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Original Research Article

Urinary Kidney Injury Molecule 1 - A Marker of Kidney Injury in Renal Transplant Patients

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Conflict of interest: Nil

Abstract:

Background: Chronic kidney disease (CKD) is a public health problem, with rising incidence of kidney failure, with poor outcome. Kidney injury molecule – 1 (KIM-1) is markedly induced in acute and chronic kidney disease.

Aim: To determine the role of KIM – 1 in assessing the severity of renal injury in renal transplant recipients.

Methodology: A case control study included 45 individuals (group A) of both genders above 18 years with renal transplant recipients and 45 age and sex matched healthy subjects (group B) with normal renal function and no evidence of underlying illness as controls. In the KDIGO guidelines, based on the fluctuant serum creatinine level i.e., ≥ 0.3 mg/dL within 48 hours, the renal transplant recipients and controls were divided into those with kidney injury (≥ 0.3 mg/dL) and those without kidney injury (< 0.3 mg/dL). KIM – 1 was measured by sandwich ELISA method. Urinary KIM-1, Serum urea, creatinine, calcium, phosphate & spot urine protein creatinine ratio was analysed using spectro-photometric analysis. Serum triglycerides, HDL & total cholesterol were estimated using enzymatic colorimetric test.

Result and Conclusion: The mean urine KIM – 1 level in renal transplant recipients with kidney injury is higher than levels in recipients and controls without kidney injury. When compared with serum creatinine and urea, KIM-1 is an early biomarker of kidney injury, which becomes obvious after the kidney damage is established. It facilitates early diagnosis of kidney injury and management strategies, thereby reducing the morbidity and mortality in renal transplant recipients.

Keywords: Urinary Kidney Injury Molecule – 1(KIM-1), Renal Transplant Recipients, Serum Creatinine, Kidney Injury, Lipid Parameters.

Introduction

Chronic kidney disease (CKD) is a public health problem, with rising incidence of kidney failure, with poor outcome. CKD is the 12th leading cause of death and 17th cause of disability. [1] Once CKD has progressed to end-stage renal disease (ESRD), patients present with a lowered quality of life and high morbidity. [2]

Kidney transplant remains the treatment of choice for end-stage renal disease (ESRD) patients; it extends their survival and improves their quality of life. [3] Early diagnosis of renal allograft dysfunction is crucial for the management and long-term survival of the patients with transplanted kidney. [4]

Acute kidney injury (AKI) of the allograft can result from different etiologies. [5] Acute kidney injury or acute renal failure is a sudden impairment of kidney function, results in retention of nitrogenous waste products, during a period of few hours to several weeks. [6]

KIM-1 is markedly induced in acute kidney injury (AKI) and chronic kidney disease (CKD). KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of prognosis. [7] KIM – 1 is a trans-membrane protein found in the renal tubules, which is not detectable in the normal kidneys, but is markedly induced and expressed following renal injury. [8]

The assessment of renal function involves measurement of serum blood urea nitrogen and serum creatinine, being insensitive and nonspecific, to detect renal injury. [9] KIM – 1 is rapidly cleaved from the apical membrane of renal tubular epithelial cells and is excreted in the tubular lumen, which

is detected in the urine much earlier than the elevated blood urea nitrogen and creatinine. [10]

Aim of the study: To determine the role of urinary kidney injury molecule – 1 (KIM – 1) in assessing the severity of the renal injury in renal transplant recipients.

Primary Objectives:

- To compare the urinary KIM-1 level among renal transplant recipients and controls
- To compare the urinary KIM-1 level among renal transplant recipients with and without acute kidney injury

Secondary Objectives:

- To determine the cutoff of urinary KIM-1 in predicting the acute kidney injury
- To elucidate the role of other serum parameters in acute kidney injury andpost renal transplant recipients

Materials and Methods:

Study centre: This is a case control study conducted in the institute of biochemistry, Madras Medical College and institute of nephrology, Rajiv Gandhi Government General Hospital, Chennai between November 2017 to March 2019.

The study was conducted after obtaining proper ethics clearance from the Institutional ethics committee. 45 unrelated individuals (group A) of both genders above 18 years with renal transplant recipients, attending the outpatient department of nephrology, were included in the study after getting informed consent. 45 Age and sex matched healthy subjects (group B) with normal renal function and no evidence of acute or chronic underlying illness was selected as controls.

