Kidney Injury Molecule -1 (KIM-1): an early novel biomarker for Acute Kidney Injury (AKI) in critically – ill patients

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Abstract Background: Acute Kidney Injury (AKI) is a major cause of morbidity and mortality especially in critically-ill patients. The lack of early biomarkers for AKI in humans has interfered with potentially effective therapies in a timely manner. Kidney Injury Molecule-1 (KIM-1) is a type I cell membrane glycoprotein, which is associated with proximal tubule cell injury/dedifferentiation. Presence of KIM-1 in the urine is highly specific for kidney injury as indicated by absence of its expression in the normal kidney; its marked upregulation with proximal tubular cell injury and/or differentiation. **Objective*:*** To investigate the role of KIM-1 as an early marker for AKI in critically-ill patients. **Methods*:*** The study was carried out on 20 critically-ill patients who were at risk for developing AKI. Other 20 healthy subjects were included as control. The Sequential Organ Failure Assessment (SOFA) score was chosen to select critically-ill patients. All candidates were subjected to thorough history taking, complete clinical examination including assessment of Glasgow coma scale & urine output as well as laboratory investigations including urinary KIM-1 (by ELISA), blood urea, serum creatinine, arterial blood gases, platelet count and serum bilirubin. **Results:** The results of our study have shown that there were no significant statistical differences between patient and control group as regards gender (12 females and 8 males for both groups) and age (51.90 $\pm$ 16.32 years for patient group and 51.60 $\pm$ 13.67 years for the control group) with *p*.value of 0.950 and 0.988 respectively. Our study has shown that KIM-1 becomes significantly elevated before a rise of serum creatinine (*p*.value 0.001) by a mean of 27.60 $\pm$15.62 hours. Urinary KIM-1 was shown to have excellent sensitivity & specificity, 90.9 % and 95.24 % respectively. Also it showed a positive predictive value of 95.24 %, and a negative predictive value of 90.9 %. Our results have also shown that urinary KIM-1 was significantly elevated on admission (7.88$\pm$1.72 ng/mL) as compared with elevation of serum creatinine (0.895$\pm$0.173 mg/dL & *p*.< 0.001), blood urea (37.4$\pm$14.53 mg/dL & *p*.< 0.001) and reduction in estimated glomerular filtration rate (eGFR) (85.2$\pm$21.02 mL/minute/1.73 m^2 & p.< 0.001). There was a significant rise of serum creatinine in patient group as compared with control group from the 2nd day (1.425$\pm$0.505 mg/dL & p. < 0.001). However this was insignificant at admission (*p*.value 0.854). Same results apply to blood urea (57.93$\pm$23.1 mg/dL & p.< 0.001 on 2nd day and 0.052 at admission). On the other hand, significant reduction in eGFR occurred only on the 3rd day (27$\pm$13.97 mL/minute/1.73 m^2 & p.< 0.001); however this reduction was insignificant early in the course of illness with p.value of 0.527 & 0.008 at admission and after 24 hours respectively. In comparison, urinary KIM-1 was significantly elevated before a rise in blood urea & serum creatinine and before a reduction in eGFR at admission (*p*< 0.001) and continued to rise significantly over the next two days. **Conclusion:** The data presented suggest that urinary KIM-1 is a reliable early marker for AKI with excellent sensitivity and specificity, especially in critically-ill patients, therefore allowing early diagnosis & institution of appropriate therapy.

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1. Introduction

Acute Kidney Injury (AKI) is a major cause of morbidity and mortality especially in critically-ill patients. The lack of early biomarkers for AKI in humans has interfered with potentially effective therapies in a timely manner (1).

AKI is generally defined as an abrupt and sustained decrease in kidney function'. Until recently there has not been a consensus on what markers best reflect kidney function, and what values of those markers discriminate normal from abnormal kidney function (2).

The Acute Dialysis Quality Initiative (ADQI) formulated the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification. RIFLE defines three grades of increasing severity of AKI - risk (class R), injury (class I) and failure (class F) - and two outcome classes (loss and end-stage kidney disease) based on changes in either serum creatinine or urine output from the baseline condition (3).

