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Kidney injury molecule-1; is it a predictive marker for renal diseases?

Deepashree Goravigere Anandkumar[1], Prashant Chippalkatti Dheerendra[1], Deepesh Vellakampadi[1], Gnanasambandan Ramanathan[2*]

[1]Consultant Nephrologist and Transplant Physician, Apollo Hospitals, Bannerghatta Road, Bangalore-560076, India
[2]School of Biosciences and Technology, Vellore Institute of Technology, Vellore-632014, Tamilnadu India

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ABSTRACT

Kidney injury is the main cause of mortality and morbidity globally. The kidney injury molecule (KIM-1) is a type 1 transmembrane protein, which is been upregulated during renal injury at high levels in urine, serum, plasma, and tissues and plays a crucial role in the pathogenesis of renal diseases. Kidney injury molecule has been used as a marker for the diagnosis of renal disease at an early stage as well as to predict the progression of disease with a clinical outcome. This review article aims to discuss and summarize the available literature data regarding KIM-1 being a potential marker for diagnostic, therapeutic, and prognosis of clinical outcomes and management in kidney diseases. We also discuss the relationship between KIM-1 and kidney injury in a few common renal diseases such as acute pyelonephritis, acute tubular nephrosis (ATN), diabetic kidney disease (DKD), acute kidney injury (AKI), chronic kidney disease (CKD), and other pathologies.

Review

Implication for health policy/practice/research/medical education:
This review adds to the body of work on kidney injury molecule 1 on different types of kidney diseases in different ethnic groups. Further, we summarize the literature data regarding KIM-1 being a potential marker for diagnostic, therapeutic, and prognosis of clinical outcomes and management in kidney diseases.

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Introduction

Renal disease results from damage to the kidneys thus losing their normal function of filtration of wastes in the body. Renal injury may be caused due to hereditary defects, immunologic reactions, or exposure to certain drugs. Lifestyle changes have an impact on modifying behavioral risk factors, development, and progression of kidney disease. As per World Health Organization (WHO), around 850 million people affected kidney related diseases, and have risen to the world's 13th leading cause of death. Further, the morbidity and mortality rate has increased from 813 000 in 2000 to 1.3 million in 2020 (1). As per GBD India, the number of cases of kidney diseases has increased from 7 008 675 in 2015 to 7 519691 in 2019 with males being affected more than females. Tamil Nadu and Uttar Pradesh have the most disability-adjusted life years concerning kidney disease. The main aim for treating kidney disease is its early detection to begin the therapy at early as possible. The research for the identification of early biomarkers to detect renal damage is a crucial and effective treatment for major renal clinical disorders, including acute kidney injury (AKI), diabetic kidney disease (DKD), chronic kidney disease (CKD), and other renal pathologies (2). Assessment of kidney function is based on a few laboratory tests which include serum creatinine, estimation of glomerular filtration rate (eGFR), blood urea nitrogen (BUN), albuminuria, and proteinuria. Most of these clinical biomarkers level tend to appear after 48-72 hours of severe renal injury which is disappointing. To aid in the early detection, differential diagnosis, and prognosis of kidney diseases, several promising kidney injury biomarkers have been

***Corresponding author**: Gnanasambandan Ramanathan, Email: gnanasambandan.r@vit.ac.in, gnans05@gmail.com

researched. These include liver-type fatty acid-binding protein (L-FABP), neutrophil gelatinase-associated lipocalin (NGAL), interleukin 18 (IL-18), and tubular enzymes like N-acetyl-β-D glucosaminidase (NAG), and γ-glutamyltransferase. Out of which kidney injury molecule-1 appears one of the promising indicators (2). KIM-1, often termed as T-cell immunoglobulin mucin-1 and hepatitis A virus cellular receptor is expressed during ischaemic or toxic injury whereas in healthy kidneys it is undetectable. The mechanism behind the loss of renal function and expression of KIM-1 remains unclear. Several pieces of evidence indicate KIM-1 as a sensitive and specific marker for a renal injury which can predict disease progression in AKI and CKD (3). Table 1 summarizes the studies conducted so far on various kidney diseases linked with KIM 1.

Rat models exposed to nephrotoxic substances like gentamicin, mercury, and chromium, were shown the urine KIM-1 to be more sensitive than serum creatinine, BUN, and urinary NAG for identifying AKI (55). Clinical and preclinical studies were shown that the urinary KIM-1 has an excellent indication for early detection of tubular damage. This review aims to discuss and summarize the available literature data regarding KIM-1 as a possible indicator for the diagnosis of renal disease at an early stage as well as to predict the progression of disease with a clinical outcome. Further, we discussed the relationship between KIM-1 and kidney injury in a few common renal diseases.