Methodology

Urine samples were collected in sterile tubes. The samples were centrifuged at 2500 rpm for about 20 minutes. Supernatant was carefully collected and stored by freezing at -20 o C. When sediments occurred during storage, again centrifugation was done. The serum was allowed to clot for 20 minutes at room temperature. Then the samples were centrifuged at 2500 rpm for 20 minutes. Supernatant was collected carefully and stored at -20 ^{o}C.

Urinary kidney injury molecule-1 (KIM-1) was estimated using Enzyme-linked immunosorbent assay (ELISA). Serum Urea – spectro-photometric method, Serum creatinine, calcium, phosphate & spot urine protein creatinine ratio was analyzed using spectro-photometric analysis. Serum triglycerides, HDL & total cholesterol were estimated using enzymatic colorimetric test.

Statistical analysis: Data were analyzed using SPSS software version 21. P value less than 0.05, considered statistically significant. Continuous variables were represented as mean and standard deviation and categorical variables were represented as frequency and percentages. Student t-test was used for analysis of age, gender, urine KIM-1, serum urea, serum creatinine, serum calcium, serum phosphorous, urine protein creatinine ratio (PCR) and eGFR. Pearson Correlation test was done to compare between urine KIM-1, serum urea, serum calcium, serum phosphorous, urine protein creatinine ratio and eGFR. ROC for urine KIM-1 was done to find the cut off for predicting kidney injury.

Results

The mean serum creatinine level in cases 1.36(± 0.40) mg/dL was higher than mean serum creatinine level in controls 0.64(± 0.13) mg/dL and the difference was statistically significant. ($p< 0.05$).

Table 1: Age and gender wise distribution of cases and controls

Age groups (n=45)	Group			
	Cases		Controls	
	Count	%	Count	%
< 30 Years	15	33.3%	14	31.1%
30 - 39 years	18	40.0%	7	15.6%
40 - 49 years	10	22.2%	9	20.0%
50 years &above	2	4.4%	15	33.3%
Gender (n=45)	Cases		Controls	
Male	32	71.1%	30	66.7%
Female	13	28.9%	15	33.3%

Table 2: Distribution of duration of post renal transplant duration (months) among renal transplant recipients

	N	Mean	Std. Deviation	Minimum	Maximum
Duration of Post-Transplant (months)	45	14.85	25.16	2.79	113.13

Table 3: Distribution of study parameters among cases and controls

	Group	Mean	Std. Deviation	p valueby 't' test
Serum creatinine (mg/dL)	Cases	1.36	0.40	
	Controls	0.64	0.13	< 0.001*
Urine KIM-1 (ng/mL)	Cases	4.65	2.54	
	Controls	1.93	1.41	< 0.001*
Blood Urea (mg/dL)	Cases	33.18	9.83	
	Controls	23.51	2.80	< 0.001*
e GFR (mL/min/1.73m2)	Cases	79.56	24.67	
	Controls	138.52	18.25	< 0.001*
Urine PCR	Cases	0.34	0.77	
	Controls	0.04	0.03	0.012*
Serum Calcium (mg/dL)	Cases	9.56	0.55	
	Controls	9.18	0.34	< 0.001*
Serum Phosphorous (mg/dL)	Cases	3.16	0.62	
	Controls	3.10	0.35	0.586
Total Cholesterol (mg/dL)	Cases	152.62	32.39	
	Controls	140.16	18.54	0.028*
Serum Triglycerides (mg/dL)	Cases	190.07	85.75	
	Controls	135.69	23.08	< 0.001*
	Cases	45.07	8.93	
Serum HDL (mg/dL)	Controls	48.47	6.61	0.043*

The mean urine KIM - 1 level in cases 4.65(± 2.54) ng/mL was higher than controls 1.93(± 1.41) ng/mL and the difference was statistically significant. The mean blood urea level in cases 33.18(± 9.83) mg/dL was higher than controls 23.51(± 2.80) mg/dL and the difference was statistically significant. The mean eGFR level in cases 79.56(± 24.67) mL/min/1.73m2 was lower than mean eGFR level in controls 138.52(± 18.25) mL/min/1.73m2 with statistical significance. The mean urine PCR level in cases 0.34(± 0.77) was higher than mean urine PCR level in controls 0.04(± 0.03) and the difference was statistically significant. The mean serum calcium level in cases 9.56 (± 0.55) mg/dL was higher than controls 9.18(± 0.34) mg/dL which was statistically significant. The mean serum phosphorous level in cases is 3.16 (± 0.62) mg/dL, which was higher than mean serum phosphorous level in controls 3.10(± 0.35) mg/dL and the difference was not statistically significant (p> 0.05).