However creatinine measurements can be affected by the clinical scenario, by the presence of chromogenic substances, including bilirubin, and by the laboratory assay utilized. There is an increasing evidence from published studies that creatinine concentration is not a decisive marker in diagnosing AKI (4). This is because of the following: ***1)*** Elevated serum creatinine concentrations are not specific for AKI and require differentiation from other prerenal or extrarenal causes of azotemia. ***2)*** Serum creatinine concentrations are not specific for renal tubular lesions, but seem to reflect the loss of glomerular filtration function, accompanying the development of AKI. ***3)*** Increases in serum creatinine are detected later than the actual GFR changes as creatinine accumulates over time. ***4)*** Serum creatinine is a poor marker of kidney dysfunction as changes in its concentrations are neither sensitive nor specific in response to slight GFR alterations and become apparent only when the kidneys have lost 50% of their functional capacity. ***5)*** Pre-existing baseline results may not always be available, and similar baseline values do not always reflect similar renal function (5, 6)

Kidney injury molecule-1 (KIM-1) is a type 1 membrane protein that is not expressed in normal kidney but is markedly upregulated in the injured proximal tubular epithelial cells of the human and rodent kidney in ischemic and toxic AKI (7). KIM-1 is also expressed in other conditions where proximal tubules are dedifferentiated e.g. renal cell carcinoma (8).

There were a number of characteristics of KIM-1 that led us to believe that the protein might be an ideal biomarker of kidney injury: the absence of KIM-1 expression in the normal kidney; its marked upregulation and insertion into the apical membrane of the proximal tubule; its persistence in the epithelial cell until the cell has completely recovered; the rapid and robust cleavage of the ectodomain and the ex vivo room temperature stability of the ectodomain (9). Presence of KIM-1 in the urine is highly specific for kidney injury. No other organs have been shown to express KIM-1 to a degree that would influence kidney excretion (10).

The Sequential Organ Failure Assessment (SOFA) score is a six-organ dysfunction/failure score measuring multiple organ failure daily. It was used to predict prognosis & mortality in critically ill patients (11-13).

This work was designed in an attempt to elucidate the role of KIM-1 as a marker for early detection of AKI in critically-ill patients.

2. Subjects and Methods:

Design and study population*:* 20 critically-ill patients admitted at Tanta University Hospitals were eligible for this study. We included 20 clinically-healthy subjects, of matched age & gender, as control group for comparison.

The study was reviewed and approved by the ethical committee at Faculty of Medicine, Tanta University, and written informed consent was obtained from all participants.

Variables: Data obtained include variables from the following domains: demographic, clinic, and specific organ involvement variables; SOFA score was also recorded.

Simultaneous to the clinical evaluation we obtained of each patient, 4 mL of aseptically-collected urine. After collection, samples were centrifuged, and an aliquot was immediately stored at −20^{o}C until KIM-1 measurement.

KIM-1 levels were measured by enzyme-linked immunosorbent assay (ELISA) (14) The detection range was 0.78 -50 ng/mL. The standard curve concentrations used for the ELISA's were 50 ng/mL, 25 ng/mL, 12.5 ng/mL, 6.25 ng/mL, 3.12 ng/mL, 1.56 ng/mL, 0.78 ng/mL.

Calculation of estimated Glomerular Filtration Rate (eGFR) (15)***:*** The Modification of Diet in Renal Disease (MDRD) Study equation was used ***for*** estimating glomerular filtration rate (GFR) from serum creatinine. ***eGFR*** *(mL/min/1.73 m2) = 186 x (Scr)-1.154 x (Age)-0.203 x (0.742 if female) x (1.212 if African-American) (conventional units).*

Statistical analyses: Statistical presentation and analysis of the present study was conducted, using the mean, standard deviation and chi-square test by SPSS V.16. Probability values of less than 0.05 were considered of statistical significance (16).

3.Results:

The study was performed on 20 patients (12 females & 8 males) with mean age of 51.90 ± 16.32 and 20 clinically-healthy subjects as control (12 females & 8 males) with mean age of 51.60 ± 13.67. There was no significant statistical difference as regards age & gender between patient and control groups, with p.value of 0.950 and 0.988 respectively (Table 1). Clinical data of the patient group as regards age, gender, SOFA score &diagnosis are illustrated in (Table 2).

Results of our study have shown that urinary KIM-1 becomes elevated before rise in serum creatinine by a mean of 27.60 ±15.62 hours. Our study has also shown that KIM-1 becomes significantly elevated before a rise of serum creatinine (*p*.value 0.001) (Table 3).

