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UTILITY OF SERUM KIDNEY INJURY MOLECULE-1 (KIM-1) AS A DIAGNOSTIC TOOL FOR EARLY MARKER FOR DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE-2 DIABETES MELLITUS

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ABSTRACT
Diabetic nephropathy (DN) presents a multifaceted challenge, representing one of the most prevalent complications arising from diabetes and a significant contributor to chronic kidney disease. Among potential biomarkers, kidney injury molecule-1 (KIM-1) stands out for its sensitivity and specificity in detecting kidney injury, as well as its prognostic potential. This study aims to investigate the utility of serum KIM-1 as an early indicator of diabetic nephropathy. A total of 126 participants diagnosed with diabetes were enrolled and categorized into two groups based on the presence or absence of microalbuminuria, representing T2DM patients with nephropathy. Standard laboratory techniques were utilized to measure parameters such as blood glucose, HbA1c, albumin and serum creatinine levels. Serum KIM-1 levels were quantified using a sandwich enzyme-linked immunosorbent assay. A significant disparity in mean serum KIM-1 levels was observed between the diabetic individuals with or without microalbuminuria ($P = 0.0001$). Furthermore, participants with an extended duration of diabetes exhibited elevated serum KIM-1 values ($P = 0.001$ in DM without microalbuminuria; $P = 0.001$ for DM with microalbuminuria). This study underscores significantly heightened serum KIM-1 levels in both diabetic groups, with a positive correlation observed between serum KIM-1 levels and the duration of diabetes. Consequently, serum KIM-1 emerges as a promising early diagnostic marker for predicting nephropathy among individuals with diabetes in our population.
KEYWORDS: KIM-1; Diabetic Nephropathy; Type II diabetes mellitus

INTRODUCTION
The escalating global incidence of type 2 diabetes presents a critical public health challenge, primarily fueled by the dual forces of increasing obesity rates and population aging. The latest estimates reveal a substantial increase in global diabetes prevalence among individuals aged 20-79, underscoring the urgency of addressing this burgeoning health concern. In 2021, the prevalence stood at 10.5%, affecting approximately 536.6 million people worldwide(Sun et al. 2022). Diabetic nephropathy (DN) is a multifaceted ailment, ranking among the most prevalent complications associated with diabetes and a leading cause of chronic kidney disease (CKD)(Kapoula et al. 2019) . It's estimated that approximately 10%–30% of Type 1 diabetes mellitus patients and 15%–40% of Type 2 diabetes mellitus patients will develop DN(Sutton 2009). Various factors, including alterations in renal hemodynamics, activation of protein kinase C, hexosamine biosynthesis, the aldose reductase pathway, and the formation of advanced glycation end products, contribute to the decline in renal function among DN patients(Campion et al. 2017). Despite the widespread use of urine microalbuminuria as a standard diagnostic tool for DN, variations in albuminuria across different ethnic groups have been observed, underscoring the need for early diagnosis and preventive measures to impede the progression to end-stage renal disease(Parving et al. 2006). Numerous studies have explored novel biomarkers for DN, targeting glomerular injury, tubular injury, inflammation, and the oxidative stress pathway to enable early identification of DN(Ma et al. 2015). However, the validation of these biomarkers remains a challenge due to their diversity.
Microalbuminuria, defined as a urinary albumin excretion rate (UAE) ranging from 30 to 300 mg/day, serves as the earliest and most frequently utilized clinical indicator of diabetic nephropathy (DN). Beyond its utility in identifying early renal damage, MA holds independent prognostic value as it is associated with heightened cardiovascular risk in individuals with diabetes (Mogensen 1984; Deckert et al. 1989; Bruno et al. 2007; Ninomiya et al. 2009). Current

studies suggest that only around 30% of individuals with microalbuminuria progress to overt nephropathy following a 10-year followup period(Rossing et al. 2005; Perkins et al. 2010). Moreover, advanced structural changes in the glomerular basement membrane may already be present by the time MA becomes clinically detectable. Indeed, emerging evidence indicates that a notable proportion of patients initially diagnosed with microalbuminuria (MA) may experience a regression to normoalbuminuria over time(Fioretto et al. 1994; Perkins et al. 2003). The collective findings underscore a shifting perspective on microalbuminuria (MA), indicating that it may serve more as a diagnostic marker rather than a definitive predictor of diabetic nephropathy (DN). Consequently, there arises a pressing need to explore and evaluate alternative biomarkers that could offer earlier insights into the development and progression of DN.

