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Association of urinary monocyte chemoattractant protein-1 (MCP-1) and kidney injury molecule-1 (KIM-1) with risk factors of diabetic kidney disease in type 2 diabetes patients

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Abstract

Purpose Urinary kidney injury molecule-1 and monocyte chemoattractant protein-1 are significance factors in the diagnosis and intervention of diabetic kidney diseases. This study determined levels of these proteins in diabetic patients with varying degrees of kidney disease and assessed their relationship with risk factors associated with diabetic kidney diseases.

Methods A total of 185 patients with type 2 diabetes were divided into three groups [low risk ($n=47$), moderate risk ($n=63$), and high risk ($n=75$)] based on the severity of diabetic kidney disease according to kidney disease: improving global outcomes guidelines. Both urinary kidney injury molecule-1 and monocyte chemoattractant protein-1 levels were measured by enzyme-linked immunosorbent assay. Student`s *t* test, analysis of variance, and Spearman's correlation were used for statistical analysis.

Results The kidney injury molecule-1-to-creatinine ratio ($P=0.035$) and monocyte chemoattractant protein-1-to-creatinine ratio ($P<0.001$) increased significantly with the increase in kidney disease severity and varied according to different albuminuria statuses and estimated glomerular-filtration rates. The monocyte chemoattractant protein-1-to-creatinine ratio showed a significant correlation with hemoglobin A1c ($P=0.002$) and inflammatory marker levels (interleukin-6, $P=0.005$; tumor necrosis factor-α, $P<0.001$).

Conclusion Urinary levels of both kidney injury molecule-1 and monocyte chemoattractant protein-1 represent distinguishing markers for the evaluation of diabetic kidney disease progression according to the associated degrees of albuminuria or/and the estimated glomerular-filtration rate. In addition, correlations between urinary monocyte chemoattractant protein-1 and glycemic and inflammatory marker levels revealed the role of hyperglycemia and chronic inflammation in the pathogenesis of diabetic kidney disease.

Keywords Diabetic kidney disease · Type 2 diabetes · Kidney injury molecule-1 · Monocyte chemoattractant protein-1 · Hyperglycemia · Chronic inflammation

Introduction

Diabetic kidney disease (DKD) is a major complication associated with diabetes mellitus and a leading cause of end-stage kidney disease. Approximately 40% of diabetic patients in the United States develop kidney disease, and pooled data from 54 countries show that > 80% of cases of end-stage renal disease (ESRD) are caused by diabetes, hypertension, or a combination of the two. The prevalence of diabetes among the Saudi population is reportedly 17.7% [1], and in 2016, the Saudi Center for Organ Transplantation statistics reported that among the Saudi population, 40% of ESRD in patients receiving hemodialysis is caused by diabetic nephropathy [2].

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Several pathogenic mechanisms are involved in DKD development and progression, including the polyol pathway, protein kinase pathway, hexosamine pathway, advanced glycation end-product (AGE) pathway, and the Janus kinase–signal-transducer-and-activator-of-transcription pathway, which results in tubular renal damage and the overexpression of urinary molecules predominantly expressed by tubular cells, including kidney injury molecule-1 (KIM-1) and monocyte chemoattractant protein-1 (MCP-1) [3]. KIM-1 is a membrane protein expressed on proximal tubular cells and maintains stability following cleavage of its ectodomain and release into the tubule lumen, resulting in detection in urine [4, 5]. Urinary KIM-1 (uKIM-1), a specific and sensitive biomarker for proximal-tubule damage, can be upregulated in proximal tubular cells during various states, including ischemia, toxic renal injury, and polycystic kidney disease, and is associated with the extent of tubulointerstitial damage and fibrosis [6–9]. In addition, uKIM-1 is elevated in patients with diabetes, even in those with normoalbuminuria, with insulin sensitivity inversely correlated with urinary KIM-1 concentrations [10]. Monocyte chemoattractant protein-1 (MCP-1) is a chemotactic factor that influences monocyte and macrophage recruitment and renal tubular damage. Urinary MCP-1 (uMCP-1) is upregulated in inflammatory renal disease and diabetic nephropathy [11–13]. Moreover, upregulated renal MCP-1 levels are induced by elevations in glucose levels, tubular-reabsorbed protein, AGEs, and angiotensin-II (AT-II) [14]. Furthermore, elevated levels of uMCP-1 in type 2 diabetes patients with deteriorating renal function correlate with risk factors associated with diabetic nephropathy [15].