Urinary KIM-1 has excellent sensitivity & specificity. The marker has a sensitivity of 90.9 %, a specificity of 95.24 %, a positive predictive value of

95.24 %, and a negative predictive value of 90.9 % (Table 4).

Our results have also shown that there is a significant rise of serum creatinine in patient group as compared with control group from the 2nd day (*p*.value 0.001). However this was insignificant at admission (*p*.value 0.854) (Table 5). Same results apply to blood urea with *p*.values of 0.001 on 2nd day and 0.052 at admission (Table 6). On the other hand, significant reduction in eGFR occurred only on the 3rd day (*p*.< 0.001); however this reduction was insignificant early in the course of illness with *p*.< 0.527 & 0.008 at admission and after 24 hours respectively (Table 7). Urinary KIM-1, however, was significantly elevated since admission and continued over the next two days (*p*.value 0.001) (Table 8).

It was noted that time elapsed between rise in KIM-1 and rise in serum creatinine was non-significantly related to age and gender (*p*.values 0.147 and 0.051 respectively) (Tables 9 & 10). Urinary KIM-1 was significantly elevated before a rise in blood urea & serum creatinine and before a reduction in eGFR at admission (*p*.value 0.001) (Table 11).

Table 1: Demographic data of patient and control groups.

	Control	Patient	*p*. value
Age (years)	51.60+13.67	51.90+16.32	0.950
Gender	8 males & 12 females	8 males 12 females	0.988

Probability values of less than 0.05 were considered of statistical significance.
Probability values of less than 0.001 were considered highly significant.

Table 2: Clinical Data of the Patient Group.

No.	Age	Gender	Diagnosis	SOFA Score	Department
1	47	Female	Haemorrhagic stroke.	19	Neuropsychiatry.
2	50	Male	Mesenteric vascular occlusion with resection anastomosis.	16	Anaesthetic ICU
3	27	Female	HELLP Syndrome.	14	Anaesthetic ICU
4	25	Female	SIRS complicating IUFD	12	Anaesthetic ICU
5	63	Female	Haemorrhagic stroke.	14	Neuropsychiatry.
6	30	Female	Fever & disturbed conscious level for investigation, encephalitis?	12	Neuropsychiatry.
7	45	Female	Ischaemic stroke.	14	Neuropsychiatry.
8	70	Male	Hepatic Encephalopathy, Cardiac cirrhosis of liver, Prosthetic mitral valve, Heart failure.	15	Cardiology
9	65	Female	Massive anterior myocardial infarction.	12	Cardiology
10	50	Male	Large subdural haematoma.	12	Neuropsychiatry.
11	44	Male	Brain tumour with haemorrhage.	12	Neuropsychiatry.
12	50	Female	Perforated duodenal ulcer complicated by peritonitis.	12	Anaesthetic ICU
13	24	Male	SIRS complicating infective endocarditis.	15	Cardiology
14	47	Female	Ischaemic stroke.	12	Neuropsychiatry.
15	70	Male	Haemorrhagic stroke.	12	Neuropsychiatry.
16	50	Female	Ischaemic stroke.	12	Neuropsychiatry.
17	20	Female	HELLP Syndrome.	12	Anaesthetic ICU
18	25	Male	Contrast-induced nephropathy.	12	Internal medicine ICU
19	45	Female	Haemorrhagic stroke.	12	Neuropsychiatry.
20	60	Male	Haemorrhagic stroke.	13	Neuropsychiatry.

HELLP: Haemolytic anaemia, Elevated Liver enzymes, Low Platelet count; NO: Number; ICU: Intensive Care Unit; SIRS: Systemic Inflammatory Response Syndrome; IUFD: Intra Uterine Foetal Death.

Table 3: Mean time elapsed between positive KIM-1 and rise of serum creatinine.

Time elapsed (In hours)	**Control**	**Patients**
Mean ±SD	0	27.60 ± 15.62
t. test	**7.901**	
***p*. value**	**0.001***	

Table 4: Number of true & false positive and true & false negative subjects (as regards KIM-1)**.**

	Positive	**Negative**
True	19	18
False	1	2

Table 5: Comparison of serum creatinine between patient and control groups at admission, at 24 & 48 hours intervals.

