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Original Research Paper

KIM-1 as an Early Indicator of Impairment of the Kidneys in Diabetic Nephropathy

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ABSTRACT:
Introduction: Diabetic kidney disease, or DKD, is a very common ailment all over the world. It is the main cause of end-stage kidney disease (ESKD) and one of the most common consequences of diabetes mellitus (DM). To replace the gold standard biomarker, the uACR there is a need to find useful biomarkers that can forecast the early development of DN to detect this clinical entity. **Material & Methods:** The study enrolled 121 diagnosed patients of Diabetes Mellitus II with microalbuminuria (DN), 121 with Diabetes mellitus II (DM II), and 121 with healthy controls. Laboratory investigations performed were FPG, PPG, HbA1c, Creatinine, KIM-1, eGFR, and uACR. **Results:** Significantly higher average levels of FPG, PPG, HbA1c, Creatinine, uACR, and KIM-1 were found in patients compared to the control group. The decrease in mean eGFR was also significant in DN than DM. There was a positive correlation between serum KIM-1 levels and uACR, unlike in patients with DM II and controls. **Conclusion:** The results suggest that KIM-1 can be considered a valuable biomarker for the early detection of DN in T2DM patients.

Keywords: kidney injury molecule 1 (KIM-1)); diabetic nephropathy; eGFR, uACR

INTRODUCTION:

Diabetic kidney disease, or DKD, is a very common ailment all over the world. It is the main cause of end-stage kidney disease (ESKD) and one of the most common consequences of diabetes mellitus (DM). Three basic axes are involved in its pathogenesis: the inflammatory, metabolic, and hemodynamic axes.[1] About 30 to 40 percent of people with type 1 or type 2 diabetes mellitus (DM) also have diabetic kidney disease (DKD).[2] The International Diabetes Federation (IDF) has released data showing that 537 million adults worldwide between the ages of 20 and 79 had diabetes in 2021, accounting for 10.5% of the world's population.[3] In India, there are presently 40.9 million people suffering from diabetes mellitus (DM).[4] By 2030, about 80–87 million people in India will be diabetic. Microvascular problems like retinopathy, neuropathy, and nephropathy have been linked to chronic diabetes.[5] The onset and course of DN are influenced by several different processes. At the moment, a common non-invasive screening method for the illness is persistent microalbuminuria along with a steady drop in estimated glomerular filtration rate (eGFR).[6] There are a number of limitations with microalbuminuria as determined by the urine albumin creatinine ratio (uACR) that impact the prognosis and early identification of DN.[7] It has been shown that some diabetic patients with microalbuminuria can return to normoalbuminuric levels while simultaneously experiencing a decrease in their urinary albumin excretion rate. In particular, microalbuminuria is diagnosed only after significant glomerular damage has occurred and does not always result in renal deterioration.[8] Therefore, it is essential to find useful biomarkers that can forecast the early development of DN to detect this clinical entity. To replace the gold standard biomarker, the uACR, several glomerular, tubular, and inflammatory indicators have recently been identified as possible markers for DN; however, most of these markers still require validation. Kidney injury molecule-1 (KIM-1), a Type I transmembrane glycoprotein secreted by renal proximal tubule epithelial cells, is a potentially useful diagnostic tool for renal tubulointerstitial damage.[9] Studies show that KIM-1 functions as a prognostic indication as well as a sensitive and specific marker of kidney injury.[10] Only a small number of research has been conducted on the usefulness of blood Kim-1 as early detection of kidney damage, and the results are inconclusive. However, numerous studies have shown that urine Kim-1 is one of the early indicators of acute renal injury or chronic kidney disease (CKD).[11]

Therefore, the aim of this study was to determine whether serum Kim-1 is effective as an early indicator of renal impairment in type 2 diabetes patients.