Although there is considerable evidence that uKIM-1 and uMCP-1 levels are altered in DKD, the degree to which these biomarkers are altered in in Saudi type 2 diabetes patients according to both proteinuric and non-proteinuric classifications. In addition, few studies have described relationships between uKIM-1 and uMCP-1 levels with risk factors associated with DKD. Therefore, this study evaluated uKIM-1 and uMCP-1 levels in diabetic patients with various degrees of kidney disease to assess relationships between urinary markers and risk factors of DKD in these patients.

Materials and methods

Study population

This was a cross-sectional study conducted at the University Diabetes Center, King Saud University, during the period from 1 April 2014 until 18 June 2015. The study was approved by the Institutional Review Board at the College of Medicine, King Saud University and conducted in accordance with the Declaration of Helsinki [16]. Informed consent was obtained from each study participant.

Exclusion criteria for the SAUDI-DKD cohort included the following conditions reported in the patient medical records: (1) current pregnancy, history of smoking, diagnosis of cancer or other renal disease, and patients exposed to radiocontrast agents or drugs that might affect their kidney functions [17]. In addition, patients who did not attend either blood or urine sampling and patients with ESRD were excluded.

Type 2 diabetes patients aged between 35 and 70 years and with at least 10 years of diabetes duration were included in this study. Of the 480 eligible type 2 diabetes patients, 279 who were lacking uKIM-1 and uMCP-1 values and 16 without demographic or clinical parameters were also excluded from the analysis, resulting in a final total of 185 patients included in the study. A diagram illustrating the flow of participants through the study is shown in Supplementary Fig 1. The power of the sample size was calculated using the PS software (https://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize).

DKD was identified clinically by a persistently high urinary albumin-to-creatinine ratio (ACR) ≥ 30 mg/g and/or sustained reduction in estimated glomerular-filtration rate (eGFR) < 60 mL/min per 1.73 m^2 [18]. According to kidney disease severity, the 185 diabetic patients were subdivided into low-risk, moderate-risk, and high-risk groups diagnosed based on chronic kidney disease (CKD) nomenclature according to kidney disease: improving global outcomes guidelines [19]. In this classification, A1, A2, and A3 represented albuminuria < 30 mg/g, 30 mg/g–300 mg/g, and > 300 mg/g, respectively, whereas G1, G2, G3a, G3b, G4, and G5 represented eGFR ≥ 90, 60–89, 45–59, 30–44, 15–29, and < 15 (all in mL/min/1.73 m^2), respectively. For risk classification, the low-risk group included the A1G1 and A1G2 categories, the moderate-risk group included the A2G1, A2G2, and A1G3a categories, and the high-risk group included the A3G1, A3G2, A2G3a, A3G3a, A1G3b, A2G3b, A3G3b, A3G4, and A3G5 categories [20].

Selected patients managed their diabetes with oral antidiabetic therapy, such as metformin, sulfonylurea, or sitagliptin, either with or without insulin therapy. Hypertension was managed with medications, including AT-II-receptor antagonists, thiazide diuretics, angiotensin-converting enzyme inhibitors, beta blockers, and calcium-channel blockers. Hyperlipidemia was managed with statins. Patients exposed to radiographic contrast agents or drugs, such as aminoglycoside, amphotericin, β-lactam antibiotics, methotrexate, cisplatin, cyclosporine, or tacrolimus, that might affect kidney function were excluded from the study. Patients with diabetic complications, including vasculopathy and retinopathy, or other associated diseases, such as hypertension

and hyperlipidemia, were included in this study, as these conditions are prevalent among DKD patients.