Methods

Literature data were searched using the key terms: KIM-1, association, biomarker, renal diseases, acute kidney injury, chronic kidney disease, lupus nephritis, nephrotic syndrome, kidney stones, polycystic kidney disease, renal cell carcinoma, diabetic nephropathy, urinary tract infection, pyelonephritis, and hydronephrosis published in PubMed, NCBI, Google scholar and web of science till September 2022. The article was published in English and full-length studies were included in this review.

KIM-1 structure

The integral membrane protein of KIM-1 is expressed in the testis, liver, and kidney. It expands 104 kDa peptide, composed of 90 kDa soluble portions and 14 kDa membrane-bound fragments. The extracellular region has a six-cysteine immunoglobulin-like rich domain, two N-glycosylation sites, and a Thr/Ser-Pro-rich domain which is specific to mucin-like O-glycosylated proteins. Similarly, the Kim-1 gene is expressed by the activation of CD4+T-cells during the helper T-cell response development. KIM-1 is often termed T-cell immunoglobulin mucin domain-1 (TIM-1) due to its expression in low levels of activated T cells. TIM-1 is a cell surface molecule of T cells that can enhance cytokine production and T-cell proliferation. The cytoplasmic region has two short splice variants, KIM-1a and KIM-1b. Tyrosine kinase phosphorylation is lacking in the KIM-1a variant which is expressed in the liver. KIM-1b has a tyrosine kinase phosphorylation motif and two conserved tyrosine residues which are expressed in kidneys (56).

Human and rat cDNAs encoding KIM-1 (in rats) were first identified using analysis between ischemic injury kidneys and normal kidneys followed by proximal tubular cell regeneration. KIM-1 is found to be less expressed or sometimes at undetectable levels in the rat kidney of adults. In response to ischemic or toxic kidney injury, it is found to be expressed by proximal tubular epithelial cells (57). Cytogenetic procedures like immunohistochemistry and *in situ* hybridization showed KIM-1 as an indicator of regeneration and proliferation in proximal tubules (58). *In vivo* studies on rats and rodents models observed the KIM 1 ectodomain cells in urine due to proximal tubular injury (59).

Molecular mechanism of KIM-1 in renal diseases

KIM-1 expression gets elevated when there is kidney injury resulting from hypoxia, toxicity, ischemia, and polycystic kidney disease and thus acts as a marker for kidney damage. The majority of KIM-1-expressing cells are found in proximal renal tubular epithelial cells that can regenerate following a kidney injury, particularly in the proximal tubule S3 outer medulla region. Mitogen-activated protein kinase (MAPK) signalling pathways cause the extracellular region of KIM-1 to be released into the renal tube cavity and then further shed into the urine after renal tubular cells are damaged (56). As a result, a disintegrin and metalloprotease (ADAM) and membrane matrix metalloproteinases (MT-MMPS) get activated (60) as shown in Figure 1. Thus, measurement of KIM-1 expression might help in the early diagnosis of CKD and AKI.

Figure 1 shows the molecular mechanism of KIM-1 in renal disease. KIM-1 expression is seen in the proximal convoluted tubule after renal injury phagocyting apoptotic cells. This leads to extracellular domain shedding and enhances apoptotic bodies and necrotic debris phagocytosis. Renal injury due to radiation, mitochondrial damage, or inflammasomes (IL-6, IL-1β, tumour necrosis factor α [TNFα]) results in renal damage which exhibits reduced phosphorylation of ERK resulting in increased phosphorylation of STAT3 downstream. These changes upregulate KIM-1 which leads to renal cortex damage. This activates ADAM and membrane-type matrix metalloproteinases (MT-MMPS) which is associated with inflammation, epithelial-mesenchymal transition (EMT), cell proliferation, angiogenesis, and apoptosis. The ERK/STAT3-KIM-1 pathway is suggested to play role in renal injury.

a. KIM-1 and AKI

KIM-1 expression levels are very high in acute renal

Table 1. Tabulates the existing literature on KIM-1 used as a biomarker for the detection of renal diseases

