urine β2m excretion exceeding the 95th percentile of the control population. There was an improvement in GFR and fall in urine β2m between 2 weeks and 3 months. However, the mean levels of urine β2m in the study population remained higher compared with healthy controls even at the end of 6 months. The study patients were relatively young without significant comorbidities. A persistently elevated urine β2m excretion is likely to reflect incomplete renal tubular repair following AKI. Even though not statistically significant, we observed that patients with urine β2m exceeding the 95th percentile of controls had lower GFRs throughout the follow-up. None of the subjects had any systemic conditions or medications that are known to be associated with increased production of β2m and excretion in urine. There was no evidence of significant proteinuria or other features to suggest any significant glomerular damage. Urine β2m is a validated marker for diagnosing proximal tubular injury. There are limited data on its prognostic utility. A recent study by Barton et al(12) showed that serum and urine β2m correlates with severity of AKI. To the best of our knowledge, the current study is the first one that attempted to look into the recovery patterns of AKI using urine β2m as a candidate marker.

Limitations

The attrition rates were high; only 60% of patients attended all 3 follow-up visits. Three-fourths of the patients had severe AKI requiring renal replacement therapy, which might explain the persistent tubular injury. The study might be underpowered for a subgroup analysis, because of a relatively smaller sample size. The results might not be generalizable to less severe forms of AKI.

CONCLUSION

Urine β2m level may be a potential early marker for persistent tubular dysfunction in patients who recover from AKI following snake envenomation. Long-term follow-up studies are required to correlate the short-term changes in urine β2m with later development of CKD.

REFERENCES

1. Burdmann Emmanuel A. Acute kidney injury due to tropical infectious diseases and animal venoms: a tale of 2 continents. Kidney Int. 2017;91:1033–1046.
2. Chawla L.S., Eggers P.W., Star R.A., Kimmel P.L. Acute kidney injury and chronic kidney disease as interconnected syndromes. N Engl J Med. 2014;371:58–66.
3. He L., Wei Q., Liu J. AKI on CKD: heightened injury, suppressed repair, and the underlying mechanisms. Kidney Int. 2017;92:1071–1083.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney Int Suppl. 2012;2:1–138.
5. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int Suppl. 2013;3:1–150
6. Peterson P.A., Evrin P.E., Berggård I. Differentiation of glomerular, tubular, and normal proteinuria: determinations of urine excretion of beta-2-microglobulin, albumin, and total protein. J Clin Invest. 1969;48:1189–1198.
7. Argyropoulos C.P., Chen S.S., Ng Y.-H. Rediscovering beta-2 microglobulin as biomarker across spectrum of kidney diseases. Front Med (Lausanne) 2017;4:73.
8. Kuwata K., Nakamura I., Ide M. Comparison of changes in urinary and blood levels of biomarkers associated with proximal tubular injury rat models. J Toxicol Pathol. 2015;28:151–164
9. Waikhom R., Sircar D., Patil K. Long-term renal outcome of snake bite and acute kidney injury: single-center experience. Ren Fail. 2012;34:271–274.
10. Herath H.M., Wazil A.W., Abeysekara D.T. Chronic kidney disease in snake envenomed patients with acute kidney injury in Sri Lanka: descriptive study. Postgrad Med J. 2012;88:138–142.
11. Bagshaw S.M., Langenberg C., Haase M. Urinary biomarkers in septic acute kidney injury. Intensive Care Med. 2007;33:1285–1296.
12. Barton K.T., Kakajiwala A., Dietzen D.J. Using the newer Kidney Disease: Improving Global Outcomes criteria, beta-2-microglobulin levels associate with severity of acute kidney injury. Clin Kidney J. 2018;11:797–802.