Kidney injury molecule-1 (KIM-1) emerges as a promising candidate, being a Type I transmembrane glycoprotein expressed on renal proximal tubule epithelial cells and playing a crucial role in tubulointerstitial damage (Kin Tekce et al. 2014). A study from three-year prospective interventional study revealed that elevated baseline levels of urinary KIM-1 were associated with a more rapid decline in glomerular filtration rate (GFR) among individuals with type 2 diabetes and diabetic nephropathy (DN). While studies have demonstrated that urinary KIM-1 serves as an early marker of acute kidney injury (AKI) and CKD, the utility of blood KIM-1 as an early marker of renal damage remains inconclusive, with limited research conducted in this area (Nielsen et al. 2012; Conway et al. 2012). Hence, the present study seeks to evaluate the usefulness of serum KIM-1 as a potential marker for DN.

MATERIALS AND METHODS

We have conducted this study after obtaining clearance from the Institute Ethics Committee (SSMC/MED/IEC-170/Nov-2023). This study enrolled a total of 126 participants from the Department of General Medicine and Nephrology at Sri Siddhartha Medical College and Hospital, Tumkur, Karnataka between November 2023 to April 2024. Two groups were included in this study. Group 1 comprised of 63 type 2 diabetic patients with microalbuminuria, group 2 included 63 type 2 diabetic patients without microalbuminuria.

Exclusion criteria for the study were of thyroid disease, those on steroids, nephrotoxic drugs.

Laboratory Investigations:

Urine examination was performed for subjects in all the groups to look for microalbuminuria by immunoturbidimetry technique. Random urine samples were collected from the patients and control subjects without any febrile illness or urinary tract infection to estimate the presence of albumin in urine. Patients were categorized under the albuminuria group only when testing for both urine samples showed positivity for albumin. The samples were centrifuged and stored at -20˚C in the deep freezer.

Blood samples were obtained from all participants in the morning following an overnight fast of 8 hours, with serum separated and stored at -80°C. Standard laboratory techniques were employed to measure blood glucose, HbA1c, albumin and creatinine levels. Serum KIM-1 levels were quantified using a sandwich enzyme-linked immunosorbent assay.

Statistical Analysis:

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 16 for Windows, Chicago, U.S.A. Comparison of parameters between groups were compared using analysis of variance (ANOVA). Pairwise comparisons between groups were used for Tukey's multiple comparison test. Correlation of Serum KIM 1 with FBS, PPBS, HbA1c, Creatinine and Albumin were used for Pearson's correlation coefficient. Receiver operating characteristic (ROC) curve along with area under the curve were performed for assessing the diagnostic utility of Serum KIM-1 levels. All statistical tests were two-tailed, and a significance level of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 126 patients (64% male and 36% female) were enrolled in this study, 63 diabetics without microalbuminuria, and 63 diabetics with microalbuminuria. The baseline characteristics of the study participants are summarized in Table 1. The mean ages were 56.03 ± 3.19 years for diabetics without microalbuminuria, and 58.97 ± 1.88 years for diabetics with microalbuminuria. Statistical significant difference in mean age was observed between the groups ($P < 0.001$). Serum creatinine levels were significantly higher in diabetics with microalbuminuria compared to diabetics without microalbuminuria ($P<0.001$). Significant differences were observed in mean serum KIM-1 levels between diabetics without microalbuminuria ($P< 0.0001$) and with diabetics with microalbuminuria ($P<0.001$).

Table 1: Comparison of parameters between groups

		Mean	Std. Deviation	F	P-value
Age	Diabetes with Micro Alb	58.97	1.88	259.344	<0.001*

	Diabetes without Micro Alb	56.03	3.19		
FBS	Diabetes with Micro Alb	234.53	11.12	939.398	<0.001*
	Diabetes without Micro Alb	194.90	19.85		
PPBS	Diabetes with Micro Alb	324.50	18.57	1953.599	<0.001*
	Diabetes without Micro Alb	243.07	14.06		
HbA1c	Diabetes with Micro Alb	11.24	1.24	453.765	<0.001*
	Diabetes without Micro Alb	9.16	0.34		
Creatinine	Diabetes with Micro Alb	0.95	0.18	12.240	<0.001*
	Diabetes without Micro Alb	0.85	0.16		
Urinary Albumin	Diabetes with Micro Alb	3.46	0.24	40.814	<0.001*
	Diabetes without Micro Alb	3.86	0.14		
Serum KIM-1	Diabetes with Micro Alb	19.74	4.09	156.490	<0.001*
	Diabetes without Micro Alb	18.07	1.87		

Note: *Statistically significant difference between the groups.

