Urinary Kidney injury molecule-1 can predict acute tubular necrosis and delayed graft function in living donor renal allograft recipients
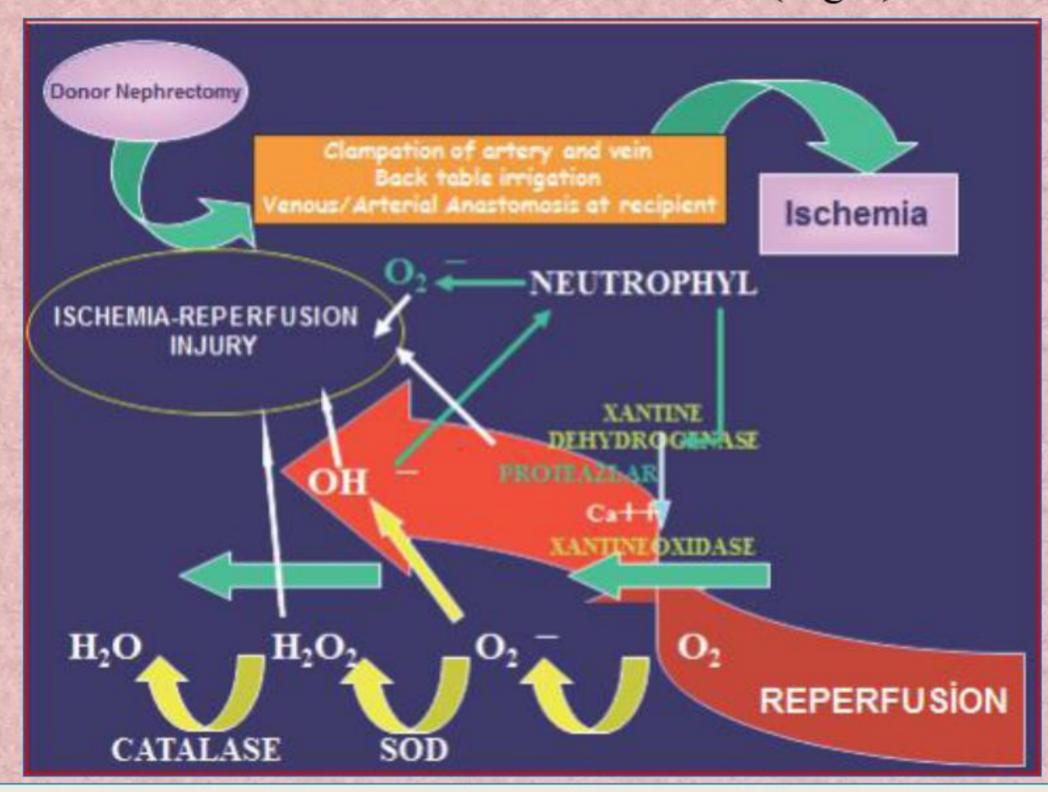
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Introduction

- Successful graft function for a long time periods depends on early and delayed graft function
- Delayed graft function (DGF)
  - A complication of early impaired graft function
  - Defined by <70% decline in serum creatinine level within 48hours of transplant,
  - Need of dialysis within 7 days after transplant
- Prevalence of DGF
  - In live related transplant is (5-10%) and
  - In cadaveric related transplant (3-40%).

- Cause for DGF
  - Acute tubular necrosis
    - Consequence of "pH paradox"
    - Free radical and reactive oxygen species mediated damage to renal tubules
- Mechanism of acute tubular necrosis(Fig.1)

- Kidney injury molecule-1
  - Single pass transmembrane glycoprotein
  - Immunoglobulin like extracellular mucine domain
  - The expression of KIM-1 upregulated after proximal tubules damage for its repairment
  - Matrix metalloproteinase cleaves ectodomaine and released in urine
- Till now the available gold standard techniques is
  - 1st Serum creatinine
    - Expressed very late until a significant damage to kidney
    - Depends on muscle mass of patient
    - Depends on patient age, gender and ethnicity
  - 2nd Biopsy of transplanted kidney
    - It is a invasive and
    - Increases the complication & jeopardized graft

Objectives

1. To determine the uKIM-1 level in urine sample of renal transplant recipient patients

2. To determine the specificity, Sensitivity, and predictive cutoff value of uKIM-1 for predicting DGF and ATN in live related renal allograft recipient

3. To determine the correlation between uKIM-1 and confounding factors of patients

4. To determine the suitability of uKIM-1 as diagnostic markers for DGF.

Materials and Methods

Patients recruitment

Live related renal transplant patient (n=56)

Immediate graft function=47	Delayed graft function=9
✓>70% Decline in serum creatinine within 48 hrs of transplant	Biopsy proven ATN
✓Patient have immediate post transplant urination >7litres	✓<70% decline in serum creatinine within 48 hrs of transplant
	✓Need of dialysis within 7 day of post transplant

- Sample collection and ELISA experiment
  Five ml urine sample was collected serially at 0, 6,12,18,24 and 48 hrs of post transplant

  Sample was centrifuged and supernatant was stored at -40 C

  ELISA was performed with urine sample with R&D duo set ELISA kit.