MATERIAL & METHODS:

After receiving ethical approval from the institutional Human ethics committee, a retrospective study was conducted on 263 participants in the biochemistry department. These included 121 diagnosed patients of Diabetes Mellitus II with microalbuminuria (DN), 121 with Diabetes mellitus II (DM II), and 121 healthy controls of similar age attending the outpatient department of Index Medical College, Hospital & Research Centre. (Malwanchal University, Indore, Madhya Pradesh). All diabetic Patients were diagnosed with DM II according to the American Diabetes Association guidelines. Patients of Diabetic Nephropathy (DN) were diagnosed based on the uACR >30 mg/g. Detailed information about the patients was gathered using a pre-test form, including their age, gender, and any family or personal history of chronic diseases. Clinical examination and laboratory investigations were done which included: 1. Morning mid-stream urine sample, obtained using disposable cups without preservatives for Quantitative measurement of urinary albumin and creatinine to calculate urinary albumin to creatinine ratio. 2. Blood samples were obtained in the morning after an overnight fast for estimation of fasting Plasma Glucose (FPG) and postprandial glucose (PPG) by GOD-POD method, HbA1c (Ion exchange resin method), Creatinine (Modified Jaffe's method) and KIM-1 (Sandwich ELISA). and 3. Calculation of estimated glomerular filtration rate (MDRD).[12]

Inclusion and Exclusion Criteria:

Both Male and Female between age 40 –70 years who satisfy the criteria of Diabetes Mellitus II with and without microalbuminuria were offered enrolment in the study.

Patients with Acute exacerbations of chronic renal insufficiency, Connective tissue disease, tumors, familial hyperlipidaemia, nephrotic syndrome, Pregnancy, debilitating disease/ disorder, or social condition that in the judgment of the investigator would interfere with or serve as a contraindication to adherence to the study protocol were excluded.

Statistical Analysis:

All the Parameters were analyzed using statistical software SPSS VERSION 27.0 and the results were expressed as Mean ± SD. The comparisons of levels of these variables among patients and controls have been done using one-way *ANOVA Post Hoc tests*. Pearson's correlation coefficient has been also used to find the correlation between eGFR and serum concentration of KIM-1.

RESULTS:

The study summarizes the Clinical and Biochemical Characteristics of all participants, presenting them as Mean ± SD in Table 1, Chart 1, and Chart 2.

Significantly higher average levels of FPG, PPG, and HbA1c were found in individuals with Type II diabetes ($p<0.001$) compared to the control group. The increase in the same variables was not significant in DN compared to DM II. In patients with diabetic nephropathy (DN), there was a positive correlation between serum KIM-1 levels and urinary albumin-to-creatinine ratio (uACR), unlike in patients with type II diabetes (DM II) and controls, where a correlation with KIM-1 was also observed. There was a noticeable difference in KIM 1 levels between individuals without diabetes and diabetes patients with diabetic nephropathy. Increase in mean Creatinine, uACR and KIM-1 and the decrease in mean eGFR were also significant in DN than DM II ('p'<0.001) but the changes in mean uACR and KIM-1 in DM II and controls were not significant. A significant difference was found in the serum levels of creatinine and eGFR between the control group and DM II ('*p'<0.002* & '*p'<0.002*) respectively.

Table: 1- Comparison of Laboratory Variables among Patients and Controls.

Parameters	DN (Mean ± SD)	DM II (Mean ± SD)	Controls (Mean ± SD)
Fasting Plasma Glucose (mg/dl)	142.95 ± 11.44	140.87 ± 11.43	87.45 ± 7.14
	'*p'=0.257*		***'p'<0.001***
Post Prandial Glucose (mg/dl)	220.32 ± 21.21	215.29 ± 21.23	123.46 ± 8.63
	'*p'=0.077*		***'p'<0.001***
HbA1c (%)	7.60 ± 0.47	7.46 ± 0.62	5.13 ± .51
	'*p'=0.100*		***'p'<0.001***
Creatinine (mg/dl)	1.33 ± 0.31	0.86 ± 0.17	

			0.77 ± 0.07
	'p'<0.001		***'p'<0.002***
eGFR (ml/min/1.73 m^2)	55.95 ± 14.89	91.08 ± 20.89	101.17 ± 18.48
	'p'<0.001		***'p'<0.001***
uACR (mg/g)	105.37 ± 60.06	13.69 ± 5.77	9.12 ± 4.11
	'p'<0.001		*'p'<0.565*
Serum KIM-1 (ng/ml)	3.46 ± 1.18	0.66 ± 0.32	0.51 ±0.27
	'p'<0.001		*'p'<0.518*

A 'p' value < 0.05 was considered significant.
A 'p' value < 0.01 was considered highly significant.