		Mean ± SD	**t. test**	***p*. value**
Serum creatinine (1st day) (mg/dl)	Control	0.905±190	**0.174**	**0.854**
	Patients	0.895±0.173		
Serum creatinine (2nd day) (mg/dl)	Control	0.980±0.164	**3.325**	**0.001***
	Patients	1.425±0.505		
Serum creatinine (3rd day) (mg/dl)	Control	0.935±0.173	**6.856**	**0.001***
	Patients	2.905±1.375		

Notes: - Blood urea & serum creatinine were measured in mg/dL.
- KIM-1 was measured in ng/mL.
-eGFR was measured in mL/minute/1.73 m^2

Table 6: Comparison of blood urea between patient and control groups at admission, at 24 & 48 hours intervals.

		Mean ± SD	**t. test**	***p*. value**
Blood urea 1st day (mg/dL)	Control	19.65±12.06	**1.235**	**0.052**
	Patients	37.40±14.53		
Blood urea 2nd day (mg/dL)	Control	16.05±10.30	**7.325**	**0.001***
	Patients	57.93±23.1		
Blood urea 3rd day (mg/dL)	Control	15.35±9.82	**10.925**	**0.001***
	Patients	111.80±41.86		

Table 7: Comparison of eGFR between patient and control groups at admission, at 24 & 48 hours intervals.

		Mean ± SD	**t. test**	***p*. value**
eGFR 1st day (mL/minute/1.73 m^2)	Control	81.25±13.49	**0.707**	**0.527**
	Patients	85.20±21.02		
eGFR 2nd day (mL/minute/1.73 m^2)	Control	74.05±10.40	**3.529**	**0.008**
	Patients	54.60±20.21		
eGFR 3rd day (mL/minute/1.73 m^2)	Control	77.75±11.23	**12.207**	**0.001***
	Patients	27±13.97		

Table 8: Comparison urinary KIM-1 between patient and control groups at admission, at 24 & 48 hours intervals.

		Mean ± SD	t. test	*p*. value
KIM-1 1st day (ng/mL)	Control	0.782±0.335	**4.880**	**0.001***
	Patients	7.88±1.72		
KIM-1 2nd day (ng/mL)	Control	0.902±0.370	**5.628**	**0.001***
	Patients	14.49±2.53		
KIM-1 3rd day (ng/mL)	Control	0.820±0.318	**4.058**	**0.001***
	Patients	25.315±5.29		

Table 9: Comparison of time interval between positive KIM-1 and rise in serum creatinine between male and female in patient group.

Time elapsed (In hours)	**Male (n=16)**	**Female (n=24)**
Mean ±SD	13.50 ± 4.88	14 ± 3.43
t. test	**0.658**	
***p*. value**	**0.147**	

Table 10: Time interval between positive KIM-1 and rise in serum creatinine in relation to age in patient group.

	Age	**Time elapsed**
Mean ±SD	43.25 ± 5.325	13.80 ± 3.21
t. test	**1.658**	
***p*. value**	**0.051**	

Table 11: Comparison of urinary KIM-1, serum creatinine, blood urea, and eGFR at admission.

	Mean ± SD	**t. test**	***p*. value**
KIM-1 1st day (ng/ml)	**7.88±1.72**	-	-
Serum creatinine 1st day (mg/dL)	0.895±0.173	**4.475**	**0.001***
Blood urea 1st day (mg/dL)	37.4±14.53	**9.528**	**0.001***
eGFR 1st day (mL/minute/1.73 m^2)	85.2±21.02	**29.321**	**0.001***

4.Discussion:

The absence of sensitive and specific biomarkers for the early detection of AKI has impaired progress in the diagnosis and treatment of patients with AKI. Traditional blood (creatinine & blood urea) and urinary markers of kidney injury (urinary casts, fractional excretion of Na^+) are insensitive for the early diagnosis of AKI (17).

Many urinary proteins have been evaluated as noninvasive indicators of renal injury. Examples include α and π glutathione-S-transferases (α and π GST) (18), neutrophil gelatinase-associated lipocalin (NGAL) (19), cysteine rich protein 61 (CYR61) (20), interleukin-18 (IL-18) (21), clusterin (22), F-actin (23), N-acetyl-β-D-glucosaminidase (NAG) (24).

However, problems with reliable use of these proteins to identify and monitor kidney injury include instability in the urine, modification due to physicochemical properties of the urine, delayed appearance, inconsistency of upregulation with different models of nephrotoxicity, absence of sustained elevation throughout the time course of renal injury to monitor progression and regression of injury and lack of a high throughput detection method (25).