Statistical Analysis

- Non parametric continuous variables were analyzed by using Mann Whitney U test.
- Categorical Variables was analyzed by Chie square test.
- Correlation was calculated by Pearson correlation coefficient ,two tailed test.
- Area under curve and receiver operating curve was plotted to determine the specificity, sensitivity and cutoff value of u Kim-1 for predicting DGF and ATN
- P value <0.05 was considered to be significant.

Results

Table 1|Demographic and clinical Profiles of Patient.

Characteristic	DGF(Mean±SD)	IGF(Mean±SD)	P -value
No. of patient	9	47	
Patient age(years)	38.0±12.94	39.68±11.86	0.702
Patient Weight(kg)	63.11±7.76	54.31±8.40	0.005
Patient Height(cm)	166.33±2.73	165.63±6.33	0.749
Patient BMI(kg/m^2)	22.93±2.81	19.74±2.85	0.003
Patient.eGFR(mL/min/1.73m^2)at1week	40.35±14.43	65.39±16.91	<0.001
Donor's Age	44.00±18.17	47.87±9.29	0.481
Donor's GFR(mL/min/1.73 m^2)	41.89±12.05	45.10±14.84	0.546
Duration of dialysis (months)	10.77 ±4.11	11.36 ±4.32	0.710
Average seven days TLC	8.88 ±1.06	8.22 ±1.97	0.33
Average seven days serum creatinine(mg/dl)	2.23 ±0.798	1.37 ±0.44	<0.001
Average seven days Urine(liter)	5.21 ±1.98	7.29 ±2.19	0.011
Baseline creatinine	1.64 ±0.89	1.11 ±0.15	<0.001
Average seven days serum Tac level(ng/ml)	10.85±3.38	11.13±3.57	0.334
Cold ischemia time(minutes)	28.11±5.68	30.02±5.71	0.362
Warm ischemia time(minutes)	4.55±1.01	3.87±1.52	0.205
HLA mismatch score 0	0	6	0.499
1	2	4	
2	1	10	
3	1	17	

Tabel-2. Normalized uKIM-1/ creatinine ratio in pg/mg at different post transplant hours

Post transplant hours	DGF (Mean+SD)	IGF(Mean+SD)	P value
0 Hrs	214.48±353.66	91.99±237.09	0.197
6 Hrs	1521.88±639.53	623.76±474.90	<0.001
12 Hrs	2201.39±810.096	934.91±831.74	<0.001
18 Hrs	2863.15±809.11	792.72±296.21	<0.001
24 Hrs	3258.76±912.57	796.93±186.68	<0.001
48 Hrs	3967.45±850.04	761.38±221.52	<0.001

Results

Table 3|Receiver operating area under curve (AUC-ROC) to predict the delayed graft function and ATN.

Time after transplant	Area Under curve	Specificity %	Sensitivity%	Predictive cut off value (pg/mg)
0 Hrs	0.583	93.6	22.2	573.60
6 Hrs	0.896	80.9	88.9	1031.19
12 Hrs	0.896	83	88.9	1263.88
18 Hrs	0.998	100	89.9	2012.36
24 Hrs	1	100	89.9	2244.64
48 Hrs	1	100	89.9	2871.42

