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Association of Matrix Metalloproteinase-9 and Tissue Inhibitor Metalloproteinase-1 with Diabetic Nephropathy in Patients with Type Ⅱ Diabetes Mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is one of the leading causes of chronic kidney disease (CKD) and end-stage renal failure worldwide. Among the factors implicated in the pathogenesis of diabetic nephropathy (DN). Dysregulation of the matrix metalloproteinases (MMPs) / tissue inhibitors of metalloproteinases (TIMPs) balance may serve as an early marker and a potential therapeutic target in DN.
Aim of the Study: To evaluate the association between serum levels of matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of metalloproteinase-1 (TIMP-1) and the progression of diabetic nephropathy in patients with T2DM.
Subjects and Methods: A case-control study was conducted at Baghdad Medical City between February and June 2025. Albumin-to-creatinine ratio (ACR) was measured in spot urine samples, the study included three groups of diabetic patients with 65 patients in each, namely the normoalbuminuria group, Microalbuminuria group and Macroalbuminuria group in addition to 65 healthy controls matched for age and sex were enrolled.
Results: The mean±SD age of participants was 55.96 ± 13.26 years, with a nearly equal male-to-female distribution. A significant higher levels of HbA1c, serum creatinine, MMP-9, and TIMP-1 reported in diabetic patients' groups compared to controls (P<0.001). The mean MMP-1 was the lowest in controls , (47.12 ± 4.49 ng/mL) and the highest (97.01 ± 8.19 ng/mL) in the Macroalbuminuria group. Similar trend was found with regards to TIMP-1, (P<0.001). Both MMP-9 and TIMP-1 showed significant positive correlations with HbA1c (r = 0.62 and 0.61), serum creatinine (r = 0.56 and 0.55), and with each other (r = 0.86; p < 0.001). ROC analysis demonstrated high diagnostic performance of both biomarkers for predicting macroalbuminuria, with a (sensitivity of 92.3%, specificity 89.7%) for MMP-9 and (sensitivity of 93.8%, specificity 87.2%) for TIMP-1.
Conclusion: Elevated serum levels of MMP-9 and TIMP-1 was associated with the severity of diabetic nephropathy in patients with T2DM. The parallel increase in both markers with worsening albuminuria and renal dysfunction suggests that dysregulation of Extracellular Matrix (ECM) remodeling contributes to Diabetic Nephropathy progression.

Keywords: *Diabetes mellitus, Diabetic Nephropathy, Type II, Matrix Metalloproteinase-9, Tissue Inhibitor Metalloproteinase-1.*

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INTRODUCTION:

Diabetes mellitus DM is a chronic, metabolic disease characterized by elevated levels of blood glucose, which leads over time to serious damage to the heart, blood vessels, eyes, kidneys and nerves [1]. The persistent elevation in blood glucose levels is due to the body's inability to produce enough insulin or inefficient insulin usage by the target cells [2]. DM represents a significant health problem worldwide due to its continuous rapid increasing in its incidence and prevalence due to changes in the lifestyle and aging of the population as well as socioeconomic factors, sedentary life, unhealthy diet and genetic factors. According to the International Diabetes Federation's global estimates in 2021, almost 537 million people between the age of 20-79 years had DM, of them more almost 36%, were unaware about their disease and its complications [3]. According to the classification of the American Diabetes Association, DM can be Type I, type II, gestational or of other classification such as monogenic diabetes syndrome, neonatal, drugs/chemicals induced, and others [4]. The complications of diabetes mellitus are distinguished in terms of being Acute complications such as Hyperosmolar hyperglycemic state [5] which may be attributed to infections, certain drugs, or cardiovascular insults [6]. The chronic complications of diabetes are broadly divided into micro vascular and macro vascular, with the former having much higher prevalence than the latter. Micro vascular complications include neuropathy, nephropathy, and retinopathy, while macro vascular complications consist of cardiovascular disease, stroke, and peripheral artery disease PAD. Diabetic foot syndrome has been defined as the presence of foot ulcer associated with neuropathy [7]. Matrix Metalloproteinases (MMPs) and Metalloproteinase Tissue Inhibitors (TIMPs). The extracellular matrix, has a crucial role in the regulation of the cell motility and cycle, apoptosis, survival, and cells' signals integration [8] . The expression of MMPs (2 and 9) is changed in diabetic patients leading to vascular complications such as micro and macroangiopathy resulting in nephropathies , however, MMP2 considered an indicator for the severity of microangiopathies while MMP9 is a good biomarker for microangiopathies, from other point of view, some experimental studies proved that MMP-9, was regulated and its activity in the endothelial cells affected by higher levels of glucose [9]. Several studies and literature have studied the these MMPs in patients with diabetic kidney diseases and there is