Disease	Population	Sample	Type of study	Outcome/Conclusion	Ref.
AKI	Cardiopulmonary bypass patients, New York	Urine	Prospective	Can be used as a marker for detecting early AKI post-cardiac surgery.	(4)
	Cardiac surgery patients, Chicago	Urine	Prospective	Can determine the prognosis of AKI and detect early AKI	(5)
	Sprague Dawley rats	Tissue	Animal	Helps to know the disease progression in rats having AKI.	(6)
	AKI patients	Urine		Can predict the prognosis of traumatic AKI patients.	(7)
	Sepsis patients	Urine	Prospective cohort	Higher uKIM-1 predicts mortality risk scores in septic AKI patients.	(8)
	Sepsis patients	Urine	Prospective	Can be used as a diagnostic marker and as well as determine prognosis in septic AKI patients.	(9)
	Mice, Rat, Human	Plasma, serum	Prospective	Can predict early AKI post-cardiac surgery.	(3)
CKD	Fischer rats	Serum	Animal	Has association with SCr, can serve as a marker for CKD	(10)
	African American & Caucasian people with atherosclerosis risk	Urine	Case-control	Cannot serve as a marker to predict CKD risk.	(11)
	South Sri Lankan farmers	Urine	Cross-sectional	Can predict renal injury among farmers.	(12)
	Male BALB/c mice	Urine	Animal	Can detect postischemic kidney injury.	(13)
LN	LN patients	Urine		Has an association with kidney injury indices, and can predict tubulointerstitial lesions.	(14)
	LN children	Urine	Cross-sectional study	Helps to predict renal activity index among children and adults of LN	(15)
	Healthy children	Urine		Has a positive association with age to predict LN activity in paediatric.	(16)
	LN patients	Urine	Cross-sectional study	Can serve as a maker for LN	(17)
	LN patients	Urine	Cross-sectional study	Correlates with tubular damage, and proteinuria in active LN group.	(18)
	LN patients	Urine		Can predict tubular injury in LN groups.	(19)
NS	NS patients	Urine	Cross-sectional	Capable of differentiating ATN and AKI in LN patients	(20)
	Children	Urine		Can predict tubulointerstitial fibrosis and has a positive correlation with proteinuria in SRNS.	(21)
Kidney stones	Kidney stone patients	Urine	Pilot study	Can predict tissue injury post SWL treatment.	(22)
	PNL patients	Urine	Randomized & prospective controlled	Can serve as a marker to predict AKI in renal stone patients after percutaneous surgery.	(23)
PKD	Advanced CKD	Urine	Prospective, randomized	Has no association with htTKV, has an independent association with eGFR decline	(24)
	Rat	Tissue	Animal	Role in cellular injury in PKD not established.	(25)
	Constructs and plasmids	Tissue		Acts as a regulatory molecule in flow-induced calcium signaling.	(26, 27)
	Mice	Tissue	Animal	Has a role in nephron loss and develops interstitial fibrosis in murine ADPKD	(28)
RCC	RCC patients	Tissue		Has a role in tumour growth, and angiogenesis.	(29, 30)
	ccRCC patients	Tissue & Urine	Prospective cohort	Correlates with tumour grade, lymphovascular invasion, and Sensitive marker for ccRCC.	(31)
	RCC patients	Plasma	Prospective cohort	Predicts RCC but did not correlate with survival rate.	(32)
	ccRCC patients	Plasma		Has high sensitivity to detect ccRCC	(33)
	RCC patients	Urine	Prospective	Can be a marker for RCC	(34)

Table 1. Continued

Disease	Population	Sample	Type of study	Outcome/Conclusion	Ref.
DN	T2D patients	Urine	Pilot study	Correlates with SCr, microalbuminuria.	(35)
	T1D patients	Urine	Cross-sectional	Correlates with resistivity index (RI)	(36)
	T1D patients	Urine	Cross-sectional	Can predict tubular damage.	(37)
	T2D patients	Urine	Cross-sectional	Can predict early renal damage	(38)
	T2D patients	Urine	Cross-sectional	No significant difference between control and normoalbuminuric groups thus cannot serve as a marker.	(39)
	T1D patients	Urine	Mendelian Randomization	Could not detect ESRD progression.	(40)
	Diabetic rats	Plasma		Levels dropped on treatment with strawberry leaves.	(41)
UTI	UTI patients	Urine	Observational case-control	Cannot serve as a biomarker for detecting/differentiating upper and lower UTIs.	(25)
	fUTI children	Urine	Prospective	Helps in the diagnosis of fUTI in children of age.	(42)
	Children	Urine	Prospective	Had a negative association with UTI in febrile and non-febrile infants.	(43)
	Wister rats	Urine	Animal	Can be used to diagnose fUTI in children.	(44)
	UTI children	Urine	Prospective	Cannot serve as a marker for AKI in UTI children. More sensitive for ischemic injury	(45)
	UTI patients	Serum & Urine	Cross-sectional	Couldn't predict AKI in UTI adults	(46)
	Children	Serum	Prospective	Had a positive association with predicting febrile UTI but had a negative association with non-febrile UTI in infants.	(47)
PN	Children	Urine	Prospective	Cannot predict APN in fUTI children.	(43)
	APN patients	Urine	Prospective	Cannot serve as a marker for AKI in PN patients.	(48)
HN	HN patients	Urine	Prospective cohort	Can serve as a marker for AKI in HN as well as measure renal injury.	(49)
	Children	Urine		Cannot serve as a marker for ON in HN children.	(50)
	Children	Urine	Prospective case-control	Has an association with obstruction worsening.	(51)
	Children	Urine	Prospective case-control	Has an association with tubular damage, renal fibrosis, and a negative correlation with DRF	(52)
	Pediatric patients	Urine	Prospective case-control	Not significant in predicting renal dysfunction in HN.	(53)
	Neonates	Urine	Prospective case-control	Can predict obstructive HN in neonates.	(54)

