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Is urinary kim-1 a better biomarker than its serum value in diagnosis of Acute Kidney Injury disease?

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Abstract:

Background: Urinary Kidney Injury Molecule 1 (KIM-1) is a proximal tubular injury biomarker for early detection of acute kidney injury (AKI)

Aim of the study: To study the accuracy of Serum (KIM-1) test and Urinary kim-1 as an earlier biomarkers rather than serum creatinine (S.Cr) in early diagnosis of (AKI) .

Methods: a prospective observational case control study was carried out on 10 adult subjects as a control group and 45 non diabetic subjects with normal serum creatinine but at risk of developing acute kidney injury recruited from intensive care unit in Port Said National hospital with normal serum creatinine and at risk of developing acute kidney injury. Age of all participants ranged from 47 years to 76 years old. Blood

and urin samples were collected to measure and compare serum creatinine ,urea, albumin/creatinin ratio ,uric acid and estimated glomular filtration rate, serum (KIM-1) and Urinary kim-1.

Results : Urinary KIM-1 represents an early marker for predicting AKI and therefore measurements of urinary KIM-1 by ELISA increased obviously by many folds in AKI patients than its average number of healthy patients at different times (baseline, 24hr, 48hr, 72hr and 96hr by 2, 4, 7, 8, and 16 times respectively more than normal subject values). While its increase in serum were high (1.5, 3. 4, 5.5 and 6.5 respectively at same period of experimental time compared to normal subjects

Conclusion: the study demonstrates that urinary and serum kim-1 are reliable markers for early detection & diagnosis of AKI. Moreover, urinary KIM-1 is more sensitive than serum KIM-1 for early detection of AKI.

Keywords

Acute kidney injury. Urine Kidney injury molecule-1. Serum Kidney injury molecule-1

Abbreviations

AKI Acute Kidney Injury

AKIN Acute Kidney Injury Network

ARF Acute Renal Failure

BUN Blood Urea Nitrogen

CKD Chronic Kidney Disease

ESRD End Stage Renal Disease

GFR Glomerular Filtration Rate

ICU Intensive Care Unit

KIM-1 Kidney Injury Molecule-1

s Cr Serum creatinine

s/uKIM-1 Serum/urine Kidney Injury Molecule-1

ROC Receiver operating characteristics

Introduction

Acute Kidney Injury Network (AKIN) criteria consider serum creatinine (SCr) as the gold standard of kidney injury . Unfortunately, creatinine is an unreliable indicator during acute changes in kidney function (Dennen et al., 2007). (SCr) levels vary widely with age, gender, muscle mass, muscle metabolism, medication and hydration status. Its concentrations may not change until a substantial portion of kidney function has already been lost, due to a large renal reserve (Hirschberg et al., 1999).

Kidney injury molecule-1 (KIM-1), a recently discovered transmembrane tubular protein, is markedly induced in renal injury including acute kidney injury (AKI) and chronic kidney disease (CKD) (Shao et al., 2014). In renal patients, KIM-1 is up-regulated in a variety of conditions including ischemia, nephrotoxic drugs, CKD, and acute/chronic renal transplant dysfunction. There are many studies shows that KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of prognosis (Rees et al., 2008). KIM-1 is considered as an ideal biomarker for kidney injury because it is not expressed in normal kidney but specifically expressed in injured proximal tubular cells, and such an expression can persist until the damaged cells have completely recovered. Moreover, the rapid and integrated cleavage of its ectodomain into the lumens of kidney tubules can make it detectable in urine(Chaturvedi et al.,2009).Urinary KIM-1 level is closely related to tissue KIM-1 and correlates with the severity of renal damage, so measurement of urinary KIM-1 is likely to be a noninvasive and sensitive method for the evaluation of kidney injury and even for monitoring of the response of treatment (Bonventre,2009)

Materials and Methods

Design : prospective observational study

Participants : the study includes 55 participants .10 participants were considered as a control group which was compared with 45 cases in ICU for 5 -7 days .Blood and urine samples were collected from both control group and cases in ICU who were at high risk of AKI .They were selected by normal creatinine level in non diabetic patients and hospitalized for 5-7 days and had causes including shock, sepsis, contrast used in coronary angiography and those with chronic use of non steroidal drugs .

