Kidney injury molecule-1 in kidney disease

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ABSTRACT

Kidney injury molecule-1 (KIM-1) is a type I membrane protein, comprising an extracellular portion and a cytoplasmic portion, which is expressed at very low levels in the normal kidney. The extracellular portion can cleave and rapidly enter tubule lumens after kidney injury, and can then be detected in the urine. It has been confirmed that the urine KIM-1 level is closely related to tissue KIM-1 level and correlated with kidney tissue damage. Not only is KIM-1 proven to be an early biomarker of acute kidney injury but it also has a potential role in predicting long-term renal outcome. This review summarizes the relationships between KIM-1 and kidney injury, especially in chronic kidney disease.

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Introduction

Chronic kidney disease is defined using Kidney Foundation Disease Outcomes Quality Initiative criteria as kidney damage or a glomerular filtration rate <60 mL/(min·1.73 m²) for ≥3 months, with or without kidney damage, which is defined as structural or functional abnormalities with or without decreased glomerular filtration rate, pathological abnormalities, markers of kidney damage, or abnormalities in imaging tests.1 Classical methods of assessing kidney function include measurement of serum urea nitrogen, creatinine, estimated glomerular filtration rate, and biomarkers which are poor sensitive and nonspecific. The changes in levels of these biomarkers need to occur 48–72 h after the kidney injury.2 Many studies show that KIM-1 is a sensitive and specific marker of kidney injury as well as a predictor of prognosis especially in acute kidney injury.3,4 However, there are also many studies about the role of KIM-1 in chronic kidney disease.

This review mainly examines the relationships between KIM-1 and kidney injury, especially in chronic kidney disease. We also discuss the structure, expression, function, and detection of KIM-1 as well as the storage of urine samples.

Structure of KIM-1

KIM-1 is a type I membrane protein, discovered by Ichimura et al. in 1998.5 It is expressed in the kidney and liver, and is a 104 kDa peptide, comprising a 14 kDa membrane-bound fragment and a 90 kDa soluble portion. The extracellular portion contains a six-cysteine immunoglobulin-like domain and a Thr/Ser-Pro-rich domain, which is characteristic of mucin-like O-glycosylated proteins.6 The cytoplasmic portion is relatively short with two splice variants, KIM-1a and KIM-1b. The KIM-1a variant lacks the tyrosine kinase phosphorylation motif and is mainly expressed in the liver. The KIM-1 genes have high homology with the monkey gene for hepatitis A virus cell receptor 1 (HAVcr-1), which is expressed by hepatocytes and could promote cellular entry of the virus in certain conditions.7–9 KIM-1 is also known as T-cell immunoglobulin mucin domains-1 (TIM-1) because of its expression at low levels by subpopulations of activated T cells. TIM-1 is a costimulatory molecule of T cells; it can enhance T-cell proliferation and cytokine production.8,10 Tami et al.9 found that immunoglobulin A (IgA) is a natural ligand of KIM-1/HAVcr-1/TIM-1 and enhances the interaction of hepatitis A virus with its receptor. The KIM-1b variant contains two conserved tyrosine residues and a tyrosine kinase phosphorylation motif; it is mainly expressed in the kidney.11 The cleavage of KIM-1 is related to metalloproteinase.6 Zhang et al.11 revealed that constitutive KIM-1 shedding was mediated by extracellular signal-regulated kinase activation and that the cleavage was accelerated by p38 mitogen-activated protein kinase activation.
Detection of urinary KIM-1

Sabbisetti et al.12 introduced two different methods for detecting urinary concentrations KIM-1 in mice after kidney injury. One is a microbead-based enzyme-linked immunosorbsorbent assay, which is very sensitive and specific. It requires only three 10 μL samples of urine to measure KIM-1 concentration, with an assay range of 12.21 pg/mL to 50 ng/mL. The other method is a laminar-flow dipstick assay, which is very rapid. It can provide a quantitative assessment of urinary KIM-1 concentration within 15 min, with an assay range of 195 pg/mL to 50 ng/mL.12 Sabbisetti et al.13 also found that increased levels of KIM-1 could be detected in the blood and serve as a biomarker of kidney injury that was not affected by liver toxicity. The size of the KIM-1 fragment in plasma and urine was similar (~90kD) in patients with acute kidney injury and chronic kidney disease.