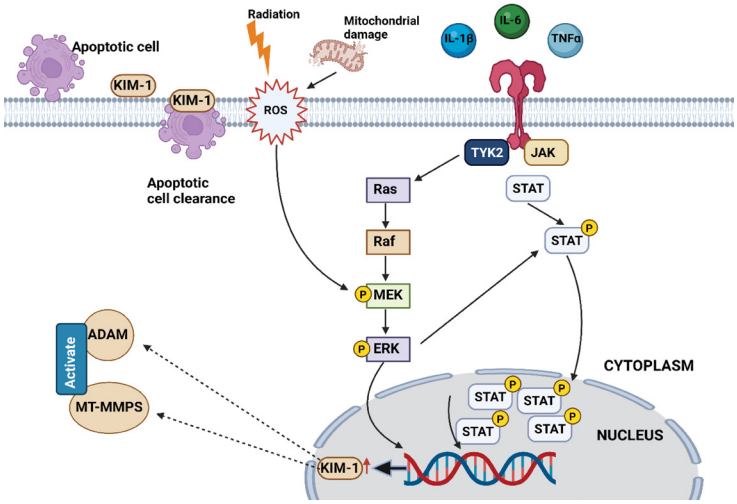

Figure 1. The molecular mechanism of KIM-1 in renal disease. It is mainly involved in MAPK and JAK/STAT pathways and ultimately activates ADAM and MT-MMPS.

tubular injury patients compared to the general population. According to the proposed mechanism, acute renal damage starts the phosphorylation of STAT3 and signal transducer and activator of transcription 3 (ERK1/2). Afterward, nuclear STAT3 binds to the KIM-1 promoter and raises the level of its mRNA and protein (61). The increase in the level of KIM-1 is an indication of declined eGFR and kidney damage. KIM-1 can be beneficial by having a protective role in renal tubules in the early stages of AKI. It can prevent renal ischemia damage by preventing GTP loading and reducing Gα12 activation (62).

b. KIM-1 and CKD

KIM-1 acts as a sensitive biomarker for CKD. Its overexpression is correlated to rapid kidney disease progression, hypertension, and inflammation of the renal tubules. According to animal studies, KIM-1 overexpression increases macrophage chemotaxis, which further encourages fibrosis and renal tubular inflammation (63). A study on clinical samples showed that the increase in KIM-1 favored the increase in renal M1-dependent mRNA expression of FNG (interferon gamma) and INOS (nitric oxide synthase 2). There was an increase in TNF-α and IL-6 and a decrease in Arg1 (arginase 1), IL-4, and IL-10 in the blood which plays a significant role in the MAPK pathway (64).

c. KIM-1 and DKD

The KIM-1 expression is elevated in the early stage of DKD mostly in the capsule of the proliferative parietal epithelium. The overexpression of KIM-1 is correlated to podocyte injury and proteinuria. The levels of MCP-1 and KIM-1 in the urine can both indicate the inflammation and be connected to how well the glomeruli are prognosticated in anti-neutrophil cytoplasmic antibodies (ANCA)-associated glomerulonephritis (65).

KIM-1 in acute kidney injury

Acute kidney injury is a kidney disease in which the plasma creatinine concentration is increased over a baseline of ≥50% within 7 days or serum creatinine increased by 0.3 mg/dL in 2 days. AKI is diagnosed based on serum creatinine concentration and urine output, in which the detection of kidney damage may be delayed. KIM-1 plays an important role in detecting AKI. Different analysis was performed in mRNA populations between normal kidneys and regenerating kidneys (after reperfusion or ischemic). It was found that KIM-1 mRNA and proteins are expressed at an increased level in proximal tubular epithelial cells (66). Urinary kidney injury molecule-1 levels were higher (0.68 and 0.65) 3h post cardiac surgery. This helps to predict AKI before serum creatinine (Scr) increases after cardiac surgery (4). Urinary kidney injury molecule-1 values measured at the time of initial development of AKI, preoperative baseline, and postoperative were compared but showed poor prediction for the disease progression. This helps in the early detection of AKI and helps in determining the prognosis of the disease (5). A cisplatin drug toxicity study with AKI rats was done to know the KIM-1 function as an indicator for disease progression. Positive immunostaining was observed after 1 day and had increased uKIM-1 levels indicating tKIM-1 as an early indicator for AKI (6). uKIM-1 levels significantly increased along with the stages of AKI. Urinary kidney injury molecule-1 were higher in deceased patients (8.9 ± 0.5 ng/L) compared to livings (6.4 ± 1.1 ng/L). The sensitivity and specificity of uKIM-1 were 77.5% and 79.5% respectively, indicating KIM-1 as a predictor for traumatic acute kidney injury (TAKI) with renal replacement (SLED-sustained low-efficiency dialysis) (7). Urinary kidney injury molecule-1 levels higher than 7.3 ng/ml can be used to predict death risk in AKI patients. Higher KIM-1 levels indicate a poor prognosis of kidney function. It can further be used as a diagnostic marker for

septic AKI (8). A study shows blood KIM-1 levels were higher in mice after 3 hours of reperfusion, and after gentamicin treatment and human plasma KIM-1 levels were elevated in post-cardiac surgery indicating KIM-1 as an early blood-based marker for AKI (3).