The Pairwise comparisons between groups of the study participants are summarized in Table 2. The mean ages difference between Diabetes with Microalbumin and Diabetes without Microalbumin were 2.93. Statistical significant difference in mean age was observed between the groups (P <0.001). The mean creatinine difference between Diabetes with Microalbumin and Diabetes without Microalbumin were 0.10. There is no statistically significant difference in mean creatinine was observed between diabetic without microalbumin and diabetic with microalbumin (P <0.045).

Table 2: Pairwise comparisons between groups

Variable	Groups		Mean Difference	Std. Error	P-value
Age	Diabetes with Micro Alb	Diabetes without Micro Alb	2.93	0.62	<0.001*
FBS	Diabetes with Micro Alb	Diabetes without Micro Alb	39.63	3.42	<0.001*
PPBS	Diabetes with Micro Alb	Diabetes without Micro Alb	81.43	3.52	<0.001*
HbA1c	Diabetes with Micro Alb	Diabetes without Micro Alb	2.09	0.19	<0.001*
Creatinine	Diabetes with Micro Alb	Diabetes without Micro Alb	0.10	0.04	0.045
Urinary Albumin	Diabetes with Micro Alb	Diabetes without Micro Alb	-0.40	0.06	<0.001*
Serum KIM-1	Diabetes with Micro Alb	Diabetes without Micro Alb	1.67	0.67	0.04

Note: *Statistically significant difference between the groups.

Correlation analyses were conducted between serum kidney injury molecule-1 (KIM-1) levels and other parameters across the groups. Patients with longer durations of diabetes exhibited higher serum KIM-1 values (P = 0.01) in diabetics with microalbuminuria compared with diabetics without microalbuminuria). Significant correlation was observed between serum KIM-1 and serum creatinine levels in any group (Table-3). There was significant correlation was found between serum KIM-1 and HbA1C in diabetics with microalbuminuria (P = 0.001), diabetics without microalbuminuria (P = 0.001), and controls (P = 0.001). These findings are further elucidated in Figure 1.

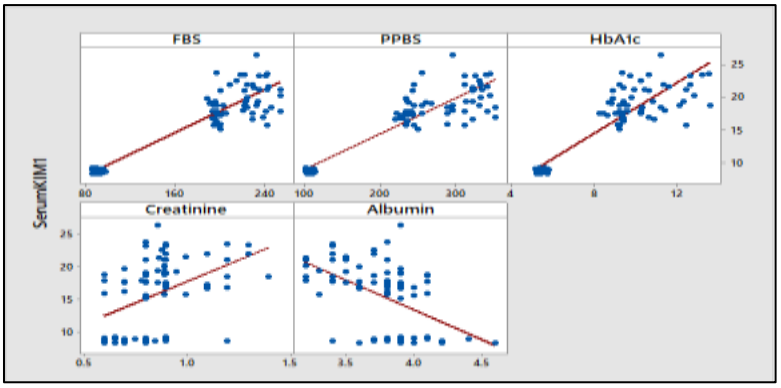

Table 3: Correlation of Serum KIM 1 with FBS, PPBS, HbA1c, Creatinine and Albumin

Parameters	Correlation	P-value
FBS	0.931	<0.001*
PPBS	0.922	<0.001*
HbA1c	0.896	<0.001*
Creatinine	0.438	<0.001*
Urinary Albumin	-0.506	<0.001*

Note: *Statistically significant difference between the groups. FBS- Fasting Blood Sugar: PPBS- Post Prandial Blood Sugar

ROC curves were carried out to access the nephropathy diagnostic values of urinary KIM-1 in type 2 diabetes patients (Figure-2). The cut-off values of urinary KIM-1 were 17.7 pg/mL. Table 4 shows the sensitivity (Se), specificity (Sp) at the cut-off value of KIM-17.7 ng/mL, the sensitivity and specificity were 87% and 77%, respectively.

