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Kidney injury molecule-1 and its diagnostic ability in various clinical conditions

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ABSTRACT

Objectives: This review evaluates the diagnostic ability of Kidney Injury Molecule 1 (Kim-1) in various clinical conditions. **Methods:** We screened literature in electronic database from January 2016 to March 2016 by the words "Kidney Injury Molecule-1"or "Kim-1" and "Acute Kidney Injury". Specific studies were selected for inclusion if they were published in English journals, in which Kim-1 was measured for diagnosis of various forms of Acute Kidney Injury in different articles.

Results: There were eight articles which met the selection criteria for inclusion in our study. Compared to non acute kidney injury (AKI) patients, Kim-1 raised significantly in different forms of AKI patients.

Conclusions: Kidney Injury Molecule-1 is a new emerging urinary biomarker in the early detection of acute kidney injury and repair of kidney cells as well. Kim-1 can detect acute tubular necrosis, a useful marker for renal proximal tubular injury and it can restore morphological integration of kidney cells followed by ischemic injury. Kim-1 can detect nephrotoxic injury and injury caused by various drugs as well.

Keywords: Kidney injury Molecule, Acute Kidney Injury

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Abbreviations:

Kidney injury molecule -1 (KIM-1), Acute tubular necrosis (ATN), Acute kidney injury (AKI), and Enzyme linked immunosorbent assay (ELISA).

INTRODUCTION

Kidney Injury Moleculr-1(KIM-1) has many characteristics that play an important role in clinical diagnosis. Various studies revealed that it might be an emerging biomarker of acute kidney injury (AKI). Normally, KIM-1 is not present in significant amount in normal urine. However, its secretion by the kidney cells were raised in acute kidney injury cases. In addition to that, its levels were raised during the process of repair mechanism as well. These levels persist until kidney cells recover from injury completely.

Conventional blood and urine tests for the diagnosis of different types of kidney diseases are insensitive and nonspecific. Recent studies elucidated that ectodomain of KIM-1 is shed from cells epithelial structures in different organs perform diverse and complex tasks but display stereotyped responses to injury. The kidney epithelium is particularly susceptible to injury due to the character of its blood supply and its ability to concentrate many toxins[1]. Injury is revealed by functional deficiencies in handling of salts and water, inability to excrete metabolic toxins, and an innate inflammatory response [2&3]. The damaged segment of the nephron can be remodeled, leading to complete functional recovery, and as such represents a general model of epithelial remodeling after injury. Excretion of apoptotic cells and necrotic debris is needed for repair of the tissue with restoration of function [4]. Excretion of apoptotic cells in time has been identified to be a fundamental component of developmental remodeling, regulation of appropriate immune response, and tissue homeostasis [5]. Furthermore, the phagocytic process itself may lead to production of anti-inflammatory cytokines [6]. KIM-1 is not detectable in the normal human urine but is raised in expression more than any other protein in the injured kidney and is localized predominantly to the apical membrane of the surviving proximal epithelial cells [7].

The purpose of this study is to analyze whether kidney injury molecule–1 (KIM-1) plays a significant role in the various clinical conditions especially in clinical diagnosis.

METHODS

The focus of the current review is to investigate the use of kidney injury molecule (KIM-1) in various clinical conditions. With this purpose in mind, we were particularly interested in papers that reported the use of KIM-1 in clinical diagnosis. To ensure the selection of relevant quality articles, we restricted our search for published papers in peer-reviewed academic journals and excluded conference proceedings, book chapters, unpublished manuscripts, dissertations, project reports, and position papers. The rationale behind such an approach is three-fold. First, the review process for publications other than journal papers are normally not that rigorous which may, in turn, lead to incomplete review and unconvincing conclusions. The journal articles undergo a rolling review schedule, with multiple review phases, ensuring the findings and conclusions about the reported assessments are valid, methodological and comprehensive [8].

Second, the journal articles are usually longer than conference papers and hence present detailed information about the assessments. Also, these other types of publications are not easy to access and may result in asymmetrical studies. Moreover, journal articles provide detailed and comprehensive information regarding the assessment presented. Although focusing only on journal articles allows a consistent and systematic review, this may omit some important research work in these publications and limit the generalizability of this finding. To gather a sufficiently comprehensive corpus for the study, we undertook extensive research on a number of available sources. This included multiple electronic databases such as MEDLINE through

PUBMED database, EMBASE between January 2016 and March 2016 was used. The search was conducted with the following search string: Kidney Injury Molecule-1, Acute Kidney Injury. Two authors independently screened all articles for inclusion.

RESULTS

In this section, we present findings from our analysis based on the criteria established. We got a total of 8 relevant articles. Urinary Kim-1 measurements are sensitive, specific and accurate prediction of nephrotoxicity in drug screens. This could enable early identification and elimination of compounds that may be nephrotoxic. In addition to that there are various clinical conditions where KIM -1 is useful to diagnose the disease such as kidney cancer, graft function and other kidney diseases.

