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Article

A comparison with micro albuminuria indicates whether urine and serum kidney injury molecule-1 can predict the onset of early diabetic nephropathy (DN).

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Abstract
Diabetic nephropathy (DN) is the most frequent consequence of DM and a significant contributor to chronic kidney disease, a multifactorial illness. Kidney injury molecule-1 (KIM-1) is a sensitive and accurate indicator of kidney damage and a predictive indicator. Aim: The present investigation aimed to examine serum and urine KIM-1 as a DN early marker. Patients and methods: The present study included 150 participants, among whom 50 non-diabetic participants were chosen as controls. One hundred diabetic participants were split into two groups based on their urine albumin/creatinine ratio (ACR) as participants with normoalbuminuria (T2DM patients without nephropathy) and microalbuminuria (T2DM patients with nephropathy). The blood glucose, HbA1c, s.urea, and creatinine levels in serum and urine were measured using standard laboratory techniques, and Elisa Essay measured serum and urine KIM-1 levels. Results: There was a distinct variation in the mean serum and urine KIM-1 between the control and diabetics without microalbuminuria (P = 0.001). Serum KIM-1 correlated with ACR (P = 0.669) in people with diabetes with microalbuminuria. Urine KIM-1 was less correlated than serum KIM-1 (p = 0.257). A strong association was found between ACR and serum KIM-1 in people with diabetes with microalbuminuria and a low correlation between ACR and urine KIM-1 in people with diabetes with microalbumin. Conclusion: According to the current investigation, diabetic groups with microalbuminuria had higher serum and urine levels of KIM-1 than the control groups. Additionally, there was a favorable correlation between serum KIM-1 and the length of diabetes. More extensive multicentric trials are also needed to assess the efficacy of serum and urine KIM-1 as a DN early marker.

Keywords: Serum /Urine KIM-1; Dibetic nephropathy; Microalbumin; DM type-2

Introduction

One of the most frequent consequences of diabetes and a significant contributor to chronic kidney disease is diabetic nephropathy (DN), a multifactorial illness (CKD)[1]. According to estimates, DN develops between 10 and 30 percent of many individuals with Type 1 diabetes and between 15 and 40 percent of many with Type 2 diabetes[2]. The leading causes of the deterioration in renal function in

DN patients are changes in renal hemodynamics, activation of protein kinase C, hexamine biosynthesis, the aldose reductase pathway, and the production of advanced glycation end products[3]. Currently, DN is diagnosed using urine microalbuminuria as a conventional diagnostic technique[3]. However, Asian, Hispanic, and Caucasian groups all showed an ethnic variance in albuminuria in DN[4]. Therefore, it is crucial to identify DN early and avoid it to stop the progression of end-stage renal disease[4]. The novel DN biomarkers have been evaluated in several investigations. The markers identify oxidative stress, inflammation, tubular injury, and glomerular injury, which aid in the early detection of DN. However, the variety of novel biomarkers means that most still need validated[5]. A promising factor in diagnosing renal tubulointerstitial damage is the TypeType I transmembrane glycoprotein kidney injury molecule-1 (KIM-1), released on renal proximal tubule epithelial cells[6]. According to studies, KIM-1 is both a sensitive and specific marker of kidney damage and a prognostic indicator[7]. Little research has looked at the utility of blood KIM-1 as an early sign of renal damage, which is equivocal. However, many studies have demonstrated that urine KIM-1 is an early indication of acute kidney injury (AKI) or CKD [8 9]. Thus, The main study's intention investigation was to assess the effectiveness of serum KIM-1 as a DN marker. This study analyzed the controls and diabetics with/without microalbuminuria regarding urine and serum KIM-1 levels.

Materials and Methods

This analysis comprised 150 participants from the Baquba Teaching Hospital, Specialized Consultation, Internal Medicine Department, and Iraq Specialized Laboratory in Baquba, Diyala, between October 2021 and February 2022. Among the 150 study participants, 50 non-diabetic participants were chosen as controls with random blood glucose <145 mg/dl and HBA1C <6%. The other 100 type 2 diabetic mellitus participants were divided into two different groups dependent on urine albumin/creatinine ratio (UACR): 50 participants with normoalbuminuria (UACR <30) and 50 participants with microalbuminuria (UACR 30-299) according to WHO criteria. Blood and urine samples were collected from all participants in the morning, and the serum and urine were separated and stored at −80°C. The blood glucose, HbA1c, urea, and creatinine levels were measured using laboratory techniques, and serum and urine KIM-1 levels were measured by sandwich enzyme-linked immunosorbent assay (HUMAN reader HR). The Statistical Package for the Social Sciences (SPSS) edition was utilized for all statistical analysis. 16 for Windows, Chicago, U.S.A. Comparisons of continuous variables between groups were performed using the analysis of variance median (interquartile range or Kruskal–Wallis tests. A comparison of nominal variables among these groups was performed using the Chi-squared test.