strong evidence that the levels of MMP-2 and -9 increased significantly in the urine of patients with type I or II DM [10,11] . On the other hand, the higher levels of these markers, have been linked to higher frequency of albuminuria and renal injury. Nonetheless, some studies have shown high concentration of MMPs in DM patients with normoalbuminuria, this may reflect the renal impairment prior to the occurrence or detection of proteinuria [12,13] . From other point of view, previous literature found lower levels of TIMP-1 and TIMP-2 in type II DM cases who had diabetic nephropathy (DN) compared to CKD non-diabetic cases or diabetic with no CKD [14] . Conversely, when there is great glomerular lesions in DM patients with DN, the concentration of TIMP was found to be elevated [15]. In Iraq, few studies are available about this topic and the Association of MMPs and Tissue Inhibitor Metalloproteinase-1 with Diabetic Nephropathy among type II diabetic Iraqi patients hence, our study sought to address the existing gap in the knowledge about this association and to contribute to the growing body of literature on this subject

PATIENTS AND METHODS:

This was a case control study conducted between February and June 2025 at Baghdad medical city and included comprising 195 patients with type 2 DM of both gender as well as, a total of 65 healthy subjects as control group.

Urinary albumin to creatinine ratio (ACR) was assessed in spot samples. Diabetic nephropathy patients be categorized based on degree of ACR, A1 (Normal to mildly increased): < 30 mg/g, A2 (Moderately increased): 30–300 mg/g, A3 (Severely increased): > 300 mg/g [16].

Ethical considerations

1. Official approval granted from the Iraqi Board for Medical Specializations.
2. Verbal consents from all volunteers were gained prior to their engagement in the study.

Inclusion criteria

1. Subjects aged 30 years and older of both genders
2. For diabetic patients, diagnosis confirmed according to the standard criteria of the clinical guidelines, Diabetic nephropathy was diagnosed when there is evidence of diabetic nephropathy (e.g., microalbuminuria, proteinuria).

Exclusion criteria

Patients with type 1 diabetes mellitus, glomerular disease, fibrosis kidney disease, polycystic kidney disease, chronic kidney disease, acute kidney injury, kidney transplant, renal tumor, pregnancy or lactation, immunosuppressive therapy, liver disease (alanine transaminase (ALT) and aspartate transaminase (AST) >3x upper limit) and cancer.

Subjects

After appropriate informed and oral consent, demographic characteristics and medical history were reported, blood pressure was measured at the time of enrollment. urine sample was collected about 10-30 ml fresh midstream clean catch urine collected into sterile urine container and tested within 1 hour. All steps were performed under proper infection control measures.

Patients were classified based on their urinary albumin to creatinine ratio into normoalbuminuria, microalbuminuria, and macroalbuminuria groups.

Study protocols and procedures:

Albumin-to-creatinine ratio (ACR) is the preferred approach to evaluating albuminuria. urinary ACR is measured in a spot urine sample. It was calculated by dividing albumin content in milligrams by creatinine concentration in grams. In urine, ACR less than 30 mg/g of albumin is considered normal. Estimated glomerular filtration rate (eGFR) may be more than 60, however, ratio that exceeding 30mg/g may indicate renal disease, as stated by NKF [17].

Microalbuminuria is defined as a daily excretion of 30–300 mg of urinary albumin, or an uACR of 3–30 mg/mmol (flagged by combilyzer13 as abnormal), on the other hand, Macroalbuminuria, or occasionally just albuminuria, is defined by urinary albumin excretion of more than 300 mg daily, or uACR more than 30 mg/mmol [18].

Creatinine in urine and Albuminuria tests were performed depends on the standard protocols applied at our setting

Sample collection:

A sample of venous blood of (5 ml) was collected from antecubital vein of each participant under complete infection control measures, the samples were sent for testing for Glycated hemoglobin (HbA1c), serum creatinine and serum MMP-9 and TIMP-1. Which were measured

using the quantitative sandwich enzyme immunoassay technique in enzyme-linked immunosorbent assay (ELISA) (ELx800).