The mean serum total cholesterol level in cases 152.62(± 32.39) mg/dL was higher than mean serum total cholesterol level in controls 140.16(± 18.54) mg/dL and the difference was statistically significant (p< 0.05). The mean serum triglycerides level in cases 190.07(± 85.75) mg/dL was higher than controls 135.69(± 23.08) mg/dL with statistical significance. The mean serum HDL level in cases 45.07(± 8.93) mg/dL was lower than mean serum HDL level in controls 48.47(± 6.61) mg/dL and the difference was statistically significant. (p< 0.05).

Table 4: Distribution of study parameters among renal transplant recipients with or without kidney injury and controls

	Kidney injury	N	Mean	Std. Deviation	p valueby 't' test
Urine KIM-1 (ng/mL)	Yes	18	4.49	2.64	
	No	72	2.99	2.34	0.020*
Blood Urea(mg/dL)	Yes	18	35.83	8.04	
	No	72	26.47	7.82	< 0.001*
e GFR (mL/min/1.73m^2)	Yes	18	59.28	12.18	
	No	72	121.48	29.41	< 0.001*
	Yes	18	0.29	0.70	
Urine PCR	No	72	0.16	0.53	0.386
Serum Calcium(mg/dL)	Yes	18	9.56	0.41	
	No	72	9.33	0.51	0.078
Serum Phosphorous (mg/dL)	Yes	18	3.23	0.60	
	No	72	3.11	0.47	0.334
Total Cholesterol (mg/dL)	Yes	18	148.61	37.72	
	No	72	145.83	23.88	0.769
Serum Triglycerides (mg/dL)	Yes	18	153.94	52.76	
	No	72	165.11	71.64	0.537
	Yes	18	43.39	9.62	
Serum HDL(mg/dL)	No	72	47.61	7.37	0.096

The mean urine KIM - 1 level in renal transplant recipients with kidney injury 4.49(± 2.64) ng/mL was higher than mean urine KIM - 1 level in renal transplant recipients and controls without kidney injury 2.99(± 2.34) ng/mL and the difference was statistically significant.

The mean blood urea level in renal transplant recipients with kidney injury 35.83(± 8.04) mg/dL was higher than mean blood urea level in renal transplant recipients and controls without kidney injury 26.47(± 7.82) mg/dL and the difference was statistically significant . The mean eGFR level in renal transplant recipients with kidney injury 59.28(± 12.18) mL/min/1.73m^2 was lower than mean eGFR level in renal transplant recipients and controls without kidney injury 121.48(± 29.41) mL/min/1.73m^2 and was statistically significant. The mean urine PCR level in renal transplant recipients with kidney injury 0.29(± 0.70) was higher than mean urine PCR level in renal transplant recipients and controls without kidney injury 0.16(± 0.53) and the difference was not statistically significant. The mean serum calcium levels in renal transplant recipients with kidney injury 9.56(± 0.41) mg/dL, was higher than mean serum calcium levels in renal transplant recipients and controls without kidney injury 9.33(± 0.51) mg/dL which was not statistically significant.

The mean serum phosphorous levels in renal transplant recipients with kidney injury 3.23(± 0.60) mg/dL was higher than mean serum phosphorous levels in renal transplant recipients and controls without kidney injury 3.11(± 0.47) mg/dL and the difference was not statistically significant. The mean serum total cholesterol levels in renal transplant recipients with kidney injury 148.61(± 37.72) mg/dL was higher than mean serum total cholesterol levels in renal transplant recipients and controls without kidney injury 145.83(± 23.88) mg/dL, and was not statistically significant. The mean serum triglycerides levels in renal transplant recipients withkidney injury 153.94(± 52.76) mg/dL was lower than mean serum triglycerides levels in renal transplant recipients and controls without kidney injury 165.11(± 71.64) mg/dL and the difference was not statistically significant . The mean serum HDL levels in renal transplant recipients with kidney injury 43.39(± 9.62) mg/dL was lower than mean serum HDL levels in renal transplant recipients and controls without kidney injury 47.61(± 7.37) mg/dL and the difference was not statistically significant.

