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Review Article

KIM-1 is a universal biomarker of kidney pathologies: True or false?

Ihor Kovalchuk[1]*, Inga Mityuryayeva[1], Ievgeniia Burlaka[1]

[1]Department of Pediatrics №4, Bogomolets National Medical University, Kyiv, Ukraine.

Correspondence: Ihor Kovalchuk, Department of Pediatrics №4, Bogomolets National Medical University, Kyiv, Ukraine. ihor.kovalchuk@gmail.com

ABSTRACT

Over the past 30 years, the world has witnessed a dramatic increase in the prevalence of diabetes and its many complications. One of these, diabetic nephropathy, is currently the leading cause of end-stage renal disease worldwide, at a tremendous human and economic cost. Comprehensive understanding of the many complex pathophysiological mechanisms and their mutual interrelationship will be mandatory to facilitate the development of novel preventive and therapeutic regimens for diabetic nephropathy.In recent years, more and more attention has been paid to the search for biomarkers of acute and chronic damage kidneys, which allows for early detection of pathological changes in the kidneys and to determine their nature, differentiate lesions of different parts of the nephron, reliable establish the pathological stage process. The search for biomarkers for increased risk for diabetic kidney disease have usually been hypothesis driven and have several markers have been suggested, but so far none of the markers have been implemented in clinical care, as validation, and confirmation of added value beyond the existing risk markers still has to be proven.The review presents literature data on preclinical and experimental studies.

Keywords: Kidney injury molecule, Diabetic kidney disease, Chronic kidney disease, Diabetic nephropathy

Introduction

Kidney injury molecule-1 (KIM-1) - transmembrane glycoprotein of the immunoglobulin superfamily, also known as HAVcr-1, the historical name in bioinformatics databases, as well as TIM-1-T cellular Ig mucin domain 1, the expression of which is shown in subpopulations of T-lymphocytes. A total of eight proteins of the TIM family were identified: 6 in rats and 3 in humans [1]. Glycoproteins contribute to the proliferation and production of cytokines, which are involved in developing immune tolerance mechanisms in the group of autoimmune and allergic diseases, including bronchial asthma [2]. The difference of KIM-1 from the rest of the representatives of this group is that it is localized not only on immunocompetent cells but mainly in the epithelium of the proximal tubules of the kidneys. Interacting with other proteins, it actively modulates processes related to injury and recovery [3, 4]. KIM-1 is determined mainly in places of accumulation of interstitial macrophages and prefibrotic lesions. Cellular and humoral reactions associated with KIM-1 are involved in a wide variety of physiological and pathological processes of the body: viral invasion, immune response, acute or chronic kidney damage, and carcinogenesis [5]. Thus, KIM-1 is considered a marker of numerous chronic fibrotic processes of kidney disease [6]. The study and research of a biomarker has a selective prognostic value for monitoring CKD, including DN. As a result of experimental studies, the role of KIM-1 was established not only as a universal biomarker but also as a therapeutic target [7].

Diabetic kidney disease (DKD) is a pathological condition that can be qualified as one of the most serious complications against the background of diabetes of both types. DKD is a severe and dangerous complication of diabetes, which is the main cause of end-stage renal disease (ESRD) [3]. Approximately 40-45% of patients with diabetes eventually develop DKD. Since the

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number of patients with diabetes has increased from 108 million in 1980 to 529 million in 2021, accordingly, the incidence of DKD remains an unsolved clinical problem [8]. In 25% of patients with type 1 diabetes, the disease progresses to ESKD. 20% of all patients with DN are patients with type 1 diabetes. As for patients with type 2 diabetes, DN remains the main cause of morbidity and mortality and accounts for almost 40% of all cases of ESKD [4]. Type 2 diabetes is the main cause of CKD and leads to the development of DN in every second patient [9]. Microalbuminuria is the earliest sign of nephropathy. However, renal function in diabetes can worsen despite normal excretion of albumin in the urine. In this regard, it is necessary to control GFR. Patients with diabetes have an increased risk of developing an infectious process, and the frequency of pyelonephritis increases. Tubulointestinal damage is a more pronounced indicator of the functional progression of the disease [10].