van de Vrie et al.14 found that urinary KIM-1 concentrations were stable in urine for up to 48 h when stored at 4 °C and for up to 6 months when stored at −80 °C, independent of the addition of protease inhibitors. Pennemans et al.15 discovered that the concentrations of urinary KIM-1 were related to the pre-freezing and thawing time. An increasing number of freeze–thaw cycles adversely affected KIM-1 measurement. Urinary KIM-1 concentrations had no relationship with the addition of protease inhibitors and centrifugation before freezing. Pennemans et al.15 suggested that urine samples should be frozen within 3 h after collection and only defrosted immediately before measurement.

KIM-1 and renal repair

After kidney injury, the proximal tubule epithelium would regenerate. This involves dedifferentiation and proliferation of viable cells bordering the damaged areas, to reconstitute an intact functional epithelial layer. A study indicates that this transition from normal epithelial cells to dedifferentiated cells is associated with a dramatic up-regulation of KIM-1 expression.5 The mechanisms of tubule epithelial cell restoration are still not clear.5 van Timmeren et al.19 found that vimentin colocalized with KIM-1 in most of the tubules in human renal disease. Vimentin is an intermediate filament involved in tubule dedifferentiation. The KIM-1-positive tubule cells had a dedifferentiated phenotype and correlated with tissue osteopontin and α-smooth muscle actin (α-SMA) levels.20–22 Osteopontin is a tubule-derived protein involved in chemotaxis and repair. KIM-1 colocalizes with bromodeoxyuridine (a marker of proliferation) and elastin (a marker of dedifferentiation) in regenerating proximal tubule epithelial cells in damaged regions after toxic or ischemic injury.5,6 KIM-1 may play a role in the regeneration process of tubule epithelial cells.

KIM-1 in healthy populations

Pennemans et al.23 established reference values for urinary KIM-1 concentration in a healthy population, taking into account possible effects of age and sex. They collected a total of 338 urine samples from nonsmoking healthy volunteers (199 women or girls, 139 men or boys). The age of volunteers ranged from 0 to 95 years. A significant positive linear association was observed between urinary KIM-1 concentration and both age and sex. Urinary KIM-1 concentrations were up-regulated with increasing age. After correcting for urinary creatinine or urinary specific gravity, Pennemans et al.23 observed a quadratic trend in age but not in sex. McWilliams et al.24 recruited a total of 291 healthy children (120 in the UK and 171 in the USA, aged from birth to 16 years). Both morning and evening urine samples were collected. Morning samples were collected from the first micturition of the day. Evening samples were collected just before the children went to bed and were stored overnight in the children’s home refrigerators. McWilliams et al.24 found that urinary KIM-1 concentrations were related to age, as had been previously reported,23 but that there was no significant association with sex. Urinary KIM-1 concentrations in African-Americans were lower than white people. There was a
diurnal variation, in that concentrations were higher in the morning. Zwiers et al. collected 106 basically healthy infants (born between 37 and 42 weeks of gestation), aged from 1 day to 1 year. Two-thirds of the study cohorts were boys. They found that urinary KIM-1 concentrations were extremely low in almost all 106 subjects (median urinary KIM-1 was 0.08 ng/mL) and not related to age, sex, or ethnicity. We speculate that different results of above researches may be related with different ethnicity, different methods of sample collecting and storage, and the different types of biomarker assays.