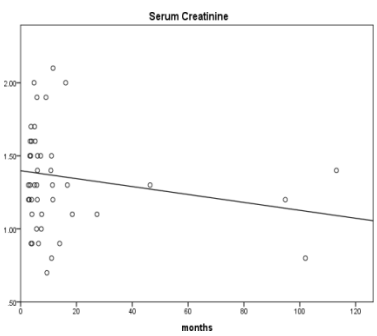


Figure 1a

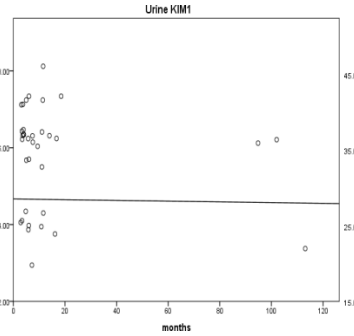


Figure 1b

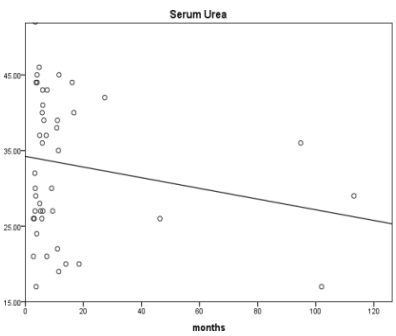


Figure 1c

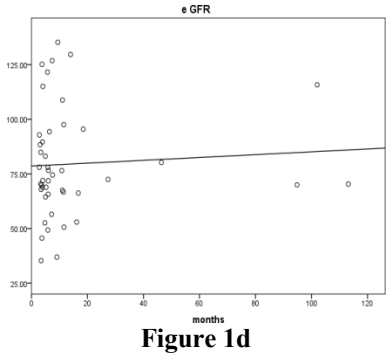
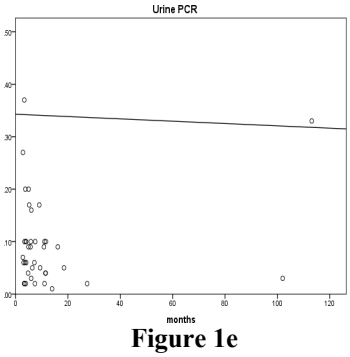


Figure 1d



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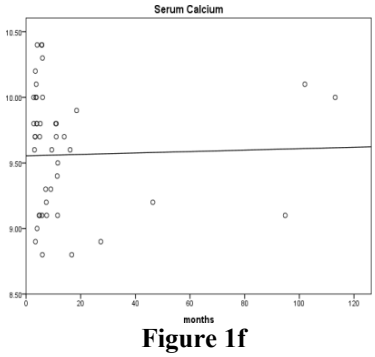