In the early stages of DKD, tubular abnormalities may precede glomerular pathology. Currently, the pathological mechanisms that initiate damage to the tubular epithelium are poorly understood. Therefore, a better understanding of the pathology of tubulointerstitial disease will lead to new targets in diagnosing and treating DKD. The KIM-1 molecule, also known as HAVcr -1 and TIM-1 is a sensitive and specific marker of DN. The review analyzes the possibility of using KIM-1 as a urinary and serological marker in kidney disease and not only [11].

The variety of expression determines various manifestations of functional activity

Mucin-like transmembrane glycoprotein type 1, of common origin with the class of immunoglobulins, promotes hepatitis A virus infection of cultured cultures of African green monkey kidneys, first described by Kaplan (1996). Named HAVcr-1 (hepatitis A virus cellular receptor 1). In the human genome, such same DNA sequence. Studying the post-ischemic recovery of rat kidney epithelium, Ichimura (1998) identified the KIM-1 (kidney injury molecule 1) gene, high levels of which were characteristic of damaged epithelial cells of the proximal tubules of the kidneys [12]. The KIM-1 gene turned out to be an analogue of HAVcr-1. Later, a group of genes was identified that regulate the hyperactivity of the respiratory epithelium (T-cell and airway phenotype regulator, Tapr) in experimental mice resistant to an asthmatic attack. This cluster of genes is united in the TIM family (T-cell immunoglobulin and mucin domain family) by the structural similarity of the proteins they encode. Tim-1 is similar to KIM-1 in rats and HAVcr-1 in humans and monkeys. Over time, eight more proteins of the TIM family were discovered: 8 in mice, 6 in rats, and 3 in humans **(Figure 1)** [13].

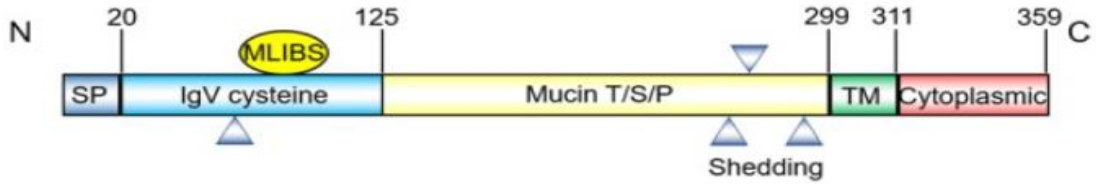

Figure 1. The structure of the KIM-1 molecule. Schematic representation of LIM-1 showing the signal peptide, IgV, mucin, transmembrane and cytoplasmic domains. Triangles indicate the predicted location of n-linked glycosylation sites. KIM-1, kidney damage molecule-1; MLIBS, metal ion-dependent ligand binding site; T/S/P, threonine/serine/proline; TM, transmembrane [3].

KIM-1 is located on the plasma membrane and forms the following domains: cytoplasmic, transmembrane, and extracellular. The structure of the extracellular part of KIM-1 contains a globular domain that is similar to the immunoglobulin V fragment, a mucin-like sequence: Mucini T\S\P, and a short peptide segment. A characteristic feature of the globular domain is a hydrophobic "pocket" (metal-ion-dependent ligand binding site, MILIBS), which forms a bond with phosphatidylserine. In intact cells, the phospholipid is located on the inner side of the cell's plasma membrane. During cell apoptosis, it moves phosphatidylserine on the outside of the membrane. This is a signal for macrophages to absorb dead cells [14]. Thus, in damaged cells, KIM-1 acts as a scavenger receptor, contributing to removing cell dendrites. Low-density lipoproteins, P-selectin, and conjugated blood bilirubin are also likely ligands that bind to the glycoprotein through the IgV domain [15]. The largest part of KIM-1 is a glycosylated mucin domain consisting of paired amino acid repeats and O-glycosylation sites. The short peptide segment located on the membrane has N-glycosylation sites and zones susceptible to the action of metalloproteinases. The free form of the KIM-1 molecule is formed as a result of proteolytic cleavage, has a mass of 90 kDa, and can be determined in blood plasma and urine. The cytoplasmic domain of KIM-1 is a structurally unstable short polypeptide. When phosphorylated, the domain promotes intracellular signal transmission in renal epithelial cells and lymphocytes [5, 7].

