ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Determination of serum KIM-1 in patients with chronic kidney injury

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Submission: 14-03-2023 Revision: 28-06-2023 Publication: 01-08-2023

ABSTRACT

Background: Chronic kidney disease (CKD) affects more than 800 million people worldwide and is one of the leading non-communicable causes of death. Despite being a latent issue, once renal damage has started, the disease can rapidly progress to an advanced stage. **Aims and Objectives:** Currently, the most commonly used markers for the diagnosis of renal disease are non-specific and insensitive. As a result, the goal of the current study is to investigate whether KIM-1 could be a precise and sensitive biomarker for identifying early kidney injury in CKD patients. **Materials and Methods:** This case–control study recruited 155 participants from the Index Medical College Hospital v Research Centre, Indore, Madhya Pradesh, based on inclusion and exclusion criteria. 150 non-CKD subjects matched for age and sex were also taken from the hospital. The levels of KIM-1 were compared between CKD and non-CKD participants. Serum creatinine, urea, and creatinine clearance were also measured. **Results:** The levels of KIM-1 were substantially higher in CKD patients than in non-CKD participants. In addition, a negative relationship between KIM-1 and creatinine clearance was observed with a $P<0.05$. **Conclusion:** KIM-1 is a precise and sensitive kidney injury biomarker that can identify early kidney injury in CKD and contribute to the progression of interstitial fibrosis in kidney disease.

Key words: Chronic kidney disease; KIM-1; Biomarker

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v14i8.53228

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

More than 10% of the world's population, or over 800 million people, suffer from chronic kidney disease (CKD), which has become one of the leading non-communicable causes of death globally. The prevalence of CKD in Asia was 11.2%, with 8.6% of that number in East Asia, 12.0% in South-East Asia, 13.1% in Western Asia, and 13.5% in South Asia. Thailand (12.4%), India (11.7%), and Malaysia (9.0%) were the three primary nations with the highest burden of CKD in Asia, and they have become major burdens on low- and middle-income nations due to an increase in mortality related to the disease during the previous 20 years. The early stages of CKD are a latent issue with related factors. Once renal damage has started, proteinuria, poor blood pressure, and glucose management, and developmental factors help the illness progress to an advanced stage.[1,2]

KIM-1 is a type I membrane protein that is 104 kDa in size and is expressed in the liver and kidney. It has two variants, KIM-1a and KIM-1b, which are both present in the very brief cytoplasmic region. KIM-1a is primarily expressed in the liver and lacks tyrosine kinase phosphorylation. HAVcr-1 is a hepatocyte-produced protein that may facilitate viral entry.[3,4] A natural ligand of KIM-1, immunoglobulin A, enhances the binding of the virus that causes hepatitis with its receptor. Two homologous tyrosine residues and a tyrosine kinase activation pattern are present in the KIM-1b variant, which is mostly produced in the kidney. Metalloproteinase is connected to KIM-1 cleavage. Activation of the extracellular signal-regulated kinase leads to constitutive KIM-1 shedding, and p38 mitogen-activated protein kinase accelerates the process. Tubule epithelial cells have the ability to undergo programmed cell death after damage (apoptosis). The elimination of apoptotic and necrotic cells is crucial to decrease inflammation and

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promote tissue regeneration. Kidney epithelial cells have a phagocytic phenotype because of the phosphatidylserine receptor KIM-1. It only recognizes the phosphatidylserine epitopes on the surface of apoptotic tubule epithelial cells.[5,6] Kidney epithelial cells have a phagocytic phenotype because of the phosphatidylserine receptor KIM-1. When combined with KIM-1, these phosphatidylserine epitopes phagocytose apoptotic and necrotic material first from tubule lumen. The phagocytic destruction of apoptotic cells is known as efferocytosis. Rapid shedding or an accumulation of soluble KIM-1 inside the extracellular matrix significantly decreases efferocytosis.[7]

The most commonly used confirmatory testing markers for the diagnosis of renal disease are serum creatinine, serum urea nitrogen, as well as creatinine clearance; unfortunately, they are all non-specific as well as insensitive for the detection of renal damage. As non-invasive indicators of renal damage, several urine proteins including biochemical markers were investigated. However, there has been little success in using them as general indicators to examine patients for renal disease and to identify the location of kidney injury. Therefore, the goal of the current study is to assess KIM-1 as a biomarker for CKD.