Figure 2| AUC-ROC to predict the delayed graft function and ATN.
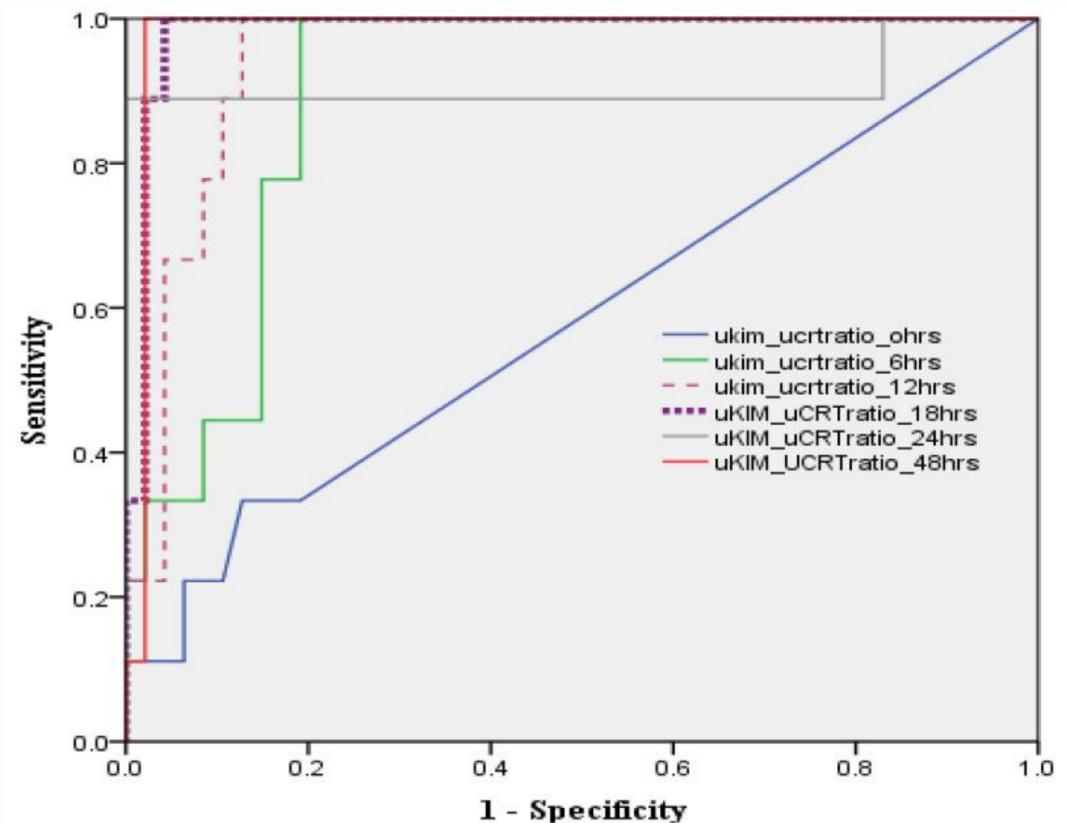

Table 4|. Urine volume at different Post transplant hours (ml)

Post transplant hours	DGF (Mean+SD)	IGF (Mean+SD)	P value
>30 min	387.02±176.96	476.50±133.35	0.227
6 Hrs	2167.33±322.59	2843.7±220.97	<0.001
12 Hrs	4395.3±383.46	5420.30±287.51	<0.001
18 Hrs	7283.55±633.11	8470.0±518.65	<0.001
24 Hrs	9584.44±728.47	11112.20±1163.4	0.004
48 Hrs	8035.22±1204.9	9845.6±932.28	0.002

Table 5| Correlation of normalized uKIM-1(ng/mg) with confounding factors of donors

Characteristics	Patient. Weight(Kg)	Patient. Height (Cm)	Patient. Age(Years)	Patient. BMI(Kg /m^2)	Seventh day eGFR	Cold ischemia time	Warm ischemia time
6 hours uKIM-1	r= 0.269 p=0.05	r=0.149 p= 0.272	r=0.003 p=0.986	r=0.175 p=0.197	r=-0.415 p=0.001	r=0.018 p=0.896	r=0.174 p=0.199
12Hours uKIM-1	r=0.115 p=0.40	r=0.008 p=0.951	r=-0.011 p=0.933	r=0.096 p=0.480	r=-0.218 p=0.106	r=-0.099 p=.466	r=0.258 p=0.055
18 Hours uKIM-1	r=0.318 p=0.017	r=0.044 p=0.746	r=-0.009 p=0.947	r=0.327 p=0.014	r=-0.498 p<0.001	r=.105 p=.440	r=0.176 p=0.194
24Hours uKIM-1	r=0.386 p=0.003	r=0.046 p=0.736	r=0.012 p=0.932	r=0.397 p=0.002	r=-0.445 p=-.001	r=-0.020 p=.833	r=0.117 p=0.390
48Hours uKIM-1	r= 0.388 p=0.003	r=-0.093 p=0.494	r=-0.045 p=0.743	r=0.377 p=0.004	r=-.473 p<0.001	r=-0.074 p=0.589	r=0.223 p=0.098

Conclusions

- Urinary Kidney injury molecule -1 is a non invasive markers of delayed graft function and acute tubular necrosis.

- At 18 hours of post transplant, uKIM-1 level can predict DGF with 100% specificity and 88.9% sensitivity at cutoff value 2012.36pg/mg.

- The level of uKIM-1 excretion do not depend on demographic and other confounding factor of patient.

- It is highly specific and sensitive markers (within 18hrs) and can be used as marker for management of renal transplant patient patient with DGF and ATN.