Results

This study included one hundred fifty patients (94% female and 56% male). Among the 150 patients, 50 were healthy controls, 50 were diabetics without microalbuminuria, and 50 were diabetics with microalbuminuria. The baseline characteristics of the study participants are documented in [Table 1]. The mean age for controls was 48.50(12) years. For people with diabetes with normoalbuminuria, it was 54.50(8) years; for diabetics with microalbuminuria, it was 59.00(12.75) years. There was a significant difference in the mean age between the groups (P-value = 0.001). The serum creatinine was significantly higher in diabetes with microalbuminuria versus diabetics without microalbuminuria (P <0.001) and control versus diabetics with microalbuminuria (P<0.001). However, there was no significant difference in serum creatinine levels between controls and diabetics without microalbuminuria (normalalbuminuria) (P= 0.765) [Table 1]. There was a

significant difference in the mean serum KIM-1 between the control and diabetic normoalbuminuria (P<0.001). Similarly, a significant differential exists between control and diabetes with microalbuminuria (P<0.001). Fortunately, there was a highly significant difference in serum KIM-1 between diabetic patients without microalbuminuria and diabetic patients with microalbuminuria (P<0.001) [Table 2] [Figure 1].

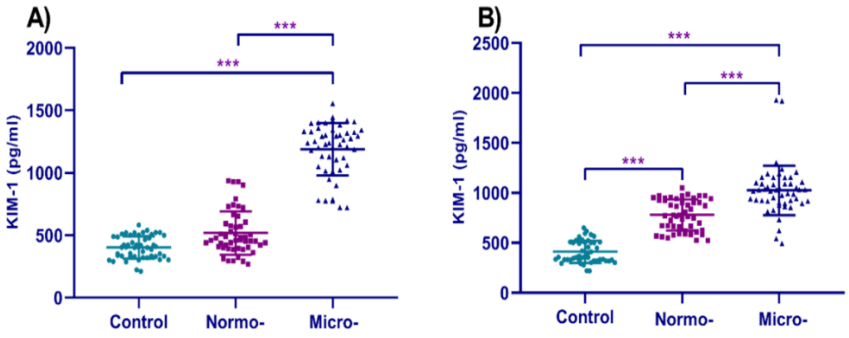

Figure 1. A) Serum KIM-1 B) Urine KIM-1.

Parameter	Control (n= 50)	Microalbumi-nuria (n= 50)	Normoalbuminu-ria (n= 50)	*P*-value[1]	P-value[2]	P-value[3]
Age (years)*	48.50(12)	59.00(12.75)	54.50(8)	<0.001		
Gender (N)†						
Males	18	24	14	0.224	0.391	0.039
Females	32	26	36			
Duration of disease	/	v9.4 ± 3.49	5.98 ± 2.33	/	/	<0.001
BMI (kg/m²)	27.53±4.46	30.15±5.68	30.80±4.29	0.012	<0.001	0.520
RBG (mg/dl)	107.1±14.16	255.2±82.41	311.3±103.2	<0.001	<0.001	0.003
HbA1c (%)	4.87±0.62	11.22±1.60	9.06±1.40	<0.001	<0.001	<0.001
S. urea (mg/dl)	39.75±7.85	29.58±7.24	32.78±8.00	<0.001	<0.001	0.039
S. creatinine (mg/dl)	0.72±0.19	0.86±0.20	0.73±0.14	<0.001	0.765	<0.001
U. creatinine (mg/dl)	112.9±46.46	50.17±30.88	85.16±50.58	<0.001	0.005	<0.001
U. albumin (mg/dl)	1.63±0.49	3.93±4.49	1.49±0.71	<0.001	0.254	<0.001

Alb/Cr ratio	15.24±18.67	86.38±55.78	18.67±6.45	<0.001	0.222	<0.001

Table 1. Studied characteristics between the groups (*n*=50).
Median (Interquartile Range);†Chi-Square; P-value of each comparison (excl. gender) is based on the Kruskal-Wallis test, P-value1: relationship between control and Microalbuminuria; P-value2: relationship between control and Normoalbuminuria; P-value3: relationship between Microalbuminuria and Normoalbuminuria.