According to these factors, patients were classified into three groups as follows:

Group I- Pre-renal acute kidney injury patients includes patients who were suffering of dehydration or bleeding, were 15 cases (27.3%).

Group II- Renal acute kidney injury patients ,includes patients who were suffering of contrast induced nephropathy or drug induced nephropathy ,Were 15 cases (27.35%).

Group III- Post renal acute kidney injury includes patients who were suffering of prostatic hyperplasia or uretric stone causing hydronephrosis , Were 15 cases (27.3%).

The total 55 subject were divided by gender as follow 26 males (47%) And 29 females (53%) , age ranged from 47 years to 76 years, weight ranged from 55 kilograms to 110 kilograms, length ranged from 160 to 189 Meter, blood pressure ranged from 90/50 to 200/110. Blood and urine samples were collected to measure and compare serum creatinine ,urea, albumin/creatinin ratio ,uric acid and estimated glomular filtration rate with serum (KIM-1) and Urinary kim-1 for 5-7 days.

Methods

Serological analysis of kidney functions

Serum creatinine, albumin, Albumin/creatinine ratio (ACR), urea, uric acid and urine microalbuminuria were determined by using an enzymatic assay (Creatinine Plus; Roche Diagnostics, Branchburg، NJ, USA) on a cobas 8000 analyzer (Roche Diagnostics) according to the manufacture illustration. In additional to measurement of urine creatinine for creatinine clearance and determine estimate glomerular filtration rate (eGFR). Glomerular filtration rate was calculated according to the Schwartz formula. Urine supernatants and serum samples were frozen until analysis at −70°C. Commercially available enzyme-linked immunosorbent assay kit (ELISA assay kit) USCN Life Science, Hankou, Wuhan, China was used to determine s/uKIM-1 and was expressed in nanograms per milligram creatinine (ng/mg cr.).

Statistical analysis

SSPS 22 package program (IBM Corp., Armonk, NY, USA) was used for statistical analyses. Evaluated data were presented as mean ± SD and percentage values. Chi-square test was used to evaluate the categorized variables. Spearman analysis was used for evaluation of the correlation of the variables between groups. p value <0.05

was taken as the statistical significance threshold level. The areas under the ROC curve (AUCs) with 95% confidence intervals (95% CI) were calculated. Also, for each timeframe, the optimal cutoff value based on the Youden index was calculated with corresponding sensitivity and specificity. Using those cutoff values, sensitivity and specificity of biomarkers for predicting AKI. Also who developed AKI later within the study period (<48 hours post-admission) after being considered AKI-free upon admission. Of these patients, the timing and absolute values of maximum biomarker levels in urine samples preceding AKI were compared with biomarker levels in the first urine and serum samples of controls. Oral and written informed consent was obtained from all subjects before the start of the study. The study was approved by the Portsaid University Ethics Committee.

Results

A total of 45 patients with AKI were studied. There were 21 (46.67%) male patients, and there were 24 (53.33%) female patients. The ages of patients ranged from 47 to 76 years.

Biochemical investigations

Table (1). Biochemical parameters of controlled and AKI patients

parameters	Baseline	24hr	48hr	72hr	96hr
uCr mean mg/dl ±SD					
Non-AKI control (n=10)	631.0 ± 87.0	611.0 ± 67.0	639.0 ± 72.0	628.0 ± 65.0	624.0 ± 59.0
AKI patients (n-45)	600.9 ± 17.15	430.1 ± 32.52	328.7 ± 18.80	168.1 ± 20.97	76.29 ± 12.37
P value <	NS	0.001	0.001	0.001	0.001
eGFR ml/min/1.73m^2 mean ±SD					
Non-AKI control 9N-10)	127.0 ± 29.40	136.0 ± 25.30	141.0 ± 32.70	147.0 ± 86.20	134.0 ± 22.55
AKI patients (N=45)	152.0 ± 7.16	122.4 ± 5.34	97.64 ± 13.41	52.42 ± 11.0	21.78 ± 5.47
P value <	NS	NS	0.001	0.001	0.001
u-kim-1 ng/mg uCr mean ng/ml ±SD					
Non-AKI control (n=10)	18.80 ± 3.91	17.60 ± 3.91	19.57 ± 3.91	20.10 ± 3.91	18.34 ± 3.91
AKI patients (n=45)	34.07 ± 5.12	77.32 ± 6.94	128.3 ± 8.97	194.1 ± 13.93	287.8 ± 29.33
P value <	0.001	0.001	0.001	0.001	0.001