The references ranges used for purpose of this study; for HbA1c, < 5.7% (Non-Diabetic), ≥ 5.7–6.4% (Prediabetes) and ≥ 6.5 % threshold to diagnose (Diabetes) [19]. For serum Creatinine, normal values: in males: 0.7–1.5 mg/dl and in Females: 0.4–1.2 mg/dl [20]

Statistical Analysis

All data were analyzed using the Statistical Package for Social Sciences (SPSS) version 26.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro–Wilk test. Comparison of means between the four groups (control, normoalbuminuria, microalbuminuria, and macroalbuminuria) was performed using one-way analysis of variance (ANOVA), followed by post-hoc multiple comparison tests (LSD) to determine the significance between individual groups. Pearson's correlation coefficient (r) was used to assess the strength and direction of the relationship between serum MMP-9, TIMP-1, HbA1c, and serum creatinine levels. Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of MMP-9 and TIMP-1 in predicting different degrees of albuminuria, and to determine the optimal cutoff values, sensitivity, specificity, and area under the curve (AUC). All statistical tests were two-tailed, and a p-value < 0.05 was considered statistically significant.

RESULTS:

The study included 260 participants; 51.5% were male, 48.5% were female. Their mean age ranged between 20 and 90 years with a mean of 55.96±13.26 years. The age and sex distribution are shown in (**Table 1**). Diabetic patients were 195 and they were subdivided into three groups according to the ACR with 65 patients in each; the normoalbuminuria, microalbuminuria and macroalbuminuria and compared to the 65 healthy subjects as control group. The comparison of clinical and biochemical variables revealed no statistically significant difference in the mean age among the study groups, (P. value >0.05). Among diabetic groups, a statistically significant difference was found in disease duration, (P. value <0.05) where the duration was lower in normoalbuminuria group compared to Microalbuminuria group and Macroalbuminuria group, the mean duration was 8.84 ± 4.39, 10.89 ± 4.30 and 13.55 ± 5.47

years, respectively, also the difference in disease duration was significant between the Microalbuminuria and Macroalbuminuria groups, (P<0.05). On the other hand, the mean HbA1c was significantly lower in controls than that in all the subgroups of diabetic patients, where the mean HbA1c was (5.56±0.46 %) in controls, compared to (7.80±0.69) in normoalbuminuria group, (7.85±0.69) in Microalbuminuria group and (7.73±0.68) Macroalbuminuria group, (P. value <0.05). Both systolic and diastolic blood pressure were significantly lower in control group compared to the diabetic groups, (P. value <0.05). The mean serum creatinine was significantly lower in controls (0.85±0.14 mg/dl), than that in diabetic groups; it was (0.85 ± 0.14) in controls compared to (2.15±0.50mg/dl) in normo-albuminuria group, (2.02±0.56mg/dl) in Microalbuminuria group, and (2.11±0.51mg/dl) in Macroalbuminuria group, (P. value <0.05). From other point of view, the pairwise post-hoc comparison between the groups, revealed that controls had singly lower HbA1c, systolic blood pressure, diastolic blood pressure, and serum creatinine compared to each of normoalbuminuria, Microalbuminuria and Macroalbuminuria diabetic groups, while the diabetic patients' groups were nor significantly different than each other in clinical and biochemical parameters except the disease duration, (**Table 2**).

Serum MMP-9 and TIMP-1 Levels

Comparison serum MMP-9 and TIMP-1 Levels across the four studied groups showed a statistically significant lower mean serum MMP-9 in control group (47.12 ±4.49ng/ml) than that in normoalbuminuria group (66.80 ±6.45ng/ml), Microalbuminuria group (81.89 ±7.46ng/ml), and Macroalbuminuria group (97.01 ±8.19ng/ml). Additionally, the mean serum MMP-9 in normoalbuminuria group was significantly lower than that in Microalbuminuria and Macroalbuminuria, as well as the mean MMP-9 in Microalbuminuria was significantly lower than that in Macroalbuminuria group, (**Table 3**).

For the tissue inhibitors metalloproteinase-1 (TIMP-1), the same trend of differences was reported where the mean TIMP-1 in control group was significantly lower than that in all diabetic groups and the mean TIMP-1 in normoalbuminuria group was significantly lower than that in Microalbuminuria and Macroalbuminuria groups and that in Microalbuminuria group was significantly lower than that in Macroalbuminuria group, the mean levels of TIMP-1 was (122.32±7.80), (150.43±9.62), (170.11±12.20), (191.63±14.68), respectively, (P. value <0.001),

however, the pairwise comparisons of each two groups revealed a high significant difference with a (P. value<0.001), as shown in (**Table 3**).