Figure 1f

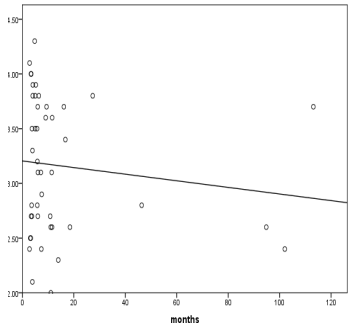

Figure 1g

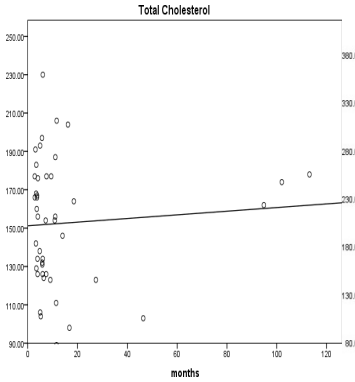

Figure 1 h

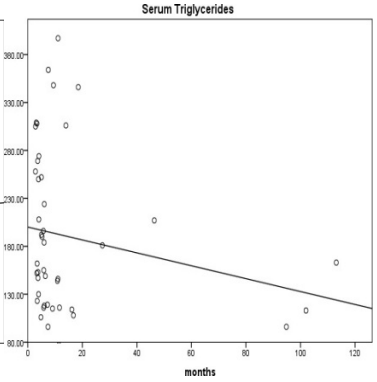

Figure 1i

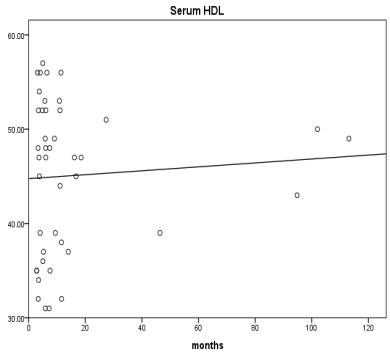

Figure j

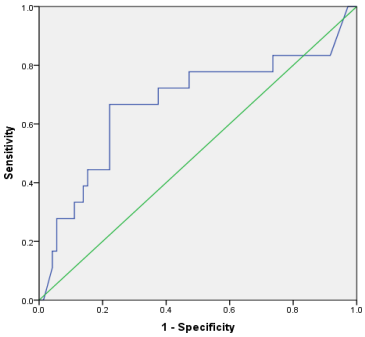

Figure k

Figure 1: Pearson's correlation between study parameters and the duration of post-transplant in renal transplant recipients

Figure 1a shows the negative correlation (r = - 0.173) between serum creatinine level (mg/dL) and duration of post-transplant (months) in renal transplant recipients but the correlation was not statistically significant. There was a negative correlation (r = - 0.009) in figure 1b between KIM – 1 level (ng/mL) and duration of post-transplant (months) in renal transplant recipients and did not show any statistical significance. In figure 1c there was negative correlation (r = - 0.181) between serum urea level and duration of post-transplant (months) in the renal transplant recipients but the correlation was not statistically significant.

There was a positive correlation (r = 0.066) between eGFR level and the duration of post-transplant in renal transplant recipients (figure 1d) but the correlation was not statistically significant. A negative correlation (r = - 0.007) between urine PCR level and duration of post-transplant (months) among the cases was shown in figure 1e, but the correlation was not statistically significant.

There was positive correlation (r = 0.025) between serum calcium level (mg/dL) and duration of post-transplant (months) in renal transplant recipients, but was not statistically significant in figure 1f. There was negative correlation (r = - 0.123) between serum phosphorus level (mg/dL) and duration of post-transplant (months) in the renal transplant recipients but the correlation was not statistically significant (figure 1g). Also a negative correlation (r = -0.074) exists between total cholesterol and duration of post-transplant among the cases but the correlation was not statistically significant (figure 1h). Figure 1i showed a negative correlation (r = - 0.197) between serum triglyceride level (mg/dL) and duration of post-transplant (months) in renal transplant recipients but the correlation was not statistically significant. There was positive correlation (r = 0.059) between serum HDL cholesterol level (mg/dL) and duration of post-transplant (months) in the renal transplant recipients but the correlation was not statistically significant (figure j).

Discussion

Biological markers for renal tubular injury are essential to detect early kidney injury and facilitate timely management. The test commonly done to detect kidney injury is serum creatinine.11 Serum creatinine has numerous limitations as marker of kidney injury, which affects its early diagnosis. Alarming levels of serum creatinine is detected after almost 50% of renal cell death has occurred. Serum creatinine levels are insensitive to small changes in GFR12. Hence it is not a novel marker for early detection of renal injury. Ideal biological markers of kidney injury are essential, which should meet the purposes such as early detection of kidney injury, identify the severity of kidney injury and to guide in the line of management. To the best of our knowledge, this study is the first case control

study on urinary KIM-1 excretion as potential biomarker for early detection of kidney injury among renal transplant recipients. So far two prospective studies done by Liangos et al., [13] and Van Timmeren et al., [14] in the year 2007 acknowledged the significance of KIM-1 among renal transplant patients. Van Timmeren et al., in the year 2007 stated that in addition to creatinine levels, determining urinary KIM-1 excretion gives a added value to identify the patients at risk for renal allograft failure [13]. A cohort study done by Liangos et al., among 201 hospitalized renal failure patients showed that KIM-1 serves as a predictor for adverse clinical outcomes. They determined that patients in the highest KIM-1quartile had 3.2-fold higher odds for dialysis requirement or hospital death than patients in the lowest quartile [14].