SCr mean mg/dl ±SD					
Non-AKI control (n=10)	0.56 ± 0.17	0.79 ± 0.52	0.81 ± 0.10	0.85 ± 0.17	0.79 ± 0.54
AKI patients (n=45)	0.76 ± 0.18	0.94 ± 0.27	1.24 ± 0.34	1.58 ± 0.38	1.98 ± 0.43
P value <	NS	NS	0.001	0.001	0.001
S urea mean mg/dl ±SD					
Non-AKI control (n=10)	18.20 ± 3.16	16.35 ± 3.16	17.25 ± 3.16	19.60 ± 3.16	20.30 ± 3.16
AKI patients (n=45)	17.09 ± 1.79	27.20 ± 9.94	34.78 ± 10.32	47.02 ± 11.35	61.73 ± 13.62
P value <	NS	0.001	0.001	0,001	0.001
S uric mean mg/dl ±SD					
Non-AKI control (n=10)	3.42 ± 0.41	4.05 ± 0.30	2.95 ± 0.61	4.56 ± 0.80	5.01 ± 0.31
AKI patients (n=45)	4.45 ± 1.29	5.31 ± 1.46	6.60 ± 1.59	7.89 ± 1.75	9.70 ± 2.32
P value <	NS	0.001	0.001	0.001	0.001
sAlb mean mg/dl ±SD					
Non-AKI control (n=10)	4.42 ± 0.20	4.62 ± 0.10	3.91 ± 0.37	4.17 ± 0.58	3.85 ± 0.76
AKI patients (n=45)	4.59 ± 0.42	4.49 ± 0.48	3.70 ± 0.44	3.04 ± 0.47	2.42 ± 0.54
P value <	NS	NS	0.001	0.001	0.001
μ–alb mean μg/dl ±SD					
Non-AKI control (n=10)	8.80 ± 1.48	7.70 ± 1.37	9.60 ± 1.50	8.15 ± 1.72	8.37 ± 1.20
AKI patients (n=45)	9.40 ± 3.19	16.09 ± 3.13	59.53 ± 6.96	117.3 ± 10.97	240.1 ± 43.0
P value <	NS	0.001	0.001	0.001	0.001
sKIM-1 ng/ml mean±SD					
Non-AKI control (n=10)	17.70 ± 1.57	19.50 ± 2.30	20.62 ± 1.40	18.78 ± 1.51	21.10 ± 3.17
AKI patients (n=45)	23.75 ± 3.78	51.05 ± 7.46	72.08 ± 9.96	93.09 ± 9.62	115.1 ± 12.0
P value <	0.001	0.001	0.001	0.001	0.001
ACR					
Non-AKI control (n=10)	1.63 ± 0.39	1.93 ± 0.28	1.82 ± 0.35	1.74 ± 0.42	1.58 ± 0.26
AKI patients (n=45)	1.60 ± 0.66	3.74 ± 0.82	18.14 ± 2.46	69.65 ± 9.95	315.3 ± 78.20
P value <	NS	0,001	0.001	0.001	0.001

urine creatinine, GFR, and urine KIM-1 in addition to serum creatinine, urea, uric acid, albumin, microalbuminurea and KIM-1. All values were represented in (Table 1).

One of the most promising biochemical parameters for predicting AKI cases at early stage as determined by serum and urine KIM-1 levels measured by ELISA technique which, represented a highly significant increase starting from baseline, and continuously elevated after 24h, 48h, 72h and 96h ($p<0.001$) of icu admission.