KIM-1 (pg/ml)	Control (n= 50)	Normoalbuminuria (n= 50)	Microalbuminuria (n= 50)	*P*-value[1]	P-value[2]	P-value[3]
S. KIM-1	403.8±89.41	518.6±173.4	1189±209.5	<0.001	<0.001	<0.001
U. KIM-1	411.5±109.4	779.4±155.3	1025±246.9	<0.001	<0.001	<0.001

Table 2. Kidney Injury Molecule (KIM)-1 in serum and urine.
***P*-value[1]: relationship between control and Normoalbuminuria; *P*-value[2]: relationship between control and Microalbuminuria; *P*-value[3]: relationship between Microalbuminuria and Normoalbuminuria**

Discussion

The current study aimed to assess the potential effectiveness of serum and urine KIM-1 as a DN early marker. Both groups in our study—DM without microalbuminuria and DM with microalbuminuria—had greater serum and urine KIM-1 values as the duration of their diabetes increased. In follow-up research with 85 individuals from the Jinnah Postgraduate Medical Center's diabetes clinic, KIM-1 was recently found to be independently correlated with BUN (r = 0.727; P < 0.001), creatinine (r = 0.510; P 0.001), and HbA1c (r = 0.401; P = 0.008) in all groups[10]. The other study, which involved 80 diabetic nephropathy patients from Egypt, discovered that urine KIM-1 levels rose as nephropathy advanced and that they were a standalone risk factor for albuminuria and estimated rate of glomerular filtration (eGFR) in diabetic subjects[11]. Additionally, a study with 482 Type 1 diabetes individuals evaluated the concentrations of KIM-1 in both their plasma and their urine, and the results showed an early renal deterioration with a doubling of KIM-1 in both their normoalbuminuria and their microalbuminuria[12]. In our research, both serum KIM-1 and urine KIM-1 were elevated in diabetics with microalbumin groups when compared to controls[13]. In Egypt (60 T2D patients), exhibit a statistically significant association (P<0.001) with microalbuminuria and age, the period of diabetes, fasting blood glucose, glycosylated hemoglobin, BUN, and creatinine. However, this study measured urinary KIM-1 but not serum KIM-1. In our analysis, urinary KIM-1 showed a negative (P <0.001) correlation with eGFR and a positive relationship with age, the duration of diabetes, fasting blood sugar, glycosylated hemoglobin, BUN, creatinine, and microalbuminuria[14]. Our investigation discovered a significant relationship between serum and urine KIM-1 and the length of diabetes. Patients with diabetes for a longer time had higher serum and urine KIM-1 values (P < 0.001 in the group of patients with microalbuminuria). Mean creatinine levels were 0.72 mg/dl in non-diabetic controls, 0.73 mg/dl in diabetes without microalbuminuria, and 0.83 mg/dl in diabetes with microalbuminuria. P = 0.0001 indicates a statistically considerable variability between the groups. However, there was no association between u.creatinine and serum or urine KIM-1 in any groups[15]. Compared to urine KIM-1, which is positively correlated with ACR, serum KIM-1 has a higher correlation. Results of this study indicate that urine KIM-1 is a sensitive measure of kidney impairment in rodents and humans with AKI[16]. However, studies evaluating the part of urinary KIM-1 as a sign of DN have been inconclusive[17]. Additionally, urine KIM-1 demonstrated a weaker correlation with early renal deterioration than serum

KIM-1. However, a study found that chronic KIM-1 expression in experimental animals was linked to severe renal failure[18].

Conclusions

According to the current investigation, diabetic groups with microalbuminuria had slightly higher serum and urine KIM-1 concentrations than the control groups. Additionally, there was a favorable correlation between serum KIM-1 and the length of diabetes. Larger multicentric trials are also needed to appraise the efficacy of serum and urine KIM-1 as a DN early marker.

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