KIM-1 in chronic kidney disease

Chronic kidney disease is a condition where there is long-term loss of kidney function due to decreased GFR. A study was conducted in various age groups on Fischer rats with ad libitum diet or calorie-restricted diet to know the relationship between KIM-1 as a biomarker for CKD by using the structural equation modeling (SEM) technique. It showed that the older the age more is the rat prone to kidney damage. KIM-1 has a positive correlation with serum creatinine indicating that KIM-1 is a marker for CKD (10). uKIM-1 levels had no association with CKD progression. It was seen in a study that uKIM-1 levels were higher in the Sri Lankan farmer population despite ACR normal levels (<30 mg/g) indicating early tubular damage, probably CKD among the agricultural community (12). Similarly, uKIM-1 levels were elevated and found to be related to tKIM-1 levels correlating with kidney tissue damage in rats having CKD (13).

KIM-1 in lupus nephritis

Systemic lupus erythematosus is an autoimmune disease that causes various tissue and organ damage leading to lupus nephritis (LN) (a form of glomerulonephritis). Urinary KIM-1 levels were higher in LN compared to controls ($P < 0.001$). Urinary kidney injury molecule-1 levels were decreased in LN after remission and there was no significant difference between controls. Urinary kidney injury molecule-1 levels were associated with Scr (r = 0.294, $P = 0.002$), proteinuria (r = 0.434, $P < 0.001$) and eGFR (r = -0.300, $P = 0.002$). Urinary kidney injury molecule-1 levels were increased more in the presence of cellular crescents (r = 0.355, $P < 0.001$) than endocapillary hypercellularity (r = 0.230, $P = 0.016$), tubular atrophy (r = 0.208, $P = 0.030$). Urinary kidney injury molecule-1 was higher in active tubulointerstitial lesions (0.458 ng/mg Cr [0.063-2.191]) than in chronic tubulointerstitial lesions (0.117 ng/mg Cr [0.071-0.168]). The increase in uKIM-1 helped in predicting tubulointerstitial lesions and kidney injury in LN and renal outcomes (14). Urinary kidney injury molecule-1 was elevated in LN patients as well as in kidney biopsy samples showing endocapillary hypercellularity. Urinary kidney injury molecule-1 can be used as a marker for renal activity index for lupus nephritis (RAIL) in children and young adults (15). Furthermore, the level of KIM-1 was studied in association with age and gender. Urinary kidney injury molecule-1 increases with the progression of age and can be used as a RAIL marker in monitoring LN in pediatrics as well as adults. Urinary kidney injury molecule-1 levels were higher in active LN patients (0.27 [0.36] ng/mg Cr) compared to non-LN patients (0.19 [0.17] ng/mg Cr). Except for complement C4, uKIM-1 (urinary KIM-1) correlated for selected immunological markers like (anti-ds DNA, complement C3, Uprot/Ucreat ratio, SLEDAI, and rSLEDAI. Urinary kidney injury molecule-1 had low sensitivity and specificity in differentiating LN patients and controls (17). The systemic lupus erythematosus (SLE) patients with active LN had increased uKIM-1 levels and tKIM-1 expression (6.7 ±0.5 versus 3.8 ±0.9 ng/day) when compared to inactive LN (7.7 ± 6.5 versus 2.3 ± 2.1 ng/day). The increase in the level ok KIM-1 helps us to know the severity of SLE patients in LN groups. Estimation of KIM-1 can predict glomerular nephritis, tubulointerstitial inflammation, renal damage, and tubule atrophy (18). Urinary kidney injury molecule-1 levels correlate with the risk of tubular interstitial injury and gene expression of urinary KIM-1 is related to tissue KIM-1 in LN patients (19).

KIM-1 in nephrotic syndrome

Nephrotic syndrome is characterized by increased proteinuria (>40 mg/m^2 hour) caused due to damage to the basement membrane in the renal glomerulus (67). Nephrotic syndrome patients with AKI had higher uKIM-1 level (4254 [815-9534] pg/mL) than compared to control (1006 [202-2539] pg/ml, $P = 0.009$). Urinary kidney injury molecule-1 had a positive correlation (r =0.4884 95% CI 0.1856 to 0.7065, $P = 0.0008$) with the histological lesions of the renal cortex in acute tubular nephrosis (ATN) patients with nephrotic syndrome. This uKIM-1 can help detect the complication in nephrotic syndrome leading to AKI or ATN (20). The uKIM-1/creatinine ratio was higher in children with idiopathic nephrotic syndrome ($P<0.02$) compared to controls. The uKIM-1/creatinine ratio was higher in children with steroid-resistant nephrotic syndrome (SRNS) ($P=0.02$) compared to children with steroid-dependent nephrotic syndrome. Urinary kidney injury molecule-1 excretion in children with idiopathic nephrotic syndrome indicates that they are at risk of developing proximal tubular injury (tubulointerstitial fibrosis) due to the correlation of uKIM-1, proteinuria, and children with SRNS which can develop early kidney damage (21).