Human kidney injury molecule-1 (KIM-1) is a type 1 transmembrane protein that is not detectable in normal kidney tissue or urine, but is expressed at very high levels in dedifferentiated proximal tubule epithelial cells in human and rodent kidneys after ischemic or toxic injury and in renal cell carcinoma (26-29). High urinary KIM-1

expression was also associated with adverse clinical outcomes in patients with AKI (30).

Urinary KIM-1 was evaluated as a marker for AKI in several studies (25, 27). In our study, we proved that urinary KIM-1 levels serve as a non-invasive, rapid, sensitive, reproducible, and potentially high throughput method to detect early kidney injury in critically-ill patients.

Yuzhao Zhou, *et al.* have concluded that KIM-1 may serve as a useful general biomarker for renal proximal tubule injury in preclinical and clinical studies of drug safety evaluation, chemical-related renal injury, and the monitoring of renal disease states (31).

The FDA and EMEA have included KIM-1 in the small list of kidney injury biomarkers that they will now consider in the evaluation of kidney damage as part of their respective drug review processes of new drugs (32).

KIM-1 has many potential uses other than a urinary biomarker for AKI. **Van Timmeren, *et al.*** evaluated its utility in renal transplant recipients. The occurrence of graft loss increased with increasing tertiles of KIM-1 excretion. KIM-1 levels predicted graft loss independent of creatinine clearance, proteinuria and donor age (33). **Ichimura, *et al.*** have provided a compelling case that activated renal proximal tubular epithelial cells also phagocytose apoptotic cells utilizing KIM-1 as a critical receptor. Ichimura study opens new avenues for research that might provide the foundations for novel treatments to protect the kidney from acute injury or to promote its repair (34).

We need to investigate whether increased KIM-1 expression enhances renal protection from nephrotoxic insult. Future studies should focus on other aspects of this biomarker as a predictor for graft loss in renal transplant patients. Also we should study whether modification of urinary levels of this biomarker would have any therapeutic benefit.

Limitations of the study include the limited number of patients. Other biomarkers for AKI had to be included for comparison. Whether a combination of biomarkers would give better sensitivity & specificity for early diagnosis of AKI should be the matter of future studies.

5. Conclusion:

From the present study, we conclude that urinary KIM-1 is a reliable early marker for AKI with excellent sensitivity and specificity, especially in critically-ill patients, as compared to traditional markers namely blood urea & serum creatinine, therefore allowing early diagnosis & institution of appropriate therapy.

Urinary KIM-1 should be included as a screening test to depict AKI in those at high risk including critically-ill patients.

References:

1. Robert W. Schrier (2004): New biomarkers for acute kidney injury. Schrier; 3: 452- 463.
2. Bellomo R, Kellum J, Ronco C (2001): Acute renal failure: time for consensus. Intensive Care Med; 27:1685-1688.
3. Bellomo R, Ronco C, Kellum JA, et al. (2004): the ADQI workgroup: Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care; 8:R204-R212.
4. Bonventre JV (2007): Diagnosis of acute kidney injury: from classic parameters to new biomarkers. Contrib Nephrol; 156: 213– 219.
5. Coca SG, Yalavarthy R, Concato J, et al. (2008): Biomarkers for the diagnosis and risk stratification of acute kidney injury: systematic review. Kidney Int; 73:1008–1016.
6. Bonventre JV (2007): Diagnosis of acute kidney injury: from classic parameters to new biomarkers. Contrib Nephrol; 156: 213– 219.
7. Ichimura T, Hung CC, Yang SA, et al. (2004): Kidney injury molecule-1: A tissue and urinary biomarker for nephrotoxicant-induced renal injury. Am J Physiol Renal Physiol; 286: F552 –F563
8. Han WK, Alinani A, Wu CL, et al. (2005): Human kidney injury molecule-1 is a tissue and urinary tumor marker of renal cell carcinoma. J Am Soc Nephrol ; 16 : 1126 –1134.
9. Waikar SS & Bonventre JV (2007): Biomarkers for the diagnosis of acute kidney injury. Curr Opin Nephrol Hypertens; 16: 557– 564.
10. Vaidya VS, Ferguson MA, Bonventre JV (2008): Biomarkers of acute kidney injury. Annu Rev Pharmacol Toxicol; 48: 463–493.
11. Jones AE, Trzeciak S, Kline JA (2009): The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Critical Care Med; 37(5):1649-54.
12. Ferreira FL, Bota DP, Bross A, et al. (2001): Serial evaluation of the SOFA scores to predict outcome in critically ill patients. JAM; 286(14):1754-8.
13. Jones AE, Trzeciak S, Kline JA (2009): The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the