Aims and objectives

Aim of the study was to assess KIM-1 as a biomarker for CKD.

MATERIALS AND METHODS

Participants in this study will be chosen from the outpatient department and inpatient department of the Department of Medicine at the Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh, based on inclusion and exclusion criteria. In the hospital laboratory, the obtained samples will be examined for serum KIM-1, urea, creatinine, and creatinine clearance. In every patient, a thorough clinical examination will be performed along with a thorough history. Before enrolling research participants, informed written permission will be requested from them after providing all necessary information regarding the study. The research will only involve individuals who have given their consent. Throughout this investigation, the privacy of the obtained data will be maintained.

Primary tubular disorders, recent or contemporaneous use of potentially nephrotoxic medicines, acute kidney damage, terminal renal failure necessitating dialysis, and patients with known neurological problems were all reasons for subject exclusion from this study.

After a 12-h overnight fast, 5 cc of venous blood from each patient will be taken under aseptic conditions. The specimens will be centrifuged at 2000 rpm for 15 min to separate the serum after the clot is retracted. To estimate KIM-1, a fraction of the serum will be collected and kept in the deep freezer at −20°C. Urea and creatinine estimates will be done using the leftover serum.

Ethical Clearance: Ethical and Research Committee of Index Medical College Hospital and Research Centre in Indore, Madhya Pradesh, gave approval to the research. (MU/MM/BNS/2021/46 date: 11/11/2021).

Statistical analysis

The SPSS software, version 20.0 for Windows, will be used to conduct statistical analysis of the gathered data. The study's laboratory test findings will be summed up as mean+SD, and comparisons between the two participating groups will be made using the student's t-test. The frequency of unsatisfactory outcomes would be compared between the two participating groups using statistical analysis. We shall evaluate the 95% confidence interval (95% CI).

RESULTS

305 participants in total were included in the research. 150 of the individuals were healthy controls, whereas 155 of the subjects had CKD.

Using an independent t-test, the serum concentrations of KIM-1, urea, creatinine, as well as creatinine clearance were compared between CKD patients and healthy controls. Between CKD and non-CKD participants, there was a statistically significant difference in serum KIM-1 levels (t-value=3.41, P=0.001). This indicates that CKD participants had a greater mean serum KIM-1 concentration than non-diabetic subjects. As shown in Table 1, creatinine clearance was considerably reduced in CKD patients compared to non-CKD, whereas urea and creatinine levels were mostly significantly higher in CKD subjects compared to non-CKD with P<0.001.

As indicated in Figure 1, there was a significant negative relationship between KIM-1 and creatinine clearance, with an r=−0.660 and a P=0.001. This indicates that serum KIM-1 levels and creatinine clearance were correlated.

DISCUSSION

A wide range of clinical disorders are referred to as CKD, including albuminuria (A), which is <30 mg of albumin per gram of creatinine, retention of uremic toxins in the body, and situations where the structure and function of the renal organ are altered. The risk factors for the development of CKD include advanced age, low birth weight, reduced

Table 1: Comparison of urea, creatinine, creatinine clearance, and KIM-1 levels between the CKD and non-CKD subjects by independent t-test

n	Case		Control		t value	P-value
	155		150			
	Mean	SD	Mean	SD		
Urea	95.729	38.2056	28.013	4.9440	21.53	<0.001
Creatinine	2.3370	0.82553	0.7653	0.09758	23.16	<0.001
Creatinine clearance	33.671	11.0472	96.907	9.2383	−54.14	<0.001
KIM-1	126.0525	56.15141	107.3800	37.28462	3.41	0.001