The expression of mRNA encoding the HAVcr-1 protein has a high specificity in the human body's tissues [16]. Recent studies of the transcriptome, as well as immunohistochemical studies, show a high content of glycoprotein in the kidney tissue, namely in the epithelial cells of the proximal tubules, in the urothelium in contrast to other tissues: testicles, glands of the small and large intestines, in the epithelium of the bile ducts of the liver and gallbladder, in bronchial epithelium, in the endometrium, in oligodendrocytes of the brain, myocytes of

skeletal muscle tissue, on cells of the immune system, its quantities are insignificant, and the level of expression is insignificant [15].

KIM-1 in a case of damage to renal tubules

Chronic kidney disease (CKD) – is the result of functional or anatomical disorders of various renal structures, while a decrease in GFR is most often due to a decrease in the number of functioning nephrons as a result of glomerulosclerosis, atrophy of renal tubules, fibrosis of interstitial renal tissue [17]. Among the most frequent causes are diabetic, hypertensive, ischemic nephropathy, rarely obstructive; acute kidney damage; tubulointerstitial kidney disease; polycystic kidney disease; and other recurrent kidney lesions of various etiologies. The pathogenesis of chronic kidney disease is complex and includes many components:

- Strengthening of systemic proinflammatory processes against the background of acute and chronic hypoxia;
- Violation of both renal and systemic microcirculation;
- Endotheliosis followed by mesangiolysis;
- Metabolic disorders inducing tissue changes due to the accumulation of modified (denatured, glycated, oxidized) proteins, oxidized low-density lipoproteins (ox-LDL), high concentrations of free fatty acids (FFA), AGEs, homocysteine, etc [18, 19].

RAAS activation, imbalance in the production of pro- and anti-inflammatory cytokines, growth factors, oxidative stress, suppressing cell apoptosis. As a result, the pathogenesis of CKD is characterized not only by metabolic but also by immunological abnormalities. Regardless of the etiology of CKD, the key pathophysiological event is renal fibrosis, which in turn is the last stage on the way to the progression of CKD [15]. Hypoxic damage is the cause of increased levels of KIM-1 in the cells of proximal renal tubules, which in turn causes chronic interstitial inflammation, deepening hypoxia, and subsequent cell damage. Increased levels of KIM-1 are determined both in acute and chronic kidney damage. It has been experimentally determined that elevated levels of KIM-1 contribute to the progression of CKD and, at the same time, are a marker of a negative prognosis of the disease [18]. Numerous results of clinical studies prove an increase in the level of the marker in urine in diabetic nephropathy with normoalbuminuria or with slight albuminuria. An increase in the level of KIM-1 is comparable to a decrease in GFR albuminuria, which indicates a connection between impaired function of glomeruli and renal tubules. It was noted that an increase in the level of KIM-1 in peripheral blood has more important clinical significance than an increase in the levels of the marker in urine. In children with type 1 diabetes, an increase in the level of KIM-1 -1 in the blood correlates with a decrease in the glomerular filtration rate. Therefore, KIM-1 is an early marker of the progression of diabetic nephropathy **(Figure 2)** [13, 20].