Data collection

Overnight-fasting serum samples were used for biochemical analyses, which included fasting blood sugar (FBS), hemoglobin A1c (HbA1c), serum creatinine, and a lipid profile [triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and total cholesterol (TC)]. Biochemical assessment was performed using an RX Daytona clinical chemistry analyzer (Randox Laboratories, Ltd., Crumlin, UK).

Random spot-urine samples were used for the analysis of albumin, creatinine, and urinary biomarkers (uKIM-1 and uMCP-1). The urinary albumin and creatinine were analyzed using an RX Daytona clinical chemistry analyzer (Randox Laboratories, Ltd.). Urinary albumin excretion was estimated by calculating the ACR (mg/g), and eGFR levels were calculated using the CKD-Epidemiology Collaboration equation [21]:

$$\mathrm{eGFR} = 141 \times \min(\mathrm{SCr}/\kappa, 1)^{\alpha} \times \max(\mathrm{SCr}/\kappa, 1)^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018\ [\text{if female}] \times \_1.159\ [\text{if black}],$$

where eGFR is expressed in mL/min/1.73 m^2, SCr (standardized serum creatinine) is expressed in mg/dL, κ is 0.7 (for females) or 0.9 (for males), α is -0.329 (for females) or -0.411 (for males), min indicates the minimum of SCr/κ or 1, max indicates the maximum of SCr/κ or 1, and age is expressed in years.

Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using the HOMA-2 calculator software (University of Oxford, Oxford, UK) [22]. Risk factors of DKD were determined according to the National Kidney Foundation guidelines [23].

Biomarker assays

Urinary biomarker levels (uKIM-1 and uMCP-1) were measured by solid-phase enzyme-linked immunosorbent assay (ELISA) using commercially available standard kits designed for random spot-urine analysis (Abcam, Cambridge, MA, USA). Both uKIM-1 and uMCP-1 levels were corrected to urine creatinine-concentration levels and represented as uKIM-1/Cr and uMCP-1/Cr, respectively. To analyze chronic inflammation, four serum inflammatory markers [interleukin-1α (IL-1α), IL-6, C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α)] were examined. Moreover, for the HOMA-IR calculation, insulin values were selected from metabolic syndrome arrays I and II and analyzed using a biochip assay (Randox evidence biochip analyzer; Randox Laboratories, Ltd.).

Statistical analysis

Data are presented as a percentage or the mean ± standard deviation for normally distributed variables and as the median (interquartile range) for non-normally distributed variables. Differences between, as well as among, groups were compared by analysis of variance. Spearman correlation coefficients were calculated to test correlations between individual variables using uKIM-1/Cr and uMCP-1/Cr as dependent variables. A box-plot diagram was used to show differences in uKIM-1/Cr and uMCP-1/Cr among diabetic patients according to albuminuria and eGFR status. Comparisons of two groups were performed using the Student's *t* test. A $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS (v.21.0; IBM Corp., Armonk, NY, USA).

Results

The demographic, clinical, and biochemical characteristics of type 2 diabetes patients according to kidney disease severity are summarized in Table 1. The number of patients categorized into each of the three groups was as follows: low risk, 47; moderate risk, 63; and high risk, 75. There were no significant differences between the three groups in terms of age, body mass index, diastolic blood pressure, or LDL and HDL levels, whereas the duration of diabetes, systolic blood pressure, TC and triglyceride levels, and glycemic parameters (HbA1c and FBS) showed significant differences between risk groups. Similarly, levels of inflammatory markers, including IL-1α, IL-6, and TNF-α, differed significantly between risk groups. In addition, uKIM-1/Cr ($P < 0.035$) and uMCP-1/Cr ($P < 0.001$) levels increased according to kidney disease severity.

