SSR Journal of Medical Sciences (SSRJMS)

Homepage: https://ssrpublisher.com/ssrjms/

Volume 3, Issue 7, 2026 ISSN: 3049-0375

Clinical Usefulness of Kidney Injury Molecule-1 (KIM-1) among Chronic Kidney Disease Patients in a Rural Tertiary Health Institution in Nigeria

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Received: *21.05.2026* | ***Accepted:*** *26.06.2026* | ***Published:*** *01.07.2026*

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DOI: *10.5281/zenodo.21079252*

Abstract **Original Research Article**

Chronic kidney disease (CKD) infiltrates every sphere of public health concern as it apparently shares link with most dreaded diseases in the society. In order to arrest the adverse outcomes that ensues from this disease it is unavoidably important to identify early, predictive and non-invasive biomarkers to detect CKD for early diagnosis among Nigerians. This study investigated a total of 270 subjects ranging from 18-92 years old, and was divided into four groups based on their eGFR. The first group contained 70 diabetic patients and hypertensive subjects with eGFR 60 ≥ 90ml/mins (Early Phase), the second group was 50 chronic kidney disease patients with eGFR 15 – 59ml/mins (Mid Phase), the third group was 50 chronic kidney disease patients with eGFR less than 15ml/mins and those in End-Stage Renal Disease (Late Phase) while the fourth group of 100 were control subjects with normal eGFR. Some biochemical parameters and KIM-1 serum of all the groups. Statistical analysis was done using SPSS. Bonferroni post-hoc option in ANOVA was used for comparison between more than two groups. Statistical significance was considered as $p < 0.05$. The level of the kidney Injury Molecule-1 increased significantly at $p \leq 0.05$ across the five stages of chronic kidney disease. KIM-1 was significantly good predictors of CKD and significantly predict the early stage of the disease. This is invariably important for early diagnosis that will foster early treatment.

Keywords: Chronic kidney disease, eGFR, Kidney Injury Molecule 1 (KIM-1).

Introduction

Chronic kidney disease is defined using Kidney Foundation Disease Outcomes Quality Initiative criteria as kidney damage or a glomerular filtration rate <60 mL/(min1.73 m^2) 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.

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 domains1 (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.

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.[33] Sabbisetti et al.[13] 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.[12,16,34,35]

Methodology

Study design and setting

The study was a case-control study, this study was designed for early detection of chronic kidney disease, which was carried out on Type2 diabetes mellitus patients, hypertensive patients, and patients living with chronic kidney disease who are attending Federal Teaching Hospital Ido-Ekiti, Ekiti State. The study consist of four groups, the first group was 50 diabetic patients and hypertensive subjects with eGFR 60 ≥ 90ml/mins, the second group was 70 chronic kidney disease patients with eGFR 15 – 59ml/mins, the third group was 50 chronic kidney disease patients with eGFR less than 15ml/mins and those in End-Stage Renal Disease while the fourth group of 100 were apparently healthy individuals in which KIM-1 as one of the important kidney biomarkers was analyzed in urine and serum of all the groups.

Ethical Clearance

The ethical clearance for this research was obtained at ethical committee Federal Teaching Hospital, Ido-Ekiti. Before the collection of the sample, information regarding the study was explained to the subjects. Oral and written consent for participation in the study were obtained.

Test and Control Group

The test group for this study were subjects in Type2 diabetes mellitus, hypertension and patients living with chronic kidney disease while the control group were subjects who do not have

any history and symptoms of diabetes mellitus, hypertension and chronic kidney disease.

Inclusion Criteria

Inclusion criteria include subjects who are Hypertensive, Type2 diabetes mellitus and those with signs and symptoms of chronic kidney disease.

Exclusion Criteria

Subjects who had undergone strenuous exercise, pre-eclampsia, HIV- Tuberculosis co-infection, those with urinary tract infections or acute illness with fever, and those who refused to give consent were excluded from the study.