Further analysis was performed to assess the correlation among the studied parameters; MMP-9, TIMP-1, HbA1c and serum creatinine, results of this analysis revealed a significant strong direct (positive) correlation between serum MMP-9 and TIMP-1 (r=0.860, P<0.001), in all the three diabetic groups. A significant moderate positive correlation between serum MMP-9 and each of HbA1c (r =0.62, p <0.001) and serum creatinine (r =0.56, p <0.001). A significant moderate positive correlation between TIMP-1 and each of HbA1c (r= 0.61, p <0.001) and serum creatinine (r =0.55, p <0.001). A significant moderate positive correlation between HbA1c and serum creatinine (r= 0.63, p <0.001), these results are shown in **(Table 4**).

Validity of MMP-9 and TIMP-1 in prediction of Albuminuria in diabetic groups

According to the Receiver operating characteristic (ROC) curve analysis, (**Figure 1**), both MMP-9 and TIMP-1 had higher area under the curve (AUC) in prediction of Macroalbuminuria, where MMP-9 had an AUC of 0.971 at a cutoff value of (>86.58 ng/mL), producing a sensitivity of 92.3% and specificity of89.7%. For TIMP-1 it showed an AUC of 0.954, at a cutoff value of (>171.75 ng/mL), producing a sensitivity of 93.8% and specificity of 87.2%, on the other hand, both tests showed high sensitivity (ranged between 87.7% and 96.9%) with an AUC between 0.354 and 0.681, however, MMP-9 showed low specificity of 32.3%, in Normoalbuminuria group and 62.1% in Microalbuminuria group, TIMP-1 was also low specific in these two groups with a specificity of 31.8% and 62.1%, respectively, (**Table 5**).

Table 1. Age and sex distribution of the study participants (N=260)

Variable	No.	%
Sex		
Female	126	48.5
Male	134	51.5
Age (year)		
≤ 40 yrs.	28	10.8
41-50 yrs.	61	23.5
51-60 yrs.	77	29.6
61-70 yrs.	55	21.2
≥ 71 yrs.	39	15.0
Mean (SD)	55.96 (13.26)	-
Range	20 - 90	-

Table 2. Comparison of clinical and biochemical parameters among the studied groups

Variable	Control	Albuminuria			
		Normo-	Micro-	Macro-	P-value
Duration of DM (years)	-	8.84 ± 4.39	10.89 ± 4.30	13.55 ± 5.47	<0.001
HbA1c (%)	5.56 ± 0.46	7.80 ± 0.69	7.85 ± 0.69	7.73 ± 0.68	<0.001
SBP (mmHg)	119.30 ± 6.78	144.53 ± 3.61	145.30 ± 3.29	144.76 ± 3.35	<0.001
DBP (mmHg)	76.92 ± 4.89	93.00 ± 2.46	92.46 ± 2.51	92.07 ± 2.48	<0.001
Serum Creatinine (mg/dl)	0.85 ± 0.14	2.15 ± 0.50	2.02 ± 0.56	2.11 ± 0.51	<0.001

SBP: Systolic blood pressure (mmHg), DBP: Diastolic blood pressure (mmHg)
All values are presented as mean ± standard deviation

Table 3. Comparison of serum matrix metalloproteinase-9 and tissue inhibitors metalloproteinase-1 among the studied groups

Group	MMP-9 (ng/mL)		TIMP-1 (ng/mL)	
	Mean	SD	Mean	SD
Control	47.12	4.49	122.32	7.8
Normoalbuminuria	66.80	6.45	150.43	9.62
Microalbuminuria	81.89	7.46	170.11	12.2
Macroalbuminuria	97.01	8.19	191.63	14.68
P. value*	<0.001		<0.001	

*Pairwise (post-Hoc) tests were significant in all comparisons; controls vs. diabetic patients' groups and diabetic patients' groups with each other P<0.001, and 0.001 for Microalbuminuria vs. Macroalbuminuria groups in both MMP-9 and TIMP-1.
SD: standard deviation

Table 4. Results of correlation analysis for the studied parameters

	Statistics	serum MMP-9	TIMP-1	HbA1c
TIMP-1	*R*	0.860	-	
	P. value	<0.001	-	
HbA1c	*R*	0.620	0.610	-
	P. value	<0.001	<0.001	-
Creatinine	*R*	0.560	0.550	0.630
	P. value	<0.001	<0.001	<0.001