KIM-1 in kidney stones

Kidney stones are a urological disorder in which crystal concretions are formed in the kidneys, with a higher risk of end-stage renal disorder (ESRD). uKIM-1 levels were higher in patients with kidney stones irrespective of stone size compared to normal individuals. A higher concentration of uKIM-1 was seen in kidney stone patients before shockwave lithotripsy (SWL) and the concentrations were back to baseline level after 2 weeks of s SWL ($P < 0.01$). There was no difference in uKIM-1 levels in samples of patients before and after ureteroscopy (fURS). Baseline voided urine samples had higher uKIM-1

compared to controls ($P < 0.01$). The decrease of uKIM-1 after SWL indicates the end for enzymatic leak and cellular injury and it does not reflect the residual damage (22). The KIM-1/Cr value was measured in patients with kidney stones who underwent percutaneous nephrolithotripsy (PNL) procedures. There was no significant difference ($P > 0.05$) between values of preoperative (2.12 ± 0.98) and 2 hours after PNL (3.32 ± 1.78). Mean values of KIM-1/Cr,24 hours post PNL (4.47 ± 2.41) were significantly higher than preoperative ($P = 0.001$). This indicates that the value of 24 hours post PLN helps in detecting early AKI (obstructive uropathy) secondary to the presence of kidney stones (23).

KIM-1 in polycystic kidney disease

Polycystic kidney disease is cilia related disorder and is of two types namely autosomal dominant polycystic kidney disease (ADPKD) and autosomal recessive polycystic kidney disease (ARPKD). Urinary KIM1KIM-1/Cr levels were higher in ADPKD patients but the values had no association between cyst size or cyst growth. Increased uKIM-1/Cr reflects the tubular cell disruption and may be a marker for several cysts and has no association with baseline height-adjusted total kidney volume (HtTKV) (24). During cystogenesis KIM-1 is expressed in dedifferentiating proximal tubules in a rat model having PKD. The role of KIM-1 in disease progression or cellular injury is still not established (25). KIM-1 is a regulatory molecule for flow-induced calcium signaling and further interacts with TRPP2 after upregulated ischemic injury in PKD (27). Tissue KIM-1 is expressed in murine ADPKD kidneys compared to normal kidneys and it is present in proximal tubules near cysts and as well as in small sized cysts. The role of KIM-1 in the cyst is still unknown but its expression is related to the dedifferentiation of epithelial cells in tubules.

KIM-1 in renal cell carcinoma

Renal cell carcinoma originates from renal tubular epithelial cells and is a heterogeneous group of cancer. Hepatitis A virus cellular receptor 1(HAVCR)/KIM-1 has a role in promoting tumour growth, angiogenic factors, and metastasis in clear cell renal cell carcinoma (ccRCC) by the activation of STAT-3 on inducing IL-6 expression. Moreover, HAVCR/KIM-1 can be conducted as a marker for tumor prognosis (29). In renal cell carcinoma patients plasma KIM-1 was elevated and was able to predict the incidence up to 5 years before diagnosis but did not correlate with the survival rate (32). Likewise urinary HAVCR/KIM-1 levels were higher in clear cell renal cell carcinoma before surgery and expression plays a role in tumour development in clear cell renal cell carcinoma. A lower membrane expression of HAVCR/KIM-1 correlates with activated shedding and increased ectodomain shedding which in turn correlates with tumour malignancy and higher cell invasiveness (30). Blood plasma levels of KIM-1 in malignant and benign renal tumor ($P<0.00001$) was higher compared to controls ($P<0.01$). KIM-1 levels correlate with the tumour stage. Thus, it can be used as a sensitive marker in ccRCC for early detection (33). Based on the tumour grade, patients had radical nephrectomy or partial nephrectomy (PN). Tissue KIM-1 was higher in radical nephrectomy groups compared to partial nephrectomy and higher tKIM-1 expression due to lymphovascular invasion had elevated uKIM-1. Tissue KIM-1 expression correlates with lymphovascular invasion, the surgery type, and tumour grade (31). uKIM-1/uCr levels were higher in preoperative and reduced in post-surgery indicating KIM-1 can serve as a surrogate marker in clear cell and papillary renal cancer (34).