Data Collection Procedure

Instruments

A semi-structured, interviewer-administered questionnaire. The socio-demographic information of each subject was collected, and the past medical history of hypertension, diabetes mellitus and renal diseases was obtained. Current history of nocturia, dysuria, haematuria, frothiness of urine and facial/leg swelling was obtained. A family history of hypertension and diabetes mellitus was also taken. Other information sought in the questionnaire consisted of cigarette smoking and alcohol intake.

Sample Collection and Processing

A total of 5ml blood was collected into a plain bottle for analysis biomarkers under investigation and Sera were obtained by centrifugation for 15 minutes at 2000g at 4°C within 30 minutes of collection and frozen properly until analysis is carried out.

Body mass index (BMI)

BMI was calculated as weight /height2 (kg/m^2). Subjects were graded as normal weight, overweight and obese when BMI was 18.5-24.9, 25-29.9 and $\geq 30 kg/m^2$ respectively. Obesity was graded as mild, moderate and severe when BMI was 30- 34.9kg/m^2, 35-39.9kg/m^2 and $\geq 40 kg/m^2$ respectively.

Height – This was measured using a stadiometer by a vertical board with an attached metric rule and a horizontal headboard. The subjects were asked to be barefooted, arms by their sides and to look straight backing the vertical board. The height was recorded to the nearest 0.1cm.

Weight – This was taken while in a light clothing with the subject standing in the centre of a weighing scale's platform. Weight was recorded to the nearest 0.1kg.

Blood Pressure Measurement

Blood pressure was measured according to the guidelines presented in the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the left arm after participants have been seated for at least five minutes. Electronic blood pressure monitor (Omron M X2 Basic, Omron Health Care Co ltd, Kyoto Japan) that has been validated by the British Hypertension Society were used with appropriate cuff. Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic BP ≥ 90mmHg or who had normal blood pressure but were pharmacologically treated for hypertension were categorized as hypertensive subjects.

Biochemical Parameters

The concentration of KIM-1 in the sera of CKD subjects and controls subjects were determined by a conventional capture ELISA method (Melsin Medical Co. Ltd. China). The standard was
provided by the manufacturer and determination was carried out according to manufacturer's instructions (Melsin Medical Co. Ltd. China) using MINDRAY MR-96A ELISA Reader.
Determination of Urea, Creatinine, Calcium, Inorganic Phosphatase, Uric Acid, Cholesterol, Triglyceride, LDL-C, HDL-C, Albumin, ACR were done using Agappe Reagent on Full Chemistry Auto-analyser Chemray 240. Na, K and Cl were determined using ION SELECTIVE

ELECTRODE 6000 Auto-analyzer Q-LYTE 60 using Standard A and B.

Statistical Analysis

Results obtained were subjected to statistical analysis using software package for social sciences version 23 SPSS. Results generated were expressed as mean ± SD, and a P- value of <0.05 was considered significant. Results obtained were presented in Tables, figures and ROC curve were also used where necessary.

RESULTS

A total of 270 participants enlisted for this study consisting of 170 participants with hypertension, diabetes and CKD while 100 participants were healthy controls. The mean and standard deviation of serum KIM-1, Urea, Creatinine, Calcium, Inorganic Phosphatase, Uric Acid, Cholesterol, Triglyceride, LDL-C, HDL-C, Albumin, ACR, Na, K and Cl are contained in Table 2. The mean serum of KIM-1, Urea, Creatinine, Inorganic Phosphatase, Uric Acid, Cholesterol, Triglyceride, LDL-C, Na were significantly higher in CKD participants compared to the control as shown in Table 2 while Albumin and HDL-C are significantly lower in subjects with CKD compared with the control as shown in Table 2. However, the levels of Cl^- and K^+ in the CKD subjects compared to the control group was not statistically significant.