In the present study tables 1 and 2 showed the difference between the groups with respect to age and gender. Majority of renal transplant recipients were less than 50 years of age with male predominance in our study. Based on the serum creatinine level, the renal transplant recipients in the study were further divided into patients with kidney injury and without kidney injury. Serum creatinine was measured at the time of collecting the urine sample for KIM-1. Subsequently the second sample for estimating serum creatinine was drawn at 48 hours after the first sample. The recent KDIGO (Kidney Disease Improving Global Outcome) [15 guideline for acute kidney injury was laid down based on the fluctuant serum creatinine level i.e., ≥ 0.3 mg/dL within 48 hours. Based on the KDIGO guideline the renal transplant recipients and controls in the study were divided into those with kidney injury (serum creatinine rise ≥ 0.3 mg/dL) and those without kidney injury (serum creatinine rise < 0.3 mg/dL). The mean duration of post-transplant was 14 months, a major group of renal transplant recipients were less than 12 months duration.

In our study the mean urine KIM – 1 level in renal transplant recipients with kidney injury was higher than renal transplant recipients and controls without kidney injury. It is evidenced by the ROC plotted with a cut off for urine KIM – 1 level to diagnose kidney injury is 4.26 ng/mL with a sensitivity of 66.7% and specificity of 78.8%, showing urine KIM-1 to be a specific biomarker for kidney injury (figure k). In addition to the findings of our study Samia and Manal in the year 201516 revealed that KIM-1 might be a specific predictor for early detection of kidney inflammation, in diabetic disease where no sign of kidney inflammation was persisted, and in diabetic nephropathy disease. They also stated that KIM-1 is expected to be a therapeutic target for kidney injury.

The higher levels of mean Sr.urea Sr.calcium Sr.phosphorous and PCR in renal transplant patients with kidney injury might be due to failure of its excretion by the injured kidneys in the present study. Also the reduction in the filtration pressure could be the probable cause for more reduction in the eGFR among renal transplant patients with kidney injury than controls and patients without kidney injury in the current study [17]. Lipid profile parameters viz., serum total cholesterol, serum triglycerides and serum HDL cholesterol were statistically significant when compared between the renal transplant recipients and controls. Whereas the difference was not statistically significant, while comparing the renal transplant recipients with/without kidney injury and controls. To date, there is only limited evidence for an association of lipid accumulation with kidney disease. However increased lipid levels could lead to structural and functional changes in cells of the juxtaglomerular apparatus, podocytes and renal tubules [17].

Pearson Correlation done to compare between duration of post transplantation with study parameters which showed a negative correlation between KIM-1, serum urea, serum creatinine, serum phosphorous, PCR, total cholesterol and triglycerides though not statistically significant. Despite of positive correlation between eGFR, serum calcium, HDL cholesterol with duration of post transplantation they did not show any statistically significant correlation. The probable cause might be due to the slower reaction of these parameters when compared to others among post-transplant patients [18].

Conclusion

This study which was undertaken in renal transplant recipients shows that urinary Kidney Injury Molecule – 1 (KIM-1) is an early biomarker of kidney injury, when compared with serum creatinine and blood urea, which becomes obvious after the kidney damage is established. Urine KIM – 1 facilitate early diagnosis of kidney injury and management strategies, thereby reducing the morbidity and mortality in renal transplant recipients.

Limitations of the study

- Small sample size
- Urinary KIM – 1 could have been analyzed at an earlier period, immediately after renal transplant.
- Periodic evaluation of serum creatinine on daily basis could not be done due to inability to access the renal transplant recipients.

Future scope of study

Further studies can be done to assess KIM – 1 as not only kidney injury marker but also in phagocytosis, apoptosis and immunological function. Newer analytical methods can be developed to estimate KIM-1 in urine and serum. Novel drug targets and advancement in pharmacological interventions reduce the disease burden and mortality. Further studies can be done on urinary KIM – 1 to analyze

any difference in gender, ethnicity and genetic characteristics. KIM – 1 may be considered as a screening tool in individuals with predisposing causes of kidney damage to initiate effective and timely managementand reduce the existing morbidity as well as eventual mortality.

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