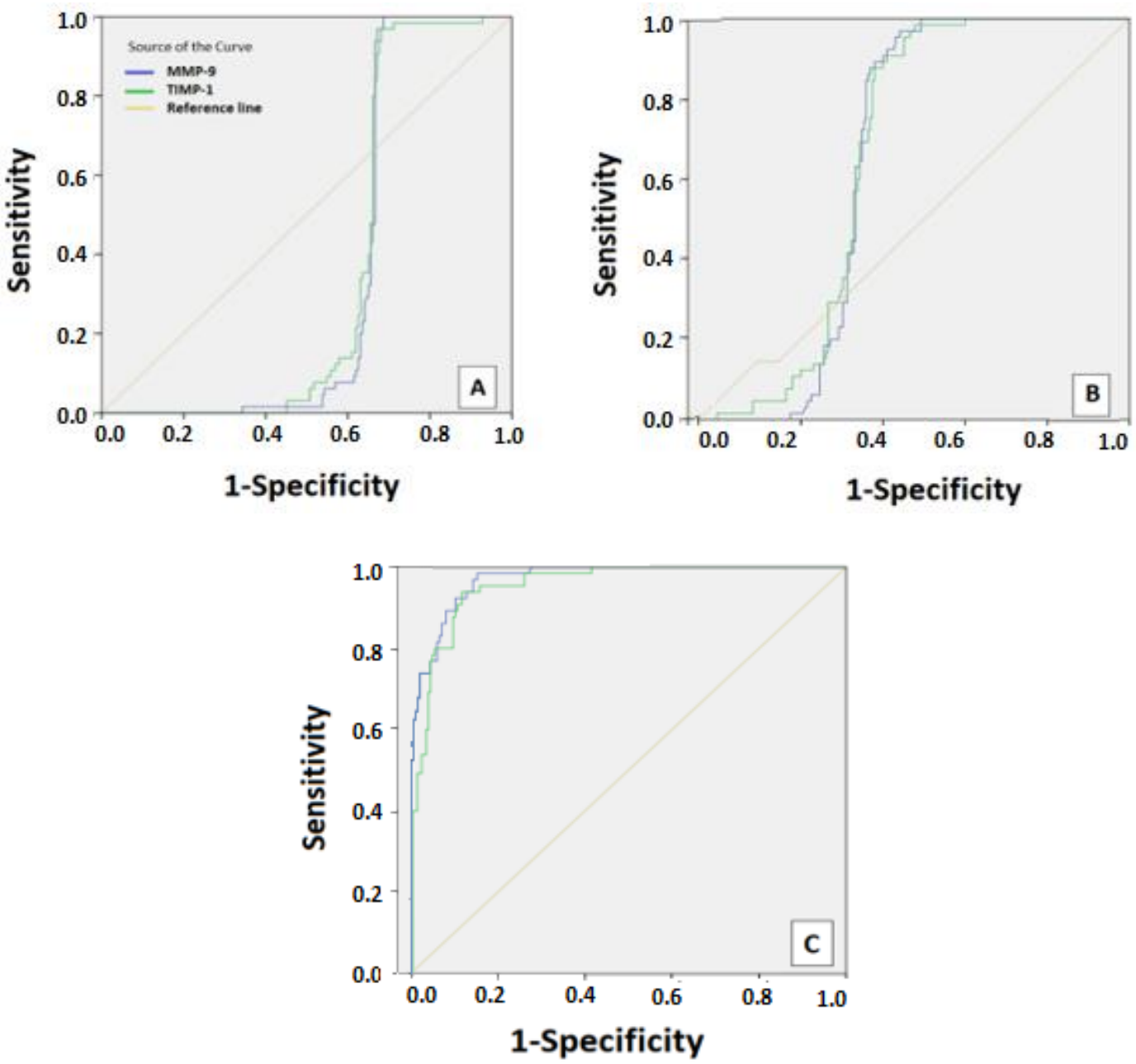

Figure 1. Receiver operating characteristic curve analysis for the validity of MMP-9 and TIMP-1 tests in prediction of albuminuria in diabetic patients' groups: (A: Normoalbuminuria group, B: microalbuminuria group, C: Macroalbuminuria group)

Table 5. Validity parameters of MMP-9 and TIMP-1 at optimal cutoff values in prediction of albuminuria based on Receiver operating characteristic analysis