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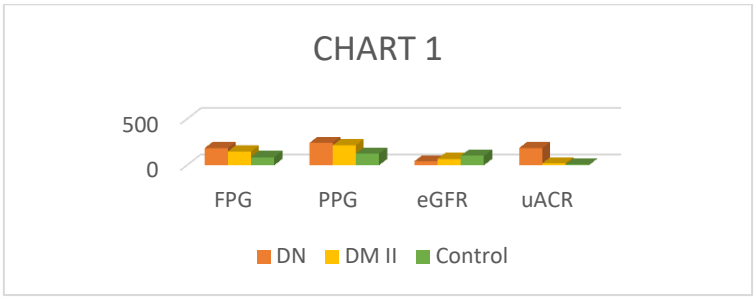

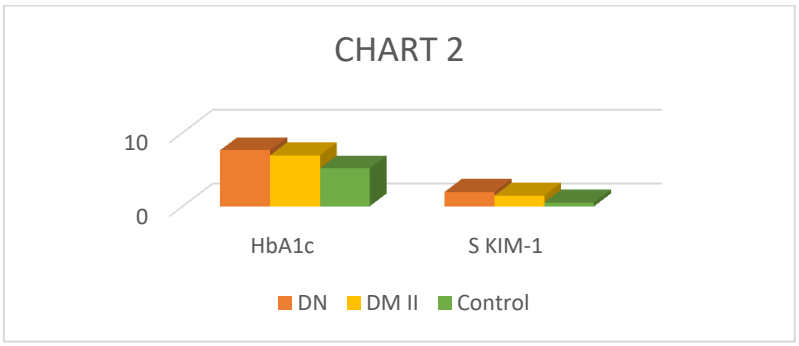

TABLE 2- Pearson correlation association between KIM-1 and uACR, eGFR, Creatinine and HbA1c in DN and DM II.

Lab variables	KIM-1	N	Pearson Correlation	'p' value
uACR	DN	121	.207	***.022***
	DM II	121	.118	.198
eGFR	DN	121	-.203	**.026**
	DM II	121	-.074	.420
Creatinine	DN	121	.246	***.006***
	DM II	121	.89	.330
HbA1c	DN	121	.022	.810
	DM II	121	.007	.936

A 'p' value < 0.05 was considered significant.
A 'p' value < 0.01 was considered highly significant.

Table 2 displays the results of Pearson's correlation analysis examining the relationship between KIM-1 and uACR, eGFR, Creatinine, and HbA1c in patients with DN and DM II. The KIM-1 level was found to have a positive correlation with uACR, Creatinine, and HbA1c, and a negative correlation with eGFR in patients with DN (r= .207, .246, .022, and -.203, respectively) and DM II (r= .118, .89, .007, and -.074, respectively). In DN, there was a significant correlation between KIM and levels of uACR, eGFR, and Creatinine ('p' values = .022, .026, and .006, respectively). However, this correlation was not significant in DM II, ('p' values = .198, .420, and .330, respectively). However, there was no significant correlation between serum KIM-1 levels and HbA1c in both DN and DM II (p values = .810 and .936 respectively).

DISCUSSION:

The present study was conducted to analyze the role of serum KIM-1 as an early marker for DN in the Department of Biochemistry, Index Medical College, Hospital & Research Centre, Indore, M. P., India. The results of this retrospective study showed that both groups with diabetic nephropathy (DN) and type II diabetes (DM II) had higher levels of serum KIM-1 compared to the control group of healthy individuals. The rise in serum KIM-1 levels in patients with diabetic nephropathy was found to be highly significant (p-value <0.001), while the increase in patients with type 2 diabetes was not significant compared to the control group. In diabetic nephropathy patients, there was a significant negative correlation between KIM-1 and eGFR, with a p-value of .026. However, in patients with type II diabetes, this finding is not considered significant (p-value = 0.420). There was no significant correlation found between the levels of serum KIM-1 and serum HbA1c in patients with either diabetic nephropathy (DN) or type 2 diabetes mellitus (DM II), with p-values of .810 and .936, respectively.

Our data aligned with the figures reported in both local and international literature by authors such as EL-Attar HA et al.,[12] Fajaryani D et al.,[13] El-Ashmawy NE et al.,[14] and others who reported that there was a notable rise in KIM-1 and Creatinine levels, as well as a decrease in eGFR, in patients with Diabetic Nephropathy compared to the control group.