**KIM-1 and acute kidney injury**

Acute kidney injury is defined by Kidney Disease Improving Global Outcomes criteria as a ≥50% increase in plasma creatinine concentration over baseline within 7 days or an increase in serum creatinine by 0.3 mg/dL within 2 days. The diagnosis of functional acute kidney injury is mainly based on an increase in serum creatinine concentration and urine output; this process may delay the detection of clinically significant kidney damage. KIM-1 is an emerging biomarker for identifying acute kidney injury. Ichimura et al. used representational difference analysis to analyze the difference in mRNA populations between regenerating kidneys after ischemic or reperfusion and normal kidneys. They found that KIM-1 mRNA and protein were expressed at high levels in regenerating proximal tubule epithelial cells. KIM-1 mRNA was dramatically up-regulated in the S3 segment of the proximal tubule in post-ischemic kidneys, where the S3 segment is highly susceptible to ischemic insult. Han et al. proved that KIM-1 is expressed at the apical aspect of proximal tubule epithelial cells but not in glomeruli with acute tubule necrosis. After ischemic kidney injury, KIM-1 could be rapidly expressed in urine within 12 h prior to regeneration of the epithelium; this expression persists over time. Urine KIM-1 levels were significantly elevated after 10, 20, or 30 min of ischemia by >16-fold, >48-fold, and >60-fold, respectively, compared with sham-operated mice (0.52 ± 3.3 ng/mg urinary creatinine). Sabbisetti et al. also found that plasma concentration of KIM-1 was positively correlated with normalized urinary KIM-1 (correcting for urinary creatinine) \((r = 0.43, p < 0.001)\) and non-normalized urinary KIM-1 \((r = 0.24, p = 0.02)\). Plasma and urinary concentrations of KIM-1 were positively correlated with normalized (correcting for urinary creatinine) and non-normalized urinary albumin concentration \((r = 0.33 (p = 0.001)\) for plasma KIM-1, \(r = 0.35 (p < 0.001)\) for urinary KIM-1), respectively. Activation of the G protein \(\alpha_{12}\) (G\(_{\alpha_{12}}\)) subunit by reactive oxygen species is a major cause of tissue damage during renal ischemia–reperfusion injury. G\(_{\alpha_{12}}\) is a molecular switch that is activated by guanosine triphosphate (GTP) binding and is inactivated when bound GTP is hydrolyzed to guanosine diphosphate (GDP). Ismail et al. found that KIM-1 blocked GTP binding onto G\(_{\alpha_{12}}\) and inhibited G\(_{\alpha_{12}}\) activation. KIM-1 could protect against G\(_{\alpha_{12}}\)-mediated tissue damage during ischemic acute kidney injury. G\(_{\alpha_{12}}\) inhibition by KIM-1 is thought to be transient because KIM-1 is expressed by proximal tubule epithelial cells only during injury and expression of KIM-1 returned to baseline (undetectable) amounts on renal recovery (after day 7 ischemia–reperfusion injury).

**KIM-1 and chronic kidney disease**

In spite of the reported functions of KIM-1 in acute kidney injury, there are some evidences for its role in chronic kidney disease. Sabbisetti et al. found that plasma and urinary KIM-1 levels increased on day 7 in mice with unilateral ureteral obstruction but that plasma creatinine levels did not change. Urine KIM-1 level had been confirmed to be closely related to tissue KIM-1 level and to correlate with kidney tissue damage. KIM-1-positive tubules are associated with aggregates of macrophages and pre-fibrotic areas with increased expression of \(\alpha\)-SMA, a marker of myofibroblast transformation. Humphreys et al. created a genetic model in mice, in which KIM-1 was expressed chronically in renal epithelial cells in the absence of injury stimulus, resulting in focal epithelial vacuolization at birth, but otherwise normal tubule histology and kidney function. Humphreys et al. demonstrated that chronic KIM-1 expression led to inflammation, tubule interstitial fibrosis, characterized by elevated monocyte chemotactic protein-1 (MCP-1) levels, and increased MCP-1-dependent macrophage chemotaxis. Mice with mutant endogenous KIM-1 were protected from fibrosis in a model of chronic kidney disease and had a reduced level of MCP-1. Humphreys et al. also found that KIM-1-positive tubule interstitium contained abundant interstitial smooth muscle actin-positive myofibroblasts. Activation and proliferation of fibroblasts and myofibroblasts result in excessive...
synthesis of extracellular matrix, eventually leading to fibrosis.16