The differences in urinary markers (uKIM-1 /Cr and uMCP-1/Cr) according to eGFR and albuminuria status are shown in Figs. 1 and 2, respectively. Patients with eGFR < 60 mL/min/1.73 m^2 showed a significant increase in urinary markers as compared to those with an eGFR > 60 mL/min/1.73 m^2. In addition, both urinary markers were higher in patients with ACR > 30 mg/g as compared with those with ACR < 30 mg/g, although uKIM-1/Cr level did not differ significantly between these two groups.

Correlations between marker levels with modifiable and non-modifiable risk factors of DKD in type 2 diabetes patients with kidney disease are shown in Table 2. uMCP-1/Cr level showed a significant relationship with the glycemic parameter HbA1c ($r = 271$; $P = 0.002$), IL-6 ($r = 0.248$; $P = 0.005$), TNF-α ($r = 0.316$; $P < 0.001$), and physical-activity levels ($r = -0.172$; $P = 0.046$), whereas uKIM-1/Cr level showed a significant positive correlation with male sex ($r = 0.299$; $P = 0.001$).

Table 1 Demographic, biochemical, and clinical characteristics, as well as urinary markers, of type 2 diabetic patients, according to different risk groups of diabetic kidney disease

Parameters	Low risk	Moderate risk	High risk	*P*
N	47	63	75	
Age, years	54.59 ± 6.60	56.06 ± 5.91	55.81 ± 6.22	0.438
Sex, *n* (M/F)	17/30	31/32	21/54	NA
BMI, kg/m^2	32.23 ± 5.66	31.63 ± 5.00	33.60 ± 5.89	0.112
Duration of diabetes, years	16.83 ± 4.86	19.33 ± 5.91	18.72 ± 5.15	0.047*
SBP, mmHg	127.17 ± 16.84	138.73 ± 15.80	144.74 ± 20.89	< 0.001*
DBP, mmHg	71.25 ± 10.00	75.03 ± 9.96	74.00 ± 11.40	0.175
FBS, mg/dL	159.88 ± 52.94	228.03 ± 88.77	221.87 ± 80.59	< 0.001*
HbA1c, %	9.91 ± 1.38	10.69 ± 1.55	10.65 ± 1.83	0.026*
Total cholesterol, mg/dL	162.34 ± 34.16	182.25 ± 46.46	202.16 ± 49.85	< 0.001*
LDL, mg/dL	122.12 ± 37.49	130.41 ± 37.11	137.61 ± 45.74	0.130
HDL, mg/dL	46.59 ± 11.65	47.61 ± 12.96	48.06 ± 12.30	0.814
Triglycerides, mg/dL	148.17 ± 61.42	180.65 ± 87.11	209.90 ± 100.14	0.001*
IL-1α, pg/mL median (IQR)	0.24 (0.16–0.32)	0.30 (0.20–0.44)	0.33 (0.22–0.66)	0.001*
IL-6, pg/mL median (IQR)	2.57 (1.66–4.07)	2.78 (1.78–4.43)	4.30 (2.37–6.13)	0.003*
CRP, ng/mL median (IQR)	2191 (1119–4034)	1837 (1082–4374)	2827 (1281–4267)	0.519
TNF-α, pg/mL median (IQR)	5.69 (3.97–7.16)	7.28 (6.44–9.06)	9.29 (7.13–14.05)	< 0.001*
HOMA-IR, median (IQR)	1.79 (1.12–3.01)	3.65 (2.07–5.06)	2.67 (1.63–4.50)	0.009*
ACR, mg/g median (IQR)	7.85 (3.88–13.67)	75.99 (41.85–143.70)	208.53 (97.50–838.63)	< 0.001*
eGFR, mL/min/1.73 m^2 median (IQR)	89 (75–96)	71 (63–78)	50 (37–54)	< 0.001*
Physical activity (%) yes	23.9	11.1	13.3	NA
Smoking (%) yes	4.3	4.8	6.7	NA
Hyperlipidemia (%) yes	85.1	82.5	94.7	NA
Hypertension (%) yes	47.7	76.2	85.3	NA
Family history of diabetes (%) yes	83.0	84.1	86.7	NA
Family history of renal diseases (%) yes	18.6	9.8	21.6	NA
uKIM-1/Cr ng/g median (IQR)	750.76 (392.57–1247.41)	789.97 (347.58–1454.68)	867.16 (513.27–1475.82)	0.035*
uMCP-1/Cr ng/g median (IQR)	173.78 (90.60–234.66)	189.02 (110.79–321.19)	259.20 (145.89–633.83)	< 0.001*