KIM-1 in diabetic nephropathy

Diabetic nephropathy (DN) is a kidney disease resulting from the worsening of renal functions noticed in CKD and ESRD. Diabetic nephropathy is staged into incipient nephropathy or microalbuminuria and overt nephropathy or macroalbuminuria. Serum KIM-1 increases along with the development of kidney disease as well as depending on the duration of diabetes. Increased duration of kidney disease results in higher KIM-1 levels. Nephropathy can be predicted with urinary KIM-1 in type 2 diabetic patients. Increased levels of KIM-1 in the urine of type 2 diabetes with nephropathy correlates with serum creatinine, urinary microalbumin, BUN, and blood urea, thus showing its role as a diagnostic and prognostic biomarker for nephropathy in type 2 diabetic patients considering other common risk factors (35). Urinary KIM-1 level seems to be increased in type 1 diabetic patients before they develop symptoms of microalbuminuria or macroalbuminuria, indicating tubular damage thus playing as a biomarker of normoalbuminuric diabetic nephropathy (36). Urinary KIM-1 is increased in the macroalbuminuria population and correlates with albumin in the urine in consideration of risk factors in early diabetic nephropathy (38). Measurement of KIM-1 gene expressions in type 2 diabetic patients helps in the early diagnosis of DN and the disease progression may be controlled which can prevent overt microalbuminuria. uKIM-1 levels were higher in albuminuric patients but had no difference between non-albuminuric and control groups, thus it cannot serve as an early diagnostic marker for diabetic nephropathy. A toxicity study was conducted on DN rats where the KIM-1 levels were elevated. Three different doses of 50 mg/kg, 100 mg/kg, and 200 mg/kg of strawberry leaf extract were used and the plasma KIM-1 levels were reduced when a high dose of 200 mg/kg was used. It can be used as a herbal medicine for diabetic nephropathy (41). Diabetic nephropathy rats with T1D had an elevated uKIM-1, on those treated with curcumin (130 mg/kg) showed a significant difference in KIM-1 gene and protein expression when compared to diabetic control groups. uKIM-1 levels were higher in DN patients

but KIM-1 had low significance for determining ESRD progression independent of albumin excretion rate (AER) (40).

KIM-1 in urinary tract infection

Urinary tract infection (UTI) is a common bacterial infection classified as a complicated and uncomplicated UTI. Infection can occur in any region of the urinary tract that is the kidney, bladder, ureter, and urethra. KIM-1 is a marker for kidney function, mediates phagocytosis, and converts proximal epithelial cells into phagocytes during kidney injury. Urinary KIM-1 is not a suitable diagnostic marker for both upper UTI and lower UTI due to its undifferentiated levels of KIM-1 in the urine of control groups and infected patients (42). Urinary KIM-1 is elevated in febrile urinary tract infection in children (0 to 4 years) and helps in the diagnosis of UTI as young children are unable to express their physical illness often and it can further help to detect renal scarring development and acute photon defects (42). Serum KIM-1 levels were high compared to urine KIM-1 and thus can be used to predict febrile UTI in infants whereas both serum and urine KIM-1 were not suitable for detecting non-febrile UTI. Urine KIM-1 of rats was increased after two days of *E. coli* injection and showed sensitivity in the diagnosis of febrile urinary tract infection in children (44). Serum and urine KIM-1 was low and couldn't be diagnosed for AKI in adults with urinary tract infections (46). Urine KIM-1 is a marker for ischemic kidney injury but is not good for screening AKI development in children having urinary tract infections (45).

KIM-1 in pyelonephritis

The complication of ascending UTI leads to acute pyelonephritis in which the kidneys are inflamed due to bacterial infections. A study showed that urine KIM-1 was less effective in diagnosing acute pyelonephritis in children having febrile UTIs (43). Urine KIM-1 levels were increased in acute pyelonephritis with AKI patients compared to non-AKI. KIM-1 can predict tubular injury but is not a marker for AKI in acute pyelonephritis (48).

KIM-1 in hydronephrosis

Hydronephrosis (HN) is a condition where urine cannot pass from the kidney to the bladder due to the enlargement of the kidney. Elevated urinary KIM-1 can be a potential biomarker for subclinical AKI in hydronephrosis patients despite the sCr level and can measure the renal injury grade which helps in treatment modification (49). The uKIM-1/uKIM-1/Cr are not early markers in pediatric patients with hydronephrosis to detect renal dysfunction as there is no significant difference between hydronephrosis groups and controls (53). The uKIM-1: Cr ratios were higher in neonates having severe obstruction hydronephrosis compared to mild obstructions and are prone to ureteropelvic junction obstruction. KIM-1 can help to diagnose prenatal hydronephrosis (54). Urine KIM-1 excretion was higher in hydronephrosis children of grade 2- to 4 but the KIM-1/Cr ratio had no diagnostic role in detecting obstructive nephropathy with hydronephrosis children (50). Moreover, uKIM-1 may be used as a biomarker for children having congenital hydronephrosis due to ureteropelvic junction obstruction as it has a relation with worsening obstruction (51). Urine KIM-1 levels can be used as a result of surgical outcomes and in the management of children with unilateral hydronephrosis as there was decreased uKIM-1 after pyeloplasty.