It is surprisingly to note that most of other biochemical parameters as serum, urea, uric acid, albumin/creatinine ratio (ACR), and urine creatinine levels showed no significant difference at 0hr of ICU admission while showed a highly significant increase at 24h, 48h, 72h and 96h ($p<0.001$) of AKI group. Meanwhile, a significant decrease in serum albumin level was detected only after passing of 24hr of icu admission.

On the other hand, no significant differences were observed in serum creatinine levels or estimate glomerular filtration rate (eGFR) was observed among AKI patients compared with control subjects up to 24h of the admission to ICU. While AKI patients showed a marked significant increase in both parameters ($p<0.001$) at 48, 72 and 96 hours of ICU admission.

Table (2): Correlation between different s/uKIM-1 at 0, 24, 48, 72 and 96 hr in relation to studied parameters among AKI patients group (n = 45).

		Baseline		24hr		48hr		72hr		96hr	
		Serum KIM-1	Urine KIM-1	Serum KIM-1	Urine KIM-1	Serum KIM-1	Urine KIM-1	Serum KIM-1	Urine KIM-1	Serum KIM-1	Urine KIM-1
eGFR	**r**	0.122	-0.009	-0.156	-0.091	-0.196	-0.303*	-0.168	0.053	-0.023	0.320*
	p	0.424	0.953	0.306	0.551	0.197	0.043	0.271	0.729	0.883	0.032
uCr	**r**	-0.150	0.070	-0.213	0.194	-0.010	-0.109	0.064	0.108	0.094	0.093
	p	0.324	0.647	0.161	0.201	0.946	0.476	0.678	0.479	0.539	0.543
sCr	**r**	0.123	-0.119	0.292	-0.106	0.047	0.006	-0.060	0.116	-0.186	0.110
	p	0.423	0.436	0.051	0.487	0.758	0.970	0.695	0.448	0.222	0.474
s. urea	**r**	0.127	0.050	0.159	-0.412*	-0.065	-0.140	-0.029	0.019	-0.134	-0.150
	p	0.404	0.747	0.297	0.005	0.669	0.359	0.850	0.903	0.379	0.325
s. uric acid	**r**	0.006	0.027	-0.293	-0.470*	-0.320*	0.032	-0.148	-0.025	0.039	-0.047
	p	0.970	0.860	0.051	0.001	0.032	0.836	0.333	0.872	0.799	0.758
s.albumin	**r**	-0.116	0.030	-0.130	0.001	0.058	0.187	0.243	-0.102	0.184	-0.118
	p	0.447	0.842	0.394	0.997	0.703	0.218	0.108	0.506	0.226	0.442
μ-albuminuria	**r**	0.114	-0.148	0.171	-0.005	0.263	0.021	0.082	-0.059	0.124	-0.239
	p	0.456	0.332	0.262	0.976	0.081	0.893	0.593	0.701	0.418	0.114
ACR	**r**	0.341*	-0.134	0.198	-0.076	0.222	0.071	-0.043	-0.063	0.054	-0.048
	p	0.022	0.379	0.193	0.621	0.142	0.644	0.777	0.681	0.723	0.756

r: Pearson coefficient *: Statistically significant at $p \leq 0.05$

the table shows positive correlation between serum KIM-1 level and ACR at o hr of ICU admission, followed by a reverse correlation between urine KIM-1 and both serum urea or uric acid at 48 hr of ICU admission.