Data are presented as percentage, mean ± standard deviation for parametric variables and median [IQR, interquartile range (25 and 75 percentile)] for non-parametric variables and compared by Analysis of Variance (ANOVA). Values of $*P < 0.05$ were considered significant

DM diabetes mellitus, *BMI* body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *FBS* fasting blood sugar, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *IL-1α* interleukin-1α, *IL-6interleukin- 6,CRP* C-reactive protein, *TNF-α* tumor necrosis factor-α, *HOMA-IR* homeostatic model assessment of insulin resistance, *ACR* albumin-to-creatinine ratio, *eGFR* estimated glomerular-filtration rate, *uKIM-1/Cr* urinary kidney injury molecule-1-to-creatinine ratio, *uMCP-1/Cr* urinary monocyte chemo-attractant protein-1-to-creatinine ratio, *NA* not applicable

Correlation analysis of uKIM-1/Cr and uMCP-1/Cr levels with DKD risk factors for total type 2 diabetes patients and type 2 diabetes patients without kidney disease is shown in Supplementary Tables 1 and 2, respectively. In type 2 diabetes patients, uKIM-1/Cr level was correlated with male sex, whereas uMCP-1/Cr level was correlated with HbA1c, IL-6, TNF-α, and physical-activity levels. In patients without kidney disease, uMCP-1/Cr level was positively correlated with only the duration of diabetes.

Discussion

In this study, we found that levels of the urinary biomarkers KIM-1/Cr and MCP-1/Cr increased according to kidney disease severity, with urinary levels of both KIM-1/Cr and MCP-1/Cr elevated along with increasing albuminuria status and eGFR. In addition, uMCP-1/Cr level was significantly correlated with HbA1c, inflammatory marker, and physical-activity levels.

KIM-1 is a transmembrane protein not expressed in normal kidneys, but upregulated following injury to proximal-tubule cells. Therefore, this suggests the presence of KIM-1 in the urine as a highly specific marker for kidney