In a study conducted by Han WK et al, noted, significant expression of KIM-1 in proximal tubule cells in biopsies from 6 of 6 patients with confirmed ATN. The normalized urinary KIM-1 levels were higher in patients with ischemic ATN compared to levels in patients with other forms of acute renal failure or chronic kidney disease. Levels of other urinary markers, consisting of total protein, gamma-glutamyltransferase, and alkaline phosphatase, did not correlate with clinical diagnostic groupings [9]. There are many studies showing KIM-1 is closely associated with acute kidney injury of different types including ATN, Ischemic and nephrotoxic cases.

In another case, forty kidney cancer and 484 non-renal tumors were analyzed by immunohistochemistry for expression of KIM-1 (group 1). Urine samples before nephrectomy and nephrectomy tissue samples were sampled from an additional 42 patients with kidney cancers, from 30 normal controls and also from 10 patients with prostate cancer (group 2). In five additional patients with kidney cancer, urine was collected before and after nephrectomy (group 3). Tissue was examined for expression of KIM-1, and cell-free urine supernatants were screened for KIM-1 by Enzyme Linked Immunosorbent Assay (ELISA). Urinary KIM-1 was normalized to the urinary creatinine concentration. Expression of KIM-1 was present in 32 tissue sections (91%) of 35 clear cell RCC (group 1). In group 2, the normalized urinary KIM-1 levels were significantly higher in patients with clear cell RCC (0.39 ± 0.08 ng/mg ; $n = 21$), compared with levels in patients with prostate carcinoma (0.12 ± 0.03 ng/mg ; $P < 0.02$; $n = 10$), or normal control subjects (0.05 ± 0.01 ng/mg ; $P < 0.005$; $n = 30$). Tissue sections from 28 (82%) of 34 primary RCC stained positively for the expression of KIM-1. In all patients with a detectable prenephrectomy urinary KIM-1 level, there was either complete disappearance or marked reduction after nephrectomy (group 3).

High KIM-1 excretion was related with proteinuria, low creatinine clearance, and high donor age. Urinary excretion of KIM-1 is an independent predictor of long-term graft loss and therefore a promising new biomarker in early prediction of graft loss [(10)]. The above stated studies revealed that the Kidney Injury Molecule -1 is a novel emerging diagnostic tool in detecting kidney disease earlier then many conventional tests.

DISCUSSION

The aim of this review was to evaluate the significant of plasma or urinary kidney injury molecule-1 (Kim-1). In a study conducted by Han WK et al, noted, increased expression of KIM-1 in proximal tubule cells in biopsies from 6 of 6 patients with confirmed acute tubular necrosis (ATN). Levels of other urinary markers, consisting of total protein, gamma-glutamyltransferase, and alkaline phosphatase, did not correlate with clinical diagnostic groupings. They revealed that soluble form of human KIM-1 can be detected in the urine of patients with Acute Tubular Necrosis (ATN) and may serve as a useful marker for kidney proximal tubule injury facilitating the early diagnosis of the disease and serving as a diagnostic tool [9] Takharu I. et al demonstrated in a study revealing structure and expression data signifies that the KIM-1 is an epithelial cell adhesion molecule up-regulated in the cells, which are dedifferentiated and undergoing replication. KIM-1 may play an important role in the restoration of the morphological integrity and function to post ischemic kidney [11]. These studies highlight the invaluable role of KIM-1 in clinical laboratory medicine.

In another study, Kim-1 protein was detected in urine of toxicant-treated rats. Cisplatin treatment results in early detection of urinary Kim-1 protein and diffuse Kim-1 expression in S3 cells of the proximal tubule of the kidney. Kim-1 can be detected in the tissue and urine on day 1 and 2 after cisplatin administration, occurring before raise in serum creatinine. The upregulation of expression of Kim-1 and its presence in the urine in response to exposure to various types of nephrotoxicants revealed that this protein may serve as a general marker for tubular injury and repair processes [12].

Therefore, urinary Kim-1 levels can help as a biomarker, rapid, sensitive, reproducible, and potentially high-throughput test to diagnose early kidney injury in studies and in preclinical drug development screens for risk-benefit profiling of pharmaceutical drugs[13]. KIM-1 is upregulated in renal disease and is associated with renal fibrosis and inflammation. Urinary KIM-1 is also associated with

inflammation and kidney function, and reflects tissue KIM-1, indicating that it can be used as a non-invasive marker in kidney disease[14].

Urinary Kim-1 seems to be sensitive and tissue-specific markers that will help detection of early acute kidney injury following exposure to nephrotoxic [15].