time of emergency department presentation. Crit Care Med.; 37(5):1649-54.
14. Shalini Chaturvedi, Takeisha Farmer, and Gordon F. Kapke (2009): Assay Validation for KIM-1: human urinary renal dysfunction biomarker. Int J Biol Sci; 5(2): 128–134.
15. Levey AS, Bosch JP, Lewis JB, et al. (1999): A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med; 130(6):461-70.
16. Aviva P and Caroline S (2005): Glossary of terms in Medical statistics at a Glance 2nd edition. By: Blackwell Publishing, Appendix D: 144-152.
17. Star RA (2000): Treatment of acute renal failure. Kidney Int.; 54:1817–1831.
18. Branten AJ, Mulder TP, Peters WH, et al. (2000): Urinary excretion of glutathione S transferases alpha and beta in patients with proteinuria, reflection of the site of tubular injury. Nephron; 85: 120-126.
19. Hilton R (2006): Acute renal failure. BMJ; 333(7572):786-90.
20. Muramatsu Y, Tsujie M, Kohda Y, et al. (2002): Early detection of cysteine rich protein 61 (CYR61, CCN1) in urine following renal ischemic reperfusion injury. Kidney Int; 62: 1601-1610.
21. Oda H, Shiina Y, Seiki K, et al. (2002): Development and evaluation of a practical ELISA for human urinary lipocalin-type prostaglandin D synthase. Clin Chem; 48: 1445-1453.
22. Aulitzky WK, Schlegel PN, Wu DF, et al. (1992): Measurement of urinary clusterin as an index of nephrotoxicity. Proc Soc Exp Biol Med; 199: 93-96.
23. Schwartz N, Hosford M, Sandoval RM, et al. (1999): Ischemia activates actin depolymerizing factor: role in proximal tubule microvillar actin alterations. Am J Physiol; 276: F544-551.
24 .Westhuyzen J, Endre ZH, Reece G, et al. (2003): Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. Nephrol Dial Transplant; 18: 543-551.
25. Mishra J, Ma Q, Prada A, et al. (2003): Identification of Neutrophil Gelatinase-Associated Lipocalin as a Novel Early Urinary Biomarker for Ischemic Renal Injury. J Am Soc Nephrol; 14:2534-2543.
26. Ichimura T, Bonventre JV, Bailly V, et al. (1998): Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is upregulated in renal cells after injury. J Biol Chem; 273:4135–4142.
27. Han WK, Bailly V, Abichandani R, et al. (2002): Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int.; 62:237–244.
28. Ichimura T, Hung CC, Yang SA, et al. (2004): Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury. Am J Physiol Renal Physiol.;286:F552–F563.
29. Lin F, Zhang PL, Yang XJ, et al. (2007): Human kidney injury molecule-1 (hKIM-1): a useful immunohistochemical marker for diagnosing renal cell carcinoma and ovarian clear cell carcinoma. Am J Surg Pathol.; 31:371–381.
30. Liangos O, Perianayagam MC, Vaidya VS, et al. (2007): Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. J Am Soc Nephrol.; 18:904–912.
31. Yuzhao Zhou, Vishal S. Vaidya, Ronald P. Brown, et al. (2008): Comparison of Kidney Injury Molecule-1 and Other Nephrotoxicity Biomarkers in Urine and Kidney Following Acute Exposure to Gentamicin, Mercury, and Chromium. Toxicol. Sci.; 101 (1): 159-170.
32. FDA News. (2008): FDA, European medicines agency to consider additional test results when assessing new drug safety collaborative effort by FDA and EMEA expected to yield additional safety data. FDA News 2008; 12 June.
33. Van Timmeren MM, Vaidya VS, Van Ree RM et al. (2007): High urinary excretion of kidney injury molecule-1 is an independent predictor of graft loss in renal transplant recipients. Transplantation; 84:1625–1630.
34. Ichimura T, Asseldonk EJ, Humphreys BD, et al. (2008): Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. J Clin Invest; 118: 1657– 1668.

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