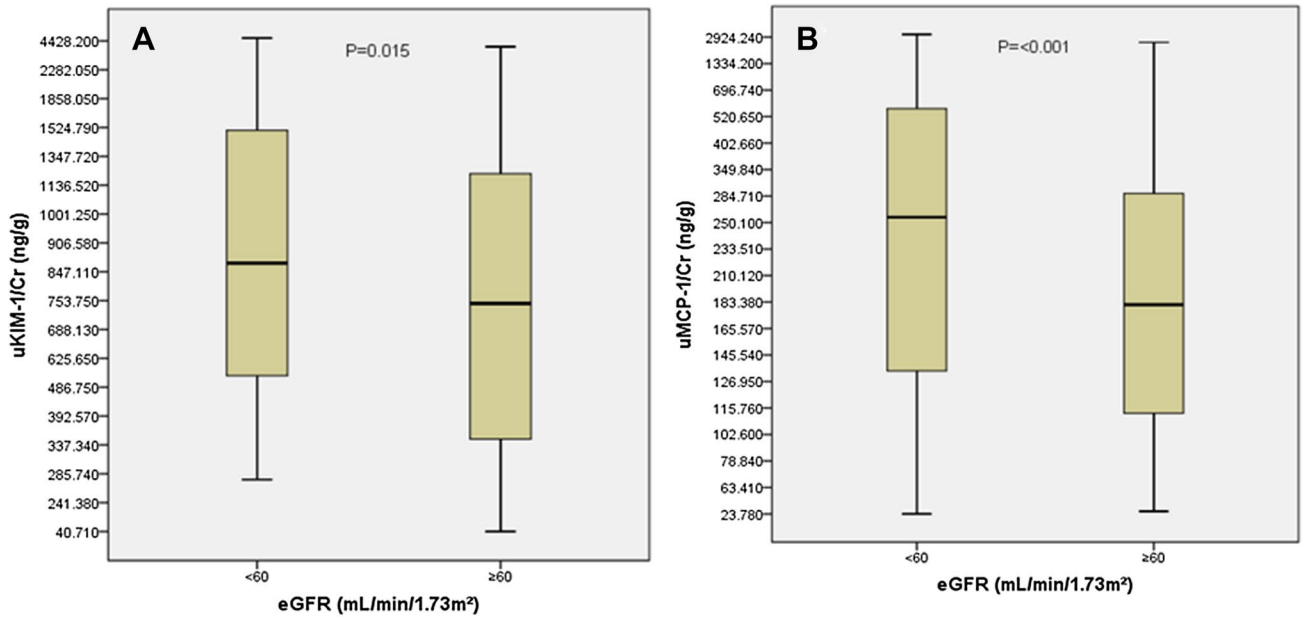

Fig. 1 Changes in uKIM-1/Cr and uMCP-1/Cr levels in type 2 diabetes patients according to eGFR status. Urinary biomarkers **a** uKIM-1/Cr and **b** uMCP-1/Cr were used to classify type 2 diabetes patients into two groups according to eGFR status: eGFR < 60 mL/min/1.73 m^2 and eGFR ≥ 60 mL/min/1.73 m^2. The center line represents the median, the boxes span from the 25th to 75th percentiles, and the error bars extend from the 10th to 90th percentiles. Differences were compared by Student's *t* test