Another study discovered that as nephropathy progresses, levels of urinary KIM-1 increase. Furthermore, this study showed that urinary KIM-1 levels are a separate risk factor for estimated glomerular filtration rate (eGFR) and albuminuria in diabetic patients.[12] According to a study by Fajaryani D et al.,[13] levels of KIM-1 were elevated in individuals with diabetes mellitus with and without diabetic nephropathy compared to those without diabetes. There were noticeable variations in KIM-1 levels among individuals without diabetes, those with diabetes but without diabetic nephropathy, and those with diabetes and diabetic nephropathy. The levels of KIM-1 were higher in diabetic patients without diabetic nephropathy compared to non-diabetic individuals. There was a notable variation in KIM 1 levels between non-diabetic subjects and diabetic patients without diabetic nephropathy. Patients with diabetes and diabetic nephropathy (DN) had higher levels of KIM-1 compared to non-diabetic individuals. There was a noticeable difference in KIM 1 levels between individuals without diabetes and diabetes patients with diabetic nephropathy. An investigation by El Ashmawy et al.,[14] discovered a positive correlation between age, the length of diabetes, fasting blood glucose, HbA1C, BUN, and creatinine and microalbuminuria. However, KIM-1 levels in serum were not measured in this study; instead, levels in urine were. Age, the length of diabetes, fasting blood glucose, HBA1C, BUN, creatinine, and microalbuminuria were all positively correlated with urinary KIM-1, while eGFR was negatively correlated ($P < 0.001$).

These results indicate that damage to the proximal tubule may exist in individuals with type 2 diabetes before microalbuminuria develops. There are many reasons to believe that KIM-1 is released into the bloodstream after damage to the kidney's proximal tubules. After injury, the polarity of tubular cells is lost, causing KIM-1 to be released directly into the interstitium. Moreover, when there is damage to the tubules, there is an increase in permeability that allows the contents of the tubules to leak back into the bloodstream.[11] Moreover, heightened permeability of small blood vessels plays a crucial role in the development of kidney disease.[15] In renal microvascular endothelial cells, the structure of the actin cytoskeleton is disturbed, leading to the breakdown of connections between cells and between cells and the surrounding matrix. This separation causes endothelial cells to detach from the basement membrane, which enables KIM-1 to enter the bloodstream.[16]

In our research, we found that serum KIM-1 levels were closely related to the levels of uACR, eGFR, and creatinine in diabetic nephropathy patients. Nevertheless, there was no correlation between serum KIM-1 levels and factors such as uACR, eGFR, creatinine, and HbA1C in patients with Type II Diabetes Mellitus. The average creatinine levels were 0.77 ± 0.07 mg/dl for healthy individuals, 0.86 ± 0.17 mg/dl for those with diabetes without microalbuminuria (DM II), and 1.33 ± 0.31 mg/dl for those with diabetes and microalbuminuria (DN). The distinction between the groups was found to be statistically significant ('p' < 0.002). Nevertheless, there was a significant link between serum KIM-1 and creatinine levels in patients with DN and type 2 DM II. In patients with DN, there was a positive correlation

between serum KIM-1 levels and uACR, unlike in patients with DM II and controls, where a correlation with KIM-1 was also observed. Research has demonstrated that urinary KIM-1 is a reliable indicator of kidney damage in both rodents and humans suffering from acute kidney injury (AKI).[17] Nevertheless, research on the use of urinary KIM-1 as an indicator of DN has produced mixed results.[18] According to the study, both the DN and DM II diabetic groups had significantly higher serum KIM-1 levels than the control group. However, we have somewhat established a correlation between KIM-1 levels and alterations in eGFR and uACR.[19] It is crucial to remember that because of the small sample size and constrained time frame of our study, the results might not be typical of the whole population. Therefore, in order to ascertain whether and how uKIM-1 can be used in clinical diagnosis, comprehensive research is imperative.

CONCLUSION:

As a result of the high levels of KIM-1 in patients with DN, as well as the correlation between KIM-1 levels and eGFR and uACR, it can be inferred that serum levels of KIM-1 could serve as crucial markers for the early detection of DN. Additionally, our research indicates that KIM-1 could be used as an early warning sign of kidney issues in individuals with type 2 diabetes.

CONFLICT OF INTEREST: None

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