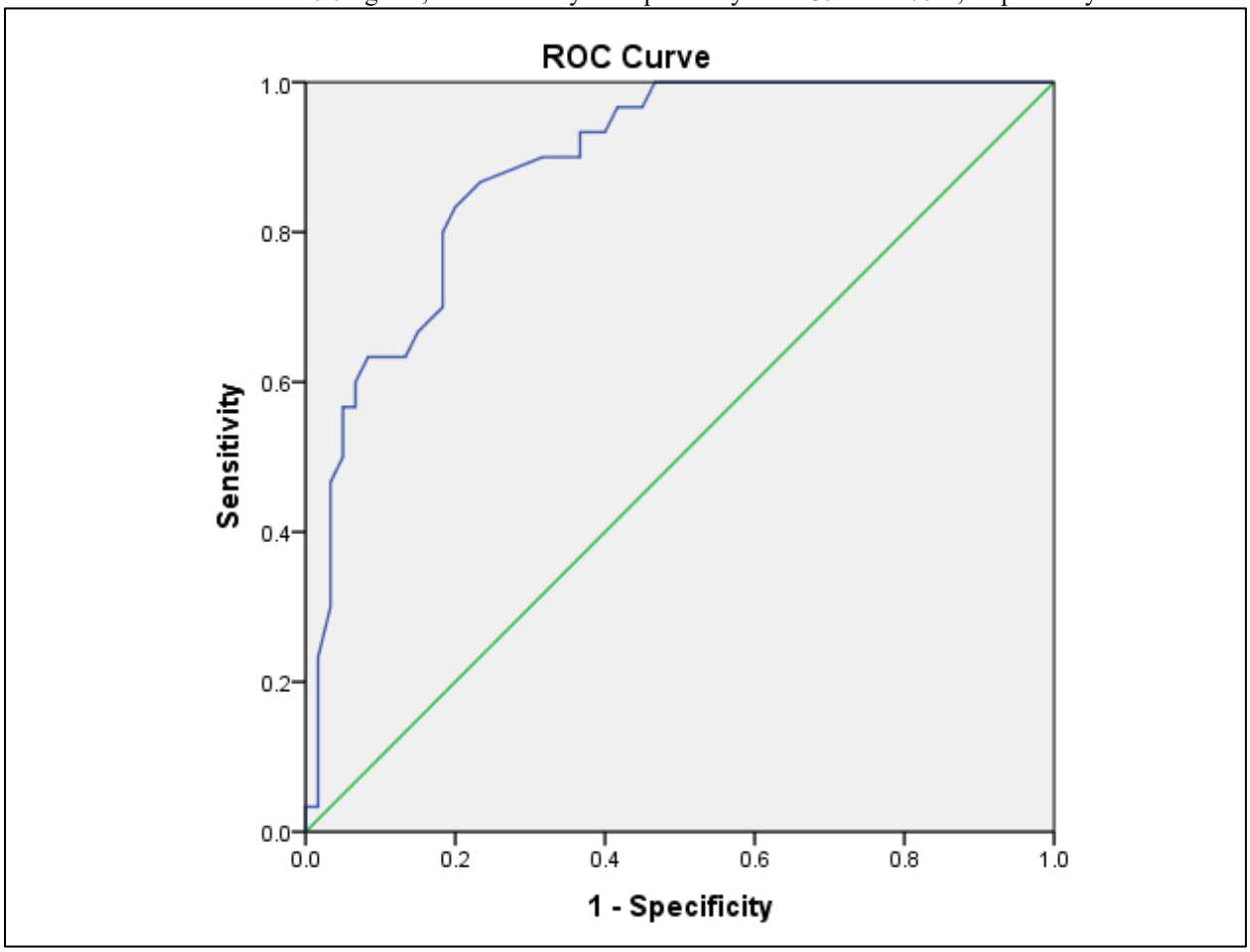

Table 4: Receiver operating characteristic (ROC) analysis (Serum KIM 1)

Factors	Value
Area under the curve	89%
P-value	<0.001*
Sensitivity	87%
Specificity	77%
Cut off value	17.7

Note: *Statistically significant difference between the groups

DISCUSSION

KIM-1 (kidney injury molecule 1) are indeed important biomarkers associated with kidney injury. KIM-1 is a transmembrane protein with an immunoglobulin and mucin domain. Studies have shown that both KIM-1 and NGAL are detectable early in cases of acute renal tubular injury. Due to their early appearance, they have been extensively researched as potential markers for identifying kidney injury, particularly in the context of chronic kidney disease (CKD)(Mishra et al. 2003; Sun et al. 2017; Zhao et al. 2019; Tanase et al. 2019; Khawaja et al. 2019) .