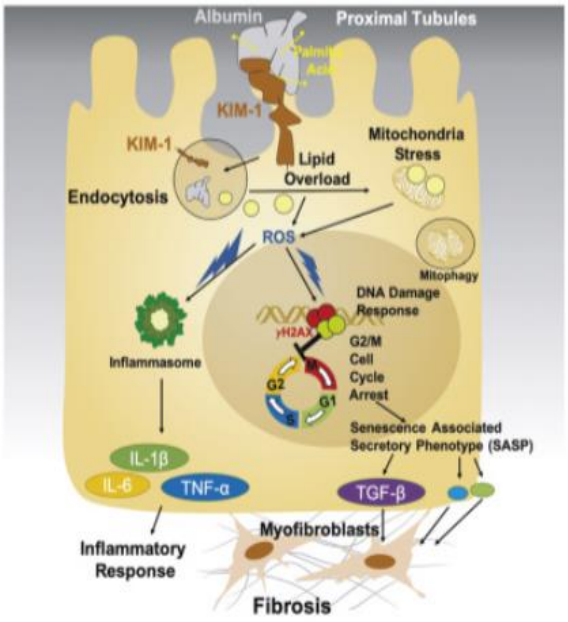

Figure 2. Role of KIM-1 in fibrosis development [20].

Diagnostic and prognostic value of the biomarker KIM-1

The transmembrane glycoprotein KIM-1, which is expressed on the apical membrane of the cells of the proximal tubules of the kidneys, is recognized as an ideal marker of kidney damage. During physiological processes in the kidneys, the molecule of kidney damage-1 is not fixed or is detected in small quantities. An increased level of KIM-1 is characteristic of various kidney lesions and depends on the severity of the course of the disease. The rapid appearance of this marker in the urine of patients with type 1 diabetes is already in the initial stages of DKD [5]. The determination of KIM-1 precedes the development of microalbuminuria, which is evidence of primary damage to the tubular department in the case of the development of diabetic nephropathy. A long-term significant increase in the level of KIM-1 in cells of the tubular epithelium, high concentrations in urine, and/or circulating blood predict the transformation of DKD to CKD and the development of ESKD [14]. Long-term elevated level of KIM-1 contributes to the development of progressive interstitial inflammation fibrosis and extrarenal manifestations of myocardial hypertrophy anemia. All this is evidence of the multifaceted role of the KIM-1 molecule in the complex pathophysiological mechanisms of DKD. Therefore, at the early stage of diabetic nephropathy, the level of the KIM-1 biomarker increases [12]. It also persists over time, which has been proven experimentally and clinically in humans and experimental animals. Long-term expression of the transmembrane glycoprotein contributes to the accumulation of albumin saturated with palmitic acid in the renal tubules, which stimulates fragmentation processes of mitochondria, proliferation, production of proinflammatory cytokines, due to the activation of the inflammatory response regulated by the activator protein – NLRP3, profibrotic cytokines, such as

transforming growth factor b-1 due to DNA damage [7]. Progressive inflammation and fibrosis of the interstitial tissue of the kidneys gradually destroy capillary blood flow, increasing local ischemia, hypoxia, and cellular stress, with subsequent damage to the tubules and the deposition of the extracellular matrix to replace the damaged molecules. The deepening of fibrous changes in the interstitium contributes to the development of glomerulosclerosis and increases the loss of albumin [21]. Thus, the mechanical, correlational cause-and-effect interrelationship of the KIM-1 biomarker, damage to the proximal renal tubules, inflammation, interstitial fibrosis, and glomerulosclerosis in a line of laboratory mice with a mucin domain is followed. Blocking the mucin domain of KIM-1 slows down the progression of DKD, including glomerulosclerosis. Inhibiting or eliminating KIM-1-related protein absorption - enriched in palmitic acid - is a new tactic in treating DKD. Therefore, KIM-1 is a universal biomarker and a possible target treatment method for many patients with CKD [13, 20].

Conclusion

At all levels of the organization of living matter, incredible contradictions and coordination of dynamics and stability, homeostasis, and imbalance are visible. KIM-1, along with other numerous biostructures, ensures homeostasis, preserves the structural and functional structure of the epithelium of the proximal parts of the nephron, is involved in the formation of both immunostimulatory and immunosuppressive reactions during various types of cellular stress. But KIM-1 also contributes to the penetration of the virus into the cell. intensity of glycoprotein expression in proximal tubular epithelial cells correlates with the severity of subsequent fibrotic processes. Increased expression in RCC cells (due to mutations) can stimulate uncontrolled proliferation and angiogenesis. Therefore, a biomarker that appears to be a promising candidate for non-invasive control of CKD, including diabetic nephropathy, requires further in-depth research and comprehensive study.

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