**KIM-1 and IgA nephropathy**

The urinary KIM-1 level was high in patients with IgA nephropathy, and was associated with proteinuria.36,37 Expression of KIM-1 is positively correlated with time-averaged proteinuria ($r = 0.470, p < 0.05$) and negatively correlated with the slope of the annual decline in estimated glomerular filtration rate ($r = −0.599, p < 0.01$).38 A previous study had shown that median urinary KIM-1 excretion was $1.7 \text{ng/min}$ in patients with IgA nephropathy, which was significantly higher than in healthy controls ($KIM-1 0.6 \text{ ng/min}$).37 High urinary excretion of KIM-1 is an independent predictor of end-stage renal disease in patients with IgA nephropathy.37 In IgA nephropathy, KIM-1-expressing cells produced more chemokines or cytokines under hypoxic conditions; these are common pathways to renal interstitial fibrosis.36,39 The fraction of KIM-1-positive tubules positively correlated with the number of infiltrated CD68-positive monocytes or macrophages ($r = 0.679, p < 0.01$) and CD3-positive T cells ($r = 0.673, p < 0.01$) in IgA nephropathy.38 Xu et al.40 studied a total of 51 IgA nephropathy patients, dividing them into two groups: 18 patients with elevated urinary KIM-1 concentration and 33 patients with normal urinary KIM-1 concentration. They discovered that tubule atrophy or interstitial fibrosis was more severe in patients with elevated urinary KIM-1 concentrations.40

However, the dynamics of KIM-1 in chronic renal damage and effects of antiproteinuric treatment on KIM-1 are unknown. Waanders et al.41 found that urinary KIM-1 levels were increased in patients with non-diabetic chronic kidney disease and reduced in parallel with proteinuria after short-term antiproteinuric therapies. Nakagawa et al.42 found that the mTOR inhibitor everolimus could reduce infiltration of macrophages and the expression of KIM-1 in the proximal tubules, restoring tubule reabsorption of albumin in chronic renal failure rats. Kramer et al.20 discovered that increased renal KIM-1 expression could be reversed in proportion to proteinuria reduction during antiproteinuric treatment of Adriamycin-induced nephropathy by using angiotensin converting enzyme inhibition and angiotensin II antagonist.

**KIM-1 and lupus nephritis**

A previous study has shown that urinary KIM-1 levels were significantly correlated with the expression of tubule KIM-1 ($r = 0.64, p = 0.004$) in patients with systemic lupus erythematosus. They also found that patients with active lupus nephritis exhibited elevated urinary KIM-1 levels compared with patients with inactive lupus nephritis. Urinary KIM-1 levels were also correlated with proteinuria ($r = 0.39, p = 0.004$) and tubule damage ($r = 0.31, p = 0.01$) in the active lupus nephritis group. This could serve as a biomarker of active lupus nephritis. The estimation of tubule KIM-1 expression in renal biopsies can predict renal damage, tubule atrophy, ongoing glomerular nephritis, and tubulo-interstitial inflammation.46

**KIM-1 and polycystic kidney disease**

Autosomal dominant polycystic kidney disease is caused by mutations in PKD1 (encoding polycystin 1) or PKD2 (encoding polycystin 2). Urinary KIM-1 levels showed marked up-regulation in cystic kidneys compared with
non-cystic control kidneys in a mouse model. A previous study had shown that KIM-1 interacted with polycystin 2 (TRPP2) and modulated the function of TRPP2 in renal tubule cells. Although the functional role of KIM-1 in cysts remains unknown, KIM-1 expression in tubules is strongly associated with partial dedifferentiation of epithelial cells. It plays a role in the development of interstitial fibrosis.