In diabetic nephropathy associated with type 2 diabetes mellitus (T2DM), histopathological changes typically involve multiple aspects of renal structure and function. These changes often manifest in various histopathological types, including disproportionate tubulo-interstitial, glomerulosclerotic, and vascular alterations. indeed, proteinuria, characterized by the presence of excess protein in the urine, is a hallmark of kidney damage and is particularly significant in the context of diabetic nephropathy. In diabetic kidney disease, proteinuria can contribute to tubular cell injury and death, further exacerbating renal dysfunction (Tervaert et al. 2010).

Recent research has emphasized the importance of identifying renal tubular injury and its association with kidney damage in patients with diabetes. Tubular injury can occur due to various factors, including the toxic effects of proteins filtered through the glomeruli and inflammatory processes within the renal tubules. KIM-1 is an emerging biomarker that have shown promise in detecting early tubular injury. As mentioned earlier, these biomarkers can appear earlier than albuminuria, which is the hallmark indicator of glomerular dysfunction. This is because in the early stages of diabetic nephropathy, changes in the glomerular basement membrane, such as thickening, may occur before significant albuminuria develops (de Carvalho et al. 2016; Żyłka et al. 2018).

This study aimed to explore the role of serum Kidney Injury Molecule-1 (KIM-1) as an early marker for diabetic nephropathy (DN). Our findings revealed elevated serum KIM-1 levels in both diabetic groups, with and without microalbuminuria, particularly among those with longer durations of diabetes. However, no significant correlation was found between serum KIM-1 and serum creatinine. These results are consistent with previous research indicating the potential of KIM-1 as a biomarker for renal injury in diabetes (Nowak et al. 2016; Ha et al. 2017; Abid Khan et al. 2019).

In comparison to other studies, our findings align with research demonstrating the association between KIM-1 and various renal parameters, including creatinine, and HbA1c (El-Ashmawy et al. 2015). Notably, our study focused on serum KIM-1 levels, while some previous studies primarily measured urinary KIM-1. The positive correlation between serum KIM-1 and the duration of diabetes underscores the potential utility of KIM-1 as an indicator of DN progression.

Despite these promising findings, our study observes significant correlations between serum KIM-1 and other parameters such as serum FBS, PPBS, creatinine, albumin and HbA1c in all groups. This contrasts with previous research associating urinary KIM-1 with markers of renal function and disease progression (El-Ashmawy et al. 2015). Further investigation is warranted to elucidate the relationship between serum KIM-1 and renal parameters in DN.

Similar sensitivities and specificities of KIM-1 in early diagnosis of diabetic nephropathy as reported in other studies suggest the reliability and consistency of these biomarkers across different research settings. The findings from Kapoula et al and Zylka et al provide valuable insights into the diagnostic utility of urinary NGAL and KIM-1 in diabetic nephropathy. Kapoula et al reported pooled sensitivity and specificity values for KIM-1 across different settings in type 2 diabetes mellitus (T2DM) patients. The sensitivity ranged from 0.42 to 1.00, with corresponding specificity ranging from 0.72 to 0.98. These results suggest a wide variability in the diagnostic performance of KIM-1, likely influenced by factors such as study population characteristics, assay methods, and disease severity. Based on these values, KIM-1 could be used as independent markers for diagnostic and prediction for diabetic nephropathy (Żyłka et al. 2018; Kapoula et al. 2019).

The limitations of our study include its single-center design with a limited number of patients, lack of urine KIM-1 measurements for comparison, absence of long-term follow-up to assess renal status decline, and failure to account for environmental and lifestyle factors that may influence disease progression. Future multicentre studies addressing these limitations are essential to validate the utility of serum KIM-1 as an early marker for DN.

CONCLUSION

Our study provides valuable insights into the potential of serum KIM-1 as an early marker for DN. However, further research is needed to confirm these findings and address the limitations outlined in this study.

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Ethical Approval: Vide no. SSMC/MED/IEC-170/NOV-2023 by institute of ethics committee of Sri Siddhartha Medical College, Tumkur, Karnataka, India.

Consent to Participate: Consent was taken from the patients.

Consent for Publication: Consent was obtained from the patients for publication of this case.

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