Similarly KIM-1 was higher in CKD subjects than in control (the levels of the KIM-1 across all the stages (stage 1: Mean±SD= 5.98±5.57, stage 2: Mean±SD= 3.54±4.26, stage 3: Mean±SD= 2.75±3.71, stage 4: Mean±SD= 4.66±5.11) is significantly (*p=0.000*) higher than its level in the control group (Mean±SD= 1.15±0.10), and by comparison with the other stages, its level in the late stage (stage 5: Mean±SD= 12.24±3.78) is more increased.

Figure 1 shows the classification of subjects (n=170) into different stages of CKD using their eGFR.

Figure 2 shows the classification of subjects (n=270) into different phases of CKD based on their stages; 170 subjects with history of hypertension, type2 diabetes mellitus, patients living with CKD and 100 subjects that does not have any history of CKD.

Table 1 shows the general characteristics of the study population. This study shows that the prevalence of chronic kidney disease is significantly (*p=0.000*) higher in those above 45years of age. Most of the participants reported family history of renal disease, currently hypertensive and diabetic which are both risk factor of developing CKD. Consumption of alcohol is significantly related to the prevalence of CKD as opposed to the smoking habit of the participants.

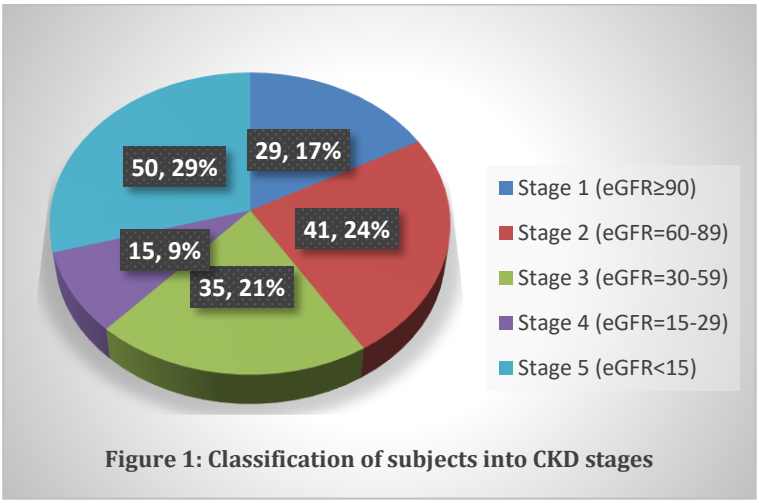

Figure 1: Classification of subjects into CKD stages

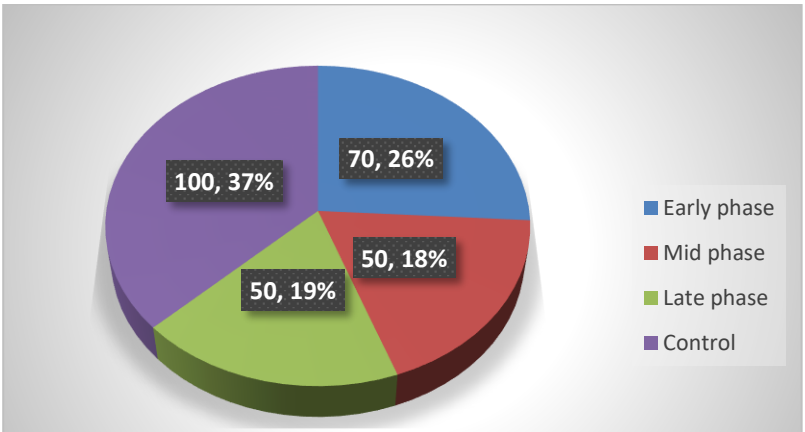

Figure 2: Classification of CKD phases

Table 1: General characteristics of the study population

Variable	Categories	CKD (n=170)	NON CKD (nCKD) (n=100)	$\chi 2$	*p-value*
AGE (Years) Mean±SD = 55.1±21.5	<45years	17 (10.0)	66 (66.0)	92.740[a]	.000
	≥45 years	153 (90.0)	34 (34.0)		
Gender	Male	69(40.6)	37(37.0)	11.990[a]	.001
	Female	101(59.4)	63(63.0)		
Body Mass Index (BMI)	Underweight (<18.5)	4(2.4)	8(8.0)	21.761[a]	.000
	Healthy weight (18.5-<25)	55(32.4)	54(54.0)		
	Over weight (25 - <30)	75(44.1)	30(30.0)		
	Obesity (≥30)	36(21.2)	8(8.0)		
Medical History					
Family history of renal disease	Yes	98 (57.6)	11 (11.0)	56.913[a]	.000
	No	72 (42.4)	89 (89.0)		