**KIM-1 and kidney transplant**

The diagnosis of chronic transplant dysfunction is characterized by renal function decline and proteinuria. However, the diagnosis of acute kidney injury mainly depends on morphologic evaluation of the allograft biopsy as the gold standard in kidney transplantation. Some researchers have shown that the urinary KIM-1 level is high in kidney transplant patients and is associated with graft loss. High urine KIM-1 levels are also associated with proteinuria, low creatinine clearance, and high donor age (all \( p < 0.01 \)) in kidney transplant patients. Zhang et al. found that the expression of tissue KIM-1 was more sensitive than histology for detecting early tubule injury, and correlated with the degree of renal dysfunction. Increased tissue KIM-1 expression was found to predict a better prognosis, given an equivalent level of renal graft dysfunction. The level of tissue KIM-1 is also a potential early marker for recovery of kidney function in patients with kidney transplants. Patients with greater levels of KIM-1 staining (2+ or 3+) had better recovery of function over the ensuing 18 months, as reflected by reductions in serum concentration of urea nitrogen, serum concentration of creatinine, and increase in estimated glomerular filtration rate. These patients had histological changes showing acute tubule damage in kidney biopsies and deterioration of kidney function. At present, the finding of fibrosis depends on the analysis of tissue in renal biopsy, which has important limitations. Nogare et al. evaluated messenger mRNA transcription and gene expression of KIM-1 in kidney tissue and in urinary sediment cells of kidney transplant patients with graft dysfunction. A significant correlation between KIM-1 gene expression in samples of urine and tissue cells was found (\( p < 0.01 \)). Nogare et al. also found that KIM-1 protein expression was increased in biopsies with interstitial fibrosis and tubule atrophy, compared with biopsies showing acute calcineurin inhibitor nephrotoxicity.

It would seem that KIM-1 is a marker of kidney graft fibrosis. Quantification of mRNA in urinary sediment cells KIM-1 may be used as a noninvasive biomarker of fibrosis in kidney grafts with interstitial fibrosis or tubule atrophy. The expression of urinary KIM-1 is an independent predictor of long-term graft loss and could prove useful as a new biomarker in the early prediction of graft loss in renal transplant recipients.

**KIM-1 and renal cell carcinoma**

A previous study has shown that KIM-1 could be detected in the urine of patients with renal cell carcinoma. Urinary KIM-1 concentrations in patients with kidney cancer before nephrectomy were significantly increased. This indicates that KIM-1 may be a new biomarker for early detection of renal cell carcinoma. Morrissey et al. observed that urinary KIM-1 excretion before nephrectomy had a positive correlation with tumor size (\( r = 0.66, p < 0.001 \)) and tumor stage. At one month after tumor excision, median urinary KIM-1 concentration could decrease by 50%. If post-nephrectomy urinary concentrations of KIM-1 do not return to an undetectable range, this may implicate an ongoing renal pathologic process, and suggest the presence of renal cell carcinoma in the contralateral kidney or other renal disease involving the proximal tubules. Shalabi et al. found that urinary neutrophil gelatinase-associated lipocalin and KIM-1 had a potential association with histopathologic features in patients with renal cell carcinoma. Analysis of these biomarkers would prevent the need for pretreatment biopsies.

**Conclusions**

KIM-1 is expressed on the apical aspect of renal proximal tubule epithelial cells and expressed at very low levels in the normal kidney. It is up-regulated in various primary and secondary kidney diseases, in allograft nephropathy. The extracellular portion of KIM-1 can cleave and rapidly enter tubule lumens after kidney injury. It is a sensitive and specific marker for renal proximal tubule damage. KIM-1 expression may play a role in the regeneration process of tubule epithelial cells. It is also associated with renal fibrosis and inflammation in chronic kidney disease. Higher tissue KIM-1 expression is found to predict a better prognostic sign, given an equivalent level of renal graft dysfunction. In renal cell carcinoma, an increased urinary KIM-1 level may imply an ongoing renal tumor pathologic process. In short, KIM-1 is a specific and sensitive biomarker of kidney injury; it can detect early kidney injury in chronic kidney disease and play a role in the development of...
interstitial fibrosis in kidney disease. It can be used to predict the progress and outcome of kidney disease.

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