Raised KIM-1 excretion was related with proteinuria, low creatinine clearance, and high donor age. Urinary excretion of KIM-1 is an independent predictor of long-term graft loss and therefore a promising marker in early prediction of graft loss [10].

Human kidney injury molecule-1 (KIM-1) is a protein that is not detectable in normal kidney tissue but is expressed at high levels in human kidneys with dedifferentiated proximal tubule epithelial cells after ischemic or toxic injury. Therefore, it was hypothesized that renal tumors express KIM-1 and release this protein into the urine [16 & 17].

SUMMARY

The present systematic review revealed that studies evaluating plasma and urinary KIM-1 might play an important role in diagnosis of acute kidney injury and repair of kidney cells as well.

Kim-1 can detect acute tubular necrosis, a very good marker of kidney proximal tubular injury and it can restore morphological integration of kidney cells followed by ischemic injury.

Kim-1 can detect nephrotoxic injury and injury caused by various drugs. Kim-1 can detect proteinuria and graft loss. Hence Kim- 1 can be used as a new diagnostic marker in the diagnosis of different types of kidney diseases including kidney cancer. Therefore, kim-1 can be added in Kidney function tests to maximize accuracy of the kidney disease.

REFERENCES

1. Bonventre, J.V. Dedifferentiation and proliferation of surviving epithelial cells in acute renal failure. *J. Am. SocNephrol.* 2003; 14:S55-S61.
2. Kelly, K.J., et al. Intercellular adhesion molecule-1 deficient mice are protected against renal ischemia. *J. Clin. Invest.* 1996; 97:1056-1063.
3. Thadhani, R., Pascual, M., Bonventre, J.V. Acute renal failure. *N. Engl. J. Med.* 1996; 334:1448-1460.
4. Henson, P.M., Hume, D.A. Apoptotic cell removal in development and tissue homeostasis.*TrendsImmunol.* 2006; 27:244-250.
5. Savill, J., Dransfield, I., Gregory, C., Haslett, C. A blast from the past: clearance of apoptotic cells regulates immune responses. *Nat. Rev. Immunol.* 2002; **2**:965-975.
6. Duffield, J.S., Ware, C.F., Ryffel, B., Savill, J. Suppression by apoptotic cells defines tumor necrosis factor-mediated induction of glomerular mesangial cell apoptosis by activated macrophages.*Am. J. Pathol.* 2001; 159:1397-1404.
7. Ichimura, T., et al. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. *J. Biol. Chem.* 1998; 273:4135-4142.
8. Kuo CY, Wu HK. Toward an integrated model for designing assessment systems: An analysis of the current status of computer-based assessments in science. ComputEduc, 2013; 68:388-403.
9. Han WK[1], Bailly V, Abichandani R, Thadhani R, Bonventre JV: Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 2002; 62(1):237-44.
10. Yuzhao Zhou, Vishal S. Vaidya, Ronald P. Brown,et al: Comparison of Kidney Injury Molecule-1 and Other Nephrotoxicity Biomarkers in Urine and Kidney Following Acute Exposure to Gentamicin, Mercury, and Chromium: Toxicol. Sci. 2008; 101(1):159-170.
11. TakaharuIchimura, Joseph V. Bonventre et al: Immunoglobulin Domain, Is Up-regulated in Renal Cells after Injury. February 13, The Journal of Biological Chemistry, 1998 ; 273:4135-4142.
12. Takaharu Ichimura, Cheng Chieh Hung, et al: Kidney injury molecule-1: a tissue and urinary biomarker for nephrotoxicant-induced renal injury, American Journal of Physiology - Renal Physiology, 2004; 286(3):F552-F563
13. Vishal S. Vaidya, Victoria Ramirez, Takaharu Ichimura, et al: Urinary kidney injury molecule-1: a sensitive quantitative biomarker for early detection of kidney tubular injury, American Journal of Physiology - Renal Physiology 2006; 290(2):F517-F529
14. MM van Timmeren, MC van den Heuvel et al: Tubular kidney injury molecule-1 (KIM-1) in human renal disease, Journal of pathology, 2007; 212(2):209–217,
15. Mirjan M. van Timmeren, Vishal S. Vaidya, Rutger M. van Ree et al: High Urinary Excretion of Kidney Injury Molecule-1 Is an Independent Predictor of Graft Loss in Renal Transplant Recipients. Transplantation. 2007; 84(12):1625–1630.
16. Won K. Han, Anwar Alinani, Chin Lee Wu. Et al: Human Kidney Injury Molecule-1 Is a Tissue and Urinary Tumor Marker of Renal Cell Carcinoma. JASN April 1, 2005; 16(4):1126-1134.
17. Won K. Han, Anwar Alinani, Chin Lee Wu. Et al: Human Kidney Injury Molecule-1 Is a Tissue and Urinary Tumor Marker of Renal Cell Carcinoma. JASN April 1, 2005; 16(4):1126-1134.