Do you have Diabetes Mellitus?	Yes	100(58.8)	10(10.0)	12.522[a]	.001
	No	70(41.2)	90(90.0)		
If yes, How long?	One year	40 (23.5)	5(5.0)	58.692[a]	.002
	Two years	21(12.4)	5(5.0)		
	more than 2 years	39(22.9)	0(0)		

	None	70 (41.2)	90 (90.0)		
Do you have Hypertension?	Yes	101(59.4)	21(21.0)	37.508[a]	.000
	No	69(40.6)	79(79.0)		
If yes, How long?	One year	27(15.9)	20(20.0)	58.607[a]	.000
	Two years	34(20.0)	0(0)		
	more than 2 years	40(23.5)	1(1.0)		
	None	69(40.6)	79(79.0)		
Currently experienced symptoms	General body Weakness and fatigue	59(34.7)	17(17.0)	68.886[a]	.000
	Weight loss	35(20.6)	15(15.0)		
	Fever	28(16.5)	12(12.0)		
	Rashes	24(14.1)	1(1.0)		
	Itching	10(5.9)	4(4.0)		
	None	14(8.2)	51(51.0)		
On any drug	No	68(40.0)	37(37.0)	0.238[a]	.625
	Yes	102(60.0)	63(63.0)		
Type of drug	Antihypertensive	70(42.9)	20(20.0)	18.840[a]	.000
	Antimalaria	69(40.6)	67(67.0)		
	Antidiabetic	28(16.5)	13(13.0)		
	None	3(1.8)	0(0)		
Lifestyle					
Do you exercise?	No	87(51.2)	24(24.0)	19.208[a]	.000
	Yes	83(48.8)	76(76.0)		
Do you smoke?	Yes	64(37.6)	33(33.0)	0.591[a]	.442
	No	106(62.4)	67(67.0)		
Do you take alcohol?	Yes	104(61.2)	63(63.0)	7.176[a]	.007
	No	66(38.8)	37(37.0)		

CKD: Chronic Kidney Disease, $p \leq 0.05$ is statistically significant.

Table 2: Comparison of parameters between the CKD and control groups

Parameters	**CKD (n=170) Mean±SD**	**Controls (n=100) Mean±SD**	***p-value***
AGE (years)	64.24±14.90	39.53±22.11	0.000

BMI (kg/m^2)	26.48±4.77	23.98±4.79	0.000
Na^+ (mmol/L)	135.27±7.04	138.67±5.73	0.000
K^+ (mmol/L)	4.04±0.65	3.97±0.65	0.376
Cl^- (mmol/L)	102.69±4.50	101.91±4.33	0.162
Urea (mmol/L)	10.70±9.09	3.82±1.23	0.000
Creatinine (umol/L)	285.95±30.60	79.23±15.82	0.000
Cholesterol (mmol/L)	4.78±0.98	4.31±1.11	0.001
Triglyceride (mmol/L)	1.07±0.41	0.94±0.37	0.009
HDLC (mmol/L)	1.08±0.31	1.17±0.26	0.018
LDLC (mmol/L)	3.21±1.00	2.73±1.13	0.000
Albumin (g/L)	32.97±2.47	37.43±4.94	0.000
IP (mmol/L)	1.50±0.29	1.12±0.20	0.000
UA (mmol/L)	0.38±0.11	0.34±0.10	0.002
Calcium (mmol/L)	1.81±0.38	2.30±0.31	0.000
ACR (mg/g)	1312.61±376.49	16.30±7.45	0.000