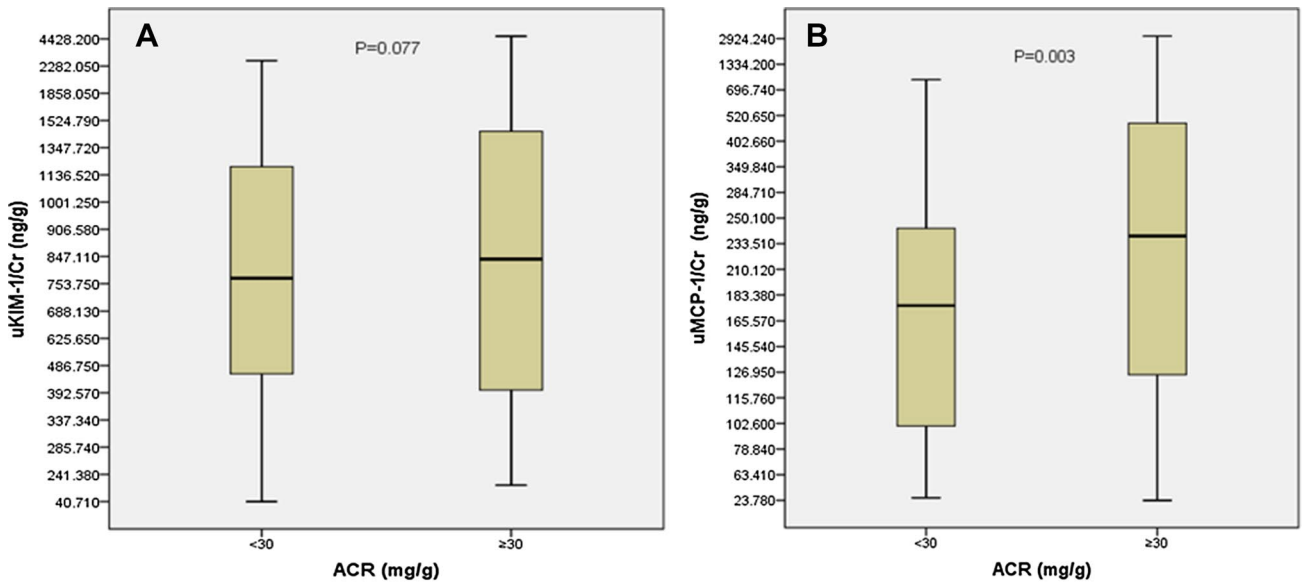

Fig. 2 uKIM-1/Cr and uMCP-1/Cr levels in type 2 diabetes patients according to albuminuria status. Urinary biomarkers **a** uKIM-1/Cr and **b** uMCP-1/Cr were used to classify type 2 diabetes patients into two groups according to the ACR: ACR < 30 mg/g and ACR ≥ 30 mg/g. The center line represents the median, the boxes span from the 25th to 75th percentiles, and the error bars extend from the 10th to 90th percentiles. Differences were compared by Student's *t* test

injury and a useful biomarker for renal proximal-tubule injury in the diagnosis of DKD [24, 25]. Several proposed mechanisms are involved in upregulated KIM-1 levels in tubular cells, with these including activation of proximal tubular cells by a tubulotoxic ultrafiltrate accompanied by excess protein load, which results in chronic damage to the tubules and induced KIM-1 production. In addition, protein overload leads to loss of tubulointerstitial perfusion as

Table 2 Correlation of uKIM-1/Cr and uMCP-1/Cr with risk factors of diabetic kidney diseases in patients with type 2 diabetic patients with kidney disease

	uKIM-1/Cr (ng/g)		uMCP-1/Cr (ng/g)	
	r	*P*	*r*	*P*
Non-modifiable				
Male sex	0.299	0.001*	0.102	0.241
DM duration	− 0.047	0.604	− 0.110	0.206
Age	0.081	0.361	0.001	0.989
Family history of renal diseases	0.024	0.793	− 0.114	0.192
Family history of diabetes	− 0.021	0.816	0.094	0.277
Modifiable				
Glycemic control				
HbA1c	− 0.101	0.261	0.271	0.002*
FBS	− 0.137	0.126	− 0.013	0.886
Hypertension	0.117	0.185	0.016	0.853
Hyperlipidemia	0.083	0.350	− 0.060	0.490
Smoking	− 0.136	0.123	0.117	0.178
Insulin resistance				
HOMA-IR	− 0.036	0.731	0.105	0.960
Chronic inflammation				
IL-1α	0.070	0.501	− 0.005	0.960
IL-6	0.164	0.070	0.248	0.005*
CRP	0.048	0.616	− 0.013	0.886
TNF-α	− 0.021	0.815	0.316	< 0.001*
Physical activity	− 0.119	0.178	− 0.172	0.046*

DM diabetes mellitus, *FBS* fasting blood glucose, *HOMA-IR* homeostatic model assessment of insulin resistance, *IL-1α* interleukin-1α, *IL-6* interleukin- 6,*CRP* C-reactive protein, *TNF-α* tumor necrosis factor-α, *uKIM-1/Cr* urinary kidney injury molecule-1-to-creatinine ratio, *uMCP-1/Cr* urinary monocyte chemoattractant protein-1-to-creatinine ratio, *r* correlation coefficient. Spearman correlation coefficient

*$P < 0.05$ was considered significant

a result of edema or loss of peritubular capillaries, potentially resulting in endothelium dysfunction and production of extracellular matrix, which causes deprivation of the oxygen supply to adjacent tubular cells and induction of KIM-1 production. Moreover, formation of protein casts following protein overload leads to subsequent tubular obstruction, mechanical stress, and increased glomerular pressure, which also results in activation of tubular cells and KIM-1 production [26]. Several studies suggest that significant elevation of uKIM-1 level in diabetic patients with albuminuria represents an early marker of tubular damage [10, 27, 28]. In the present study, we found that KIM-1/Cr level increased along with the severity of DKD, although this was not statistically significant according to albuminuria status alone. A possible reason for this is that uKIM-1 could be excreted before albuminuria, making it unlikely that this marker could distinguish DKD prior to pathological elevations in albuminuria status [27, 29].