Group	Test	Cut off value (ng/mL)	AUC	Sensitivity	Specificity	P-value
Normoalbuminuria	MMP-9	>55.76	0.354	96.9%	32.3%	<0.001
	TIMP-1	>134.41	0.359	96.9%	31.8%	0.001
Microalbuminuria	MMP-9	>72.33	0.673	89.2%	62.1%	<0.001
	TIMP-1	>158.52	0.681	87.7%	62.1%	<0.001
Macroalbuminuria	MMP-9	>86.58	0.971	92.3%	89.7%	<0.001
	TIMP-1	>171.75	0.954	93.8%	87.2%	<0.001
All test results in (ng/mL) AUC: area under the ROC curve						

DISCUSSION:

The demographic characteristics of the present study reflect a population typically affected by type 2 diabetes mellitus (T2DM) and its renal complications. Our findings showed that the mean age of the studied group was almost 56 years which indicated that most our cohort were at middle or later adulthood age which the typical age at which the risk of DM is the higher as well as the likelihood of having DN is much increase because the cumulative effect of higher glycemic levels. Several epidemiological and clinical studies have shown a significant link between advancing age in diabetic patients and the risk of DN [21,22] . In our study, males represented 51.5% and females were 45.5%, this sex distribution was almost equal, and it is better to control the possible confounding effect of the sex on the outcomes of the study, however, the sex distribution in previous studies is varied where some studies documented that DN is more frequent in men than women due to biological variation between both sexes, hormonal profile, fat distribution and renal hemodynamics [23], conversely, some investigators reported higher frequency of DN in diabetic women [24] . Our findings showed significant lower HbA1c levels in controls compared to the three diabetic patients' groups (normoalbuminuria, Microalbuminuria and Macroalbuminuria group), this was not unexpected where DM patients often had higher HbA1c levels regardless the glycemic control. There is strong evidence for decades that link between higher HbA1c levels and

microalbuminuria in DM patients and higher likelihood of DN [25]. From other point of view, HbA1c levels were almost similar across normo-, micro-, and macroalbuminuria (~7.7–7.9%). The variability and duration of exposure—rather than a single HbA1c value can be a better predictor of albuminuria progression. With regards to the blood pressure of the studied groups, we found that diabetic patients had generally higher blood pressure compared to controls, this can indicates that elevated blood pressure, even, in normotensive cases, they were at the upper borders, therefore, blood pressure could be additional factor that increases the risk of renal injury in diabetic patients with albuminuria [26]. Our findings showed elevated serum creatinine in DM patients across the three DM groups compared to controls, this findings consistent with that reported in literature and clinical guidelines [27,28]. In our study we documented that MMP-9 and TIMP-1 concentration were significantly elevated in all diabetic patients in the three groups compared to controls, ($P<0.001$). The higher levels of these two markers across the stages of albuminuria indicated that both markers can involve in early renal impairment. Our findings supported the previously documented findings that proved significant correlations between elevated MMP-9 level and higher MMP-9/TIMP-1 ratio with worsening of renal function [29,30]. Furthermore, in an earlier study conducted in 2005, Wang et al. found that MMP-9 and TIMP-1 levels were elevated in DM patients with macroangiopathy, those authors emphasized the role of these markers in vascular and renal complications correlating with disease severity and reinforcing their roles in DM related vascular and renal complications [31]. We further assessed the correlation between the studied parameters and markers and found significant strong positive correlation between MMP-9 and TIMP-1 which indicated the regulative association between these two markers, however, data from Cakirca and Turgut (2018) study documented high levels of both MMP-9 and TIMP-1 in diabetic individuals with normo- and microalbuminuria and their imbalance leading to the impaired turn-over of the Extracellular Matrix (ECM) [29]. Additionally, the observed moderate positive correlations between MMP-9 and HbA1c ($r = 0.62$), and between TIMP-1 and HbA1c ($r = 0.61$), indicated that both markers are associated with poor glycemic control. The results corroborate studies that show the effects that chronic hyperglycemia has on the remolding of the ECM and on the expression of inflammatory markers. For example, increased levels of HbA1c have been found to be correlated with high levels of MMP-9 in

diabetic patients presenting complications such as nephropathy and retinopathy [22]. We found a significant moderate correlation between MMP-9 and TIMP-1 from one side a gains serum creatinine from the other side and this suggestive for the link between ECM remodeling and renal impairment identified by lower eGFR and higher serum creatinine [30]. Furthermore, the positive correlation between HbA1c and creatinine (r = 0.63) supports the established association between poor glycemic control and kidney damage in diabetes.