Table 3: Level of KIM-1 in the serum of the subjects with the control

	Biomarkers	**KIM-1 (Mean±SD)**
	CKD Stage	
Early Stage	Stage 1 (N=36)	5.98±5.57
	Stage 2 (N=54)	3.54±4.26
Mid Stage	Stage 3 (N=55)	2.75±3.71
	Stage 4 (N=15)	4.66±5.11
Late stage	Stage 5 (N=50)	12.24±3.78
	Control (N=60)	1.15±0.10
	F-statistics	53.841
	p-value	0.000

Table 4: Pearson's Correlation between serum creatinine, eGFR and KIM-1

		KIM-1 (ng/ml)	Creatinine (umol/L)	eGFR (ml/min)
N=170				
KIM-1 (ng/ml)	*r*	1	.418**	-.538**
	p		.000	.000
Creatinine (umol/L)	*r*	.418**	1	-.673**
	p	.000		.000
eGFR (ml/min)	*r*	-.538**	-.673**	1
	p	.000	.000	
***. Correlation is significant at the 0.05 level (2-tailed).**				
****. Correlation is significant at the 0.01 level (2-tailed).**				

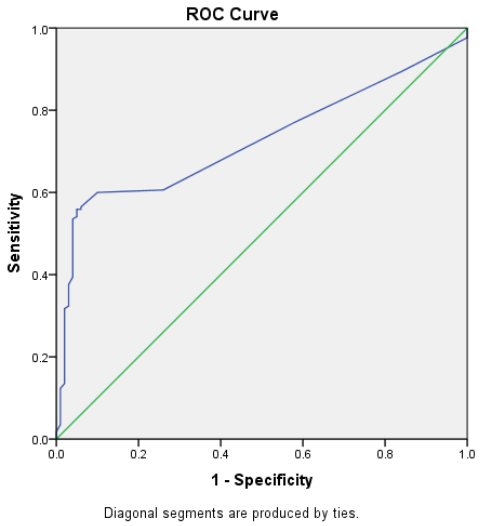

Figure 3: ROC curve determining the usefulness of KIM-1 in the diagnosis of chronic kidney disease.

DISCUSSION

KIM-1 has been shown to be a good predictor of renal injury prior to detectable changes in eGFR (Nicholas et al, 2008, Han et al., 2002). It was suggested by Zeisberg et al., 2010 that it could be a potential biomarker of chronic kidney disease due to tubulointerstitial damage. The prediction of chronic kidney disease using KIM-1 was confirmed by this study as the logistic regression model showed that it can significantly predict its early detection as the eGFR was used to evaluate this. The correlation between KIM-1 and eGFR was found to be negative as was also observed in the study of Peng et al., 2022. Findings from this study showed significant ($p<0.05$) increase in the level of KIM-1 from the early stage of CKD to the late stage. There was observed a significant correlation ($r=0.418$, $p=0.000$) between KIM-1 and creatinine as opposed to Peng et al., 2022 who stated that the two were uncorrelated. However, the positive correlation ($r=0.280$, $p<0.05$) they established in

their study between KIM-1 and β-2-M is also confirmed in this study (r=0.194, p<0.05). The result for the ROC analysis of the beta2-microglobulin in chronic kidney disease showed an AUC of 0.726.

CONCLUSION

In CKD, Serum KIM-1 would be a useful biomarker of early diagnosis even when serum creatinine is still within the normal range despite that the kidney may have damaged to the tune of 40-50%.

ACKNOWLEDGEMENT

The author thank the staff of Federal Teaching Hospital, Ido-Ekiti, Ekiti State, Nigeria.

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