MCP-1 is a secreted protein that regulates the migration and infiltration of blood monocytes and tissue macrophages via interaction with C–C chemokine receptor type 2. Renal cells produce MCP-1 in response to a variety of proinflammatory stimuli, and its expression has been identified in kidney diseases that involve significant inflammation, including diabetic nephropathy [30-33]. Exposure of proximal tubular cells to high protein concentrations results in increased synthesis of cytokines/chemokines, such as MCP-1, IL-8, and transforming growth factor-β [34]. In the present study, we found elevated uMCP-1 associated with increased DKD severity, which were significantly elevated with increased albuminuria status and decreased eGFR. This suggests that protein overload might contribute to renal damage, thereby increasing MCP-1 levels in renal tubules and further accelerating DKD progression. In addition, the previous studies reported elevated uMCP-1 levels in diabetic patients along with increasing albuminuria severity [15, 31, 33].

An elevated innate immune response and inflammation are essential contributing factors to the development of renal injury in diabetic patients [35]. In the present study, uMCP-1/Cr level was significantly correlation with elevations in the inflammatory markers IL-6 and TNF-α, suggesting inflammation as a major cause of renal disease, and that inflammatory cytokines play a critical role in the pathogenesis of renal tubular damage. TNF-α increases MCP-1 levels via the phosphoinositide 3-kinase (PI3K)/AKT-signaling pathway, and a significant positive correlation between TNF-α, CRP, and uMCP-1 levels was reported in patients with DKD [32, 36]. In addition, *Mcp1*-knockout mice with streptozotocin-induced diabetic nephropathy displayed reduced macrophage recruitment and activation in the kidneys and were protected from glomerular damage, thereby suggesting that MCP-1 facilitates the inflammatory process [37]. Moreover, high glucose conditions stimulate the formation of reactive oxygen species and upregulate MCP-1 levels via activation of nuclear factor kappa B and glucose-induced expression of MCP-1 in mesangial cells is regulated by protein kinase C [38]. The previous studies demonstrated a significant positive correlation between MCP-1 level and glycemic control [12, 14]. In agreement with these studies, our findings indicated a positive correlation between uMCP-1 and HbA1c levels.

Our study population received diabetes management, as well as management for any related complications, through different medications for diabetes, hypertension, and hyperlipidemia. Despite this, the study population displayed overall poor glycemic control. Therefore, this suggested that hyperglycemia along with chronic inflammation plays a significant role in DKD pathogenesis and, by extension, upregulated uMCP-1 expression and excretion.

This study has several limitations. First, all examinations were confined to Saudi patients with type 2 diabetes, and, therefore, the results might not be generalizable to other ethnicities. In addition, the effect of drugs on either proteinuria or eGFR was not considered, because our patient cohort had histories of > 10 years of diabetes mellitus, and many presented with diabetic complications, including vasculopathy, retinopathy, hypertension, and hyperlipidemia, conditions prevalent among DKD patients. Therefore, most of our patient cohort was prescribed drugs to manage their complications. Moreover, the sample size of this study was insufficient to determine the diagnostic utility of uKIM-1 and uMCP-1 for DKD. Furthermore, this study was conducted using a cross-sectional design but not with longitudinal observations. Further investigation is necessary to determine whether patients exhibiting elevated excretion of urinary markers are more vulnerable to impaired renal function or DKD progression.

Conclusion

In summary, we found uKIM-1 and uMCP-1 levels to be elevated along with DKD progression. Moreover, our findings suggested that uMCP-1, rather than uKIM-1, might serve as a more accurate marker for evaluating DKD progression according to albuminuria status, as correlations between uMCP-1 and glycemic and inflammatory markers provided insight into the pathological role of hyperglycemia and chronic inflammation in DKD progression.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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