KIM-1 and cardiorenal syndrome

Cardiorenal syndrome is a condition in which the heart or kidney organ fails, causing acute or chronic dysfunction in the other organ. Pathophysiology, such as neurohormonal system activation and decreased renal perfusion is poorly established. Due to delayed diagnosis, the clinical result of cardiorenal syndrome is still dismal with a significant mortality rate. As a result, investigations are currently being conducted to check the clinical relevance of novel biomarkers. A study revealed KIM-1 as an excellent prognostic marker for acute tubular injury in individuals with chronic heart failure following diuretic therapy discontinuation and reintroduction. KIM-1 levels rose exponentially after 8 hours of diuretics discontinuation, elevated for three days, and then returned to normal after 4 hours of furosemide was restarted (68). KIM-1 outperformed other indicators like NGAL and NAG conducive to tubular injury which is undetected by traditionally used biomarkers. In chronic heart failure patients, KIM-1 was linked to an increased risk of hospitalization or death regardless of GFR (69). More research is needed to determine the functional relevance of KIM-1 in the early diagnosis and evaluation of cardiorenal syndrome.

KIM-1 and myocardial infarction

Although the factors driving renal failure are poorly understood, progressive deterioration in renal function concurs with myocardial infarction (MI). These patients have a significant mortality rate with 20% of the hospitalized myocardial infarction patients having a renal impairment (70). Inflammatory response and various TNFα transforming growth factor beta (TGF-β), and IL-6 cytokines seemed to assist in renal fibrosis in the pathophysiology after myocardial infarction (71). In both animals and humans after acute myocardial infarction neurohormonal activation and hemodynamic disturbance affect cardiac pump function leading to systemic hypoperfusion or hypotension of the kidney (72). Lekawanvijit et al in his study demonstrated that staining of tubules of MI^{+} rats showed a positive result for KIM-1 concluding it to be a useful biomarker for the early detection of kidney disease (73).

KIM-1 and COVID-19

Renal abnormalities are prominent in COVID-19 patients, and AKI is related to a poor prognosis and a high death rate. KIM-1 is known as a marker for AKI and tubular damage. KIM-1 expression is not seen in normal kidneys, but it is substantially enhanced in proximal tubular cells after injury. KIM-1 helps to regenerate wounded tubules by acting as a scavenging receptor, aiding the removal of apoptotic and necrotic cells from the tubular lumen and tubulointerstitial fibrosis and inflammation are bestowed by chronic KIM-1 expression. In viruses like Dengue and Ebola, KIM-1 interacts with phosphatidylserine binding residues within the extracellular immunoglobulin variable (IgV) domain and phosphatidylserine on the viral envelope causing virus internalization (74). SARS-CoV-2 is another type of enveloped virus. According to a recent study, for SARS-CoV-2-associated AKI, KIM-1 is not just a biomarker but binds to the SARS-CoV-2 receptor binding domain through IgV as a receptor. Likewise, KIM-1 is involved in SARS-CoV and MERS-CoV invasions. The viral invasion is intervened by angiotensin-converting enzyme-2 (ACE2) and KIM-1 resulting in acute tubular injury, and the consequent elevation of KIM-1 increases SARS-CoV-2 entrance, creating a vicious cycle in the kidney. However, it is vague how KIM-1 improves SARS-CoV-2 internalization following binding. Another finding is that a KIM-1-derived antagonist peptide with a flexible linker like three glycines covers two SARS-CoV-2 contacting motifs. The peptide efficiently prevents the KIM-1 and SARS-CoV-2 connection, which may aid in the development of novel drugs (75).

Conclusion

Kidney injury molecule-1 is present in the renal proximal tubule of epithelial cells and is usually expressed in normal kidneys at a very low concentration. Serum and urinary KIM-1 has been upregulated due to ischemic or toxic injury in many primary and secondary renal diseases. It is a sensitive and specific marker for tubular injury as well as it can predict early kidney injury. Mostly urinary KIM-1 shows to be more specific than serum or plasma KIM-1 indicating its role as a non-invasive marker for predicting diseases at an earlier onset. KIM-1 can serve as a marker for diagnostic, therapeutic, and prognosis of clinical outcomes and management in renal diseases.

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Authors' contribution

Conceptualization: GR and DGA.
Methodology: PCD and DV.
Validation: GR and DGA.
Formal analysis: PCD and DV.
Investigation: GR and DGA.
Resources: PCD and DV.
Data curation: GR and DGA.
Writing–original draft preparation: GR, DGA, PCD and DV.
Writing–review and editing: GR, DGA, PCD and DV.
Visualization: GR and DGA.
Supervision: GR.
Project administration: GR.

Conflicts of interest

The authors declare that no conflict of interest.

Ethical issues

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