Table (3): Comparison between mean values for 3 sub-groups pre-renal, renal and post-renal according to Serum KIM-1

	Baseline	24 hours	48 hours	72 hours	96 hours
Pre-renal (n = 15)	23.47±3.64	50.58±9.61	70.54±12.49	93.54±10.43	115.0±12.63
Renal (n = 15)	24.58±4.42	51.56±7.85	77.15±7.86	97.12±7.31	120.88±12.26
Post-renal (n = 15)	23.21±3.34	51.01±4.52	68.54±7.08	88.61±9.45	109.29±8.41
Total AKI (n = 45)	23.75±3.78	51.05±7.46	72.08±9.96	93.09±9.62	115.06±12.0

Table (4): Comparison between mean values for 3 sub-groups pre-renal, renal and post-renal according to Urine KIM-1

	Baseline	24 hours	48 hours	72 hours	96 hours
Pre-renal (n = 15)	35.59±6.69	81.81±7.02	128.67±11.08	192.11±13.33	285.67±28.45
Renal (n = 15)	33.03±3.71	76.82±7.08	129.05±5.90	193.81±12.92	277.55±29.94
Post-renal (n = 15)	33.59±4.47	73.34±3.63	127.13±9.65	196.30±15.99	300.29±26.72
Total AKI (n = 45)	34.07±5.12	77.32±6.94	128.28±8.97	194.07±13.93	287.84±29.33

Table (5): Sensitivity and specificity of s/u KIM-1, s. creatinine and s. urea of AKI patients (n = 45) at different experimental time schedule.

Time	0hr				24hr				48hr				72hr				96hr			
Parameter	**AUC**	**Cut off#**	**Sensitivity**	**Specificity**	**AUC**	**Cut off#**	**Sensitivity**	**Specificity**	**AUC**	**Cut off#**	**Sensitivity**	**Specificity**	**AUC**	**Cut off#**	**Sensitivity**	**Specificity**	**AUC**	**Cut off#**	**Sensitivity**	**Specificity**
sKIM-1 ng/ml	0.928*	>20	80.0	100.0	1.000*	>20	100.0	100.0	1.000*	1.000*	1.000*	1.000*	1.000*	>20	100.0	100.0	1.000*	>20	100.0	100.0
uKIM-1 ng/ml	0.996*	>28	95.56	100.0	1.000*	>28	100.0	100.0	1.000*	1.000*	1.000*	1.000*	1.000*	>28	100.0	100.0	1.000*	>28	100.0	100.0
sCr mg/dl	0.559	≤0.8	66.67	50.0	0.658	>1	31.11	100.0	0.893*	0.893*	0.893*	0.893*	0.996*	>1	95.56	100.0	1.000*	>1	100.0	100.0
surea mg/dl	0.583	≤18	84.44	40.0	0.871*	>19	80.0	80.0	0.978*	0.978*	0.978*	0.978*	1.000*	>24	100.0	100.0	1.000*	>24	100.0	100.0

AUC: Area Under a Curve*: Statistically significant at $p \leq 0.05$ #Cut off was choose according to Youden index

Sensitivity and specificity of serum and urine KIM-1 as well as kidney function parameters (serum urea and creatinine) were determined at different time of experimental schedule in order to identify which parameter more sensitive and specific at early AKI condition. It is clear to note that both specificity and sensitivity of serum and urine KIM-1 very high at 0hr (80-100%) while serum urea and creatinine were very low at 0hr (40-84%) and increase gradually to reach the maximum after 96hr as represented in table 3

Discussion

Known kidney biomarkers are serum creatinine, blood urea nitrogen, urinary microalbumin, and total volume of urine may be detected after at least 24hour of kidney injury . An early detection of AKI requires more sensitive biomarkers than the current traditional methods **(Bihorac *et al.*, 2013)**. Diagnosis of AKI in the reversible stage, depends on the time passed to detect a significant level of biomarkers as soon as the damage has been occurred**.** The specificity of these biomarkers, which are produced from the damaged renal cells and its concentration, should be proportional to the extent and level of damage **(Mårtensson *et al.*, 2012)**. **I**n our study، serum creatinine and eGFR were significantly affected after passing of 48hours because neither creatinine nor BUN can change quickly enough during injury due to the fact that individuals with normal renal function have a functional reserve which compensates for nephron injury **(Ding and Mak 2015).** The current opinion is that serum creatinine is considered to be a poor indicator of acute renal damage or injury.