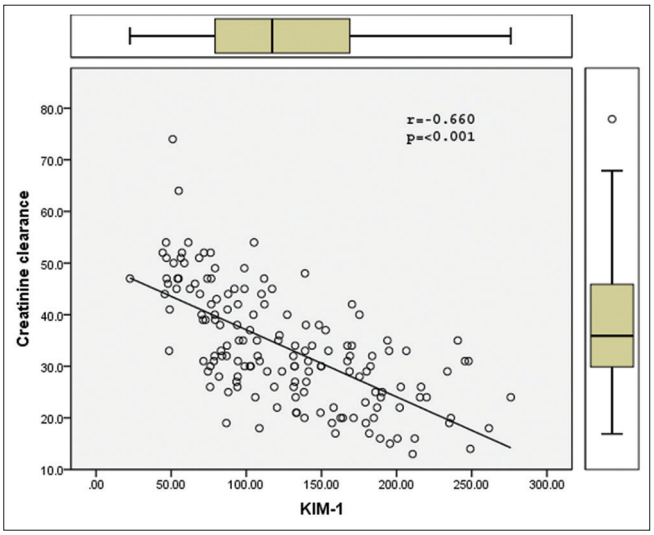

Figure 1: Correlation between creatinine clearances with KIM- 1 in CKD subjects by Karl Pearson's correlation coefficient method

renal mass, genetics, cardiovascular disease, diabetes, smoking, obstructive urinary disorders, urolithiasis, glomerulonephritis, interstitial nephritis, exposure to nephrotoxic drugs, and low socioeconomic status.[8-10]

Physicians can reduce the growth of the disorder and decrease its symptoms by establishing a timely diagnosis and providing the appropriate therapy. Researchers have created a variety of markers to evaluate kidney function over the years. The glomerular filtration rate (GFR) has been considered the most accurate indicator of renal function due to its downturn following systemic kidney injury. In addition to GFR, several other renal parameters in patients with CKD also decrease at the same time. A healthy kidney's GFR is 90 mL/min/1.73, whereas kidney disease in its latter stages is characterized by a value of <15 mL/min/1.73, as determined by the 2009 kidney disease: Improving global outcomes patient care guideline.[11,12] A GFR below 60 mL/min/1.73 over a period of at least 3 months is the standard GFR threshold for CKD. Alternative methods were used to determine how successfully exogenous substances were eliminated by filtration alone because it was difficult to assess GFR directly.[13]

In the normal kidney, KIM-1 is expressed at extremely low levels on the apical surface of renal tubular epithelial cells. In allograft nephropathy and other secondary and primary kidney disorders, it is upregulated. After kidney damage, the extracellular component of KIM-1 can split and quickly enter tubule lumens. It is an accurate and reliable indicator of renal proximal tubule injury. KIM-1 expression may influence tubule epithelial cell renewal. In CKD, it is also linked to inflammation and renal fibrosis. When kidney transplant dysfunction is the same, gradient boosting KIM-1 expression is observed to indicate a better prognostic indication.[14] To investigate serum KIM levels and their relationship to altered kidney function in 155 CKD patients and 150 participants without CKD, we conducted this case–control study. We found that CKD participants had significantly higher serum KIM-1 levels than non-CKD subjects (P=0.001). Similarly, this study showed that KIM-1 had a significant positive correlation with both urea and creatinine, with a P<0.05. A significantly unfavorable correlation between KIM-1 levels and creatinine clearance was also observed. Serum KIM-1 levels seemed to be strongly associated with renal features, following several investigations that revealed similar correlations between KIM-1 levels and renal parameters in patients.[15-18]

Limitations of the study

This study did not account for other potential factors that could affect KIM-1 levels and kidney function, such as comorbidities, medications, and lifestyle factors. These factors may have influenced the results and should be considered in future studies.

CONCLUSION

Individuals with CKD had significantly higher blood concentrations of KIM-1 and creatinine than the control group. Therefore, the diagnosis of CKD can be made using both of these criteria simultaneously. The serum levels of KIM-1 and creatinine were related to each other, demonstrating the importance of these indicators' combined serum levels for identifying CKD. KIM-1 is a precise and sensitive kidney injury biomarker that can identify early kidney injury in CKD and contribute to the

progression of interstitial fibrosis in kidney disease. It has the potential to predict how renal disease will develop and progress.

ACKNOWLEDGMENT

The authors thanks the management of Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh, India for their research support.

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Authors Contribution:
AB- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis, manuscript preparation and submission of article, design of study, statistical analysis and interpretation; **SN-** Concept, design, clinical protocol, manuscript preparation, editing, review manuscript, design of study, statistical analysis and interpretation.

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Source of Funding: Nil, **Conflicts of Interest:** None declared.