Many studies found novel biomarkers that were highly specific to kidney injury as compared to another organ's injury and increases markedly with renal damage earlier than other traditional markers as serum creatinine and urea as KIM-1 **(Mårtensson *et al.*, 2012).** This biomarker which directly measures injury and can also be easily detected from body fluids like blood or urine can help to monitor injury, and could provide detailed data before the occurrence of late consequences of injury like decrease in GFR.

Strength of this work is the use of blood and urine samples obtained from an ICU hospitalized patient with different symptoms that suggest they may suffer from AKI, and start collecting sample before elevation of the traditional used biomarker creatinine.

This study found that serum creatinine level increased after 48 hour of acute kidney injury by almost one to two folds than normal subjects' value, serum urea and uric acid increased after 24 hour of acute kidney injury by one to two folds than normal subjects' value, serum Albumin decreased after 48 hour of acute kidney injury by one-fold lower than normal subjects' value, microalbuminuria start elevation after 24 hour of acute kidney injury by one to two folds than normal subjects' value, Serum Albumin/ Creatinine ratio start elevation after 24 hour of acute kidney injury by two to three folds than normal subjects' value, Estimated Glomular Filtration Rate

decreased after 48 hour of acute kidney injury by almost one-fold lower than normal .subjects' value

Both Serum KIM-1 and urine KIM-1 start elevation after 12 hours of admission to Intensive care unit in cases at high risk of acute kidney injury by one-fold than normal subjects' value, while after 24-hour Serum KIM-1 increase by three folds but Urin KIM-1 increase by almost four folds, after 48 hours Serum KIM-1 increase by four folds, but Urin KIM-1 increase seven folds, after 72 hours Serum KIM-1 increase by 5.5 folds but Urin KIM-1 increase by eleven folds, after 96 hours Serum .KIM-1 increase by 7 folds, but Urin KIM-1 increase by sixteen folds.

So in this study both urin and serum kim-1 were noticed to be increased after 12 hours while serum creatinin increase after 48 hours and it was noticed that the rate of elevation and number of folds in urinary kim-1 is higher than serum kim-1. Therefore we concluded that kim-1 is better urinary biomarker than measuring its serum value. This elevation may be due to a single transmembrane domain that undergoes membrane-proximal cleavage, which leads to the release of soluble KIM-1 ecto-domain into the urine.

These data are in agreement with previously published data (**In *et al.*, 2017**), these higher fold difference is enough to make uKIM-1 a better biomarker in urine than serum. The reason of these phenomena is happening because KIM-1 biomarker itself is localized in kidney, exactly in proximal tubule. When the kidney starts to lose its function, the ecto-domain starts to shield out and separated then excreted in urine, so only after 12 hour we will obviously notice a great increase in its urinary levels. Lower increase in serum levels of kIM-1 due to its reabsorption after separation in kidney proximal tubule, or increased genetically translation of this protein due to its role of proximal tubule injury repair people.

In the cases of urine and serum, KIM-1 measured by ELISA kit, their levels after 96 hours increased 7-9 times in serum and 16 -18 times in urine than the baseline measurement, while serum creatinine and other traditional measurements maxed out at around 3-5 times the baseline measurements. Serum KIM-1 doesn’t have light spot like urine KIM-1 so this study may give a comparing hand in comprising urinary and serum KIM-1 measured by ELISA technique.

further studies are needed to give a clear comparison and description of AKI cases by traditional and new biomarkers, which are highly agreed with our data that called a window for new biomarker of AKI. From this window, our following studies will be on genetic expression of KIM-1 molecule .

Conclusion

We have examined the renal biomarkers nowadays available for an early diagnosis of AKI. The two high-molecular weight bio-markers urine and serum kim-1 are reliable markers in early detection & diagnosis of AKI .KIM-1 is better urinary biomarker.

Both biomarkers are characterized by being reliable, non-invasive, sensitive, specific, early markers of detecting AKI and before deterioration of patient and before detection of any rise of serum creatinine to decrease mortality and improve outcome of cases when treated early. Therefore, our study recommends using these new biomarkers in prediction and early intervention to treat AKI rather than old traditional biomarkers.

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