Predictive Value of Serum MMP-9 and TIMP-1 in Detecting Diabetic Macroalbuminuria

The progression of diabetic nephropathy is closely associated with changes in extracellular matrix turnover, regulated by matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). In this context, the current study evaluated the diagnostic utility of serum MMP-9 and TIMP-1 levels for predicting macroalbuminuria in diabetic patients using receiver operating characteristic (ROC) curve analysis. Findings of Receiver operating characteristic analysis showed that MMP-9 and TIMP-1 had high predictive values for macroalbuminuria. MMP-9 had an area under the receiver operator characteristic curve (AUC) of 0.971 with a cutoff value of >86.58 ng/mL, giving a sensitivity of 92.3% and specificity of 89.7%. The TIMP-1 had an AUC of 0.954 with a cut-point of >171.75 ng/mL, producing a sensitivity of 93.8% and specificity of 87.2%. High levels of AUC indicate that both the markers have high precision in differentiating patients with extensive kidney involvement. These results are confirmed by previous studies. Cakirca and Turgut (2018) have noted that MMP-9 and TIMP-1 levels significantly increased in diabetic individuals with albuminuria, marking their participation in prompt detection of renal damage [29] . Shet et al. (2014) further validated that MMP-9 levels were significantly elevated in microalbuminuric patients as compared to non-microalbuminuric patients, implying the slow increase of the latter marker with increasing severity of the disease [30]. TIMP-1's predictive strength aligns with observations from Papadopoulou-Marketou et al. (2021), where TIMP-1 levels correlated positively with markers of renal dysfunction and early nephropathy in type 1 diabetes [32].

CONCLUSION:

Elevated serum levels of MMP-9 and TIMP-1 was associated with the severity of diabetic nephropathy in patients with T2DM. The parallel increase in both markers with worsening albuminuria and renal dysfunction suggests that dysregulation of Extracellular Matrix (ECM) remodeling contributes to Diabetic Nephropathy progression. Both MMP-9 and TIMP-1 were significantly elevated in diabetic patients across all strata of albuminuria (Normo, Micro and Macroalbuminuria) compared to healthy population. Both markers, were significantly associated with higher levels of HbA1c and serum creatinine. The MMP-9 and TIMP-1 showed excellent performance as predictors of albuminuria in Macroalbuminuria group with excellent sensitivity and specificity. Higher sensitivity rates but low specificity rates were reported in other diabetic patients' groups. Therefore, we recommend including these markers as an additional test to the routine tests for assessment of renal function in diabetic patients that may help for early detection of renal impairment and to prevent poor progression in renal function and irreversible renal damage. However, further studies including multiple centers and larger population are still need for more assessment

BIBLIOGRAPHY:

1. World Health Organization. Global report on diabetes. Geneva: World Health Organization; 2016.
2. Bereda G. Brief overview of diabetes mellitus. Diabetes Manag. 2021;S1:21-7.
3. Bae JH, Han KD, Ko SH, Yang YS, Choi JH, Choi KM, et al. Diabetes fact sheet in Korea 2021. Diabetes Metab J. 2022;46(3):417-26.
4. Jwad SM, Al-Fatlawi HY. Types of diabetes and their effect on the immune system. J Adv Pharm Pract. 2022;4(1):21-30.
5. Adeyinka A, Kondamudi NP. Hyperosmolar hyperglycemic syndrome. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2023.
6. Rosager EV, Heltø AL, Fox Maule CU, Friis-Hansen L, Petersen J, Nielsen FE, et al. Incidence and characteristics of the hyperosmolar hyperglycemic state: a Danish cohort study. Diabetes Care. 2024;47(2):272-9.
7. Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M. Complications of diabetes 2017. J Diabetes Res. 2018;2018:3086167.
8. Kapoor C, Vaidya S, Wadhwan V, Kaur G, Pathak A. Seesaw of matrix metalloproteinases (MMPs). J Cancer Res Ther. 2016;12(1):28-35.
9. Derosa G, Avanzini MA, Geroldi D, Fogari R, Lorini R, De Silvestri A, et al. Matrix metalloproteinase 2 may be a marker of microangiopathy in children and adolescents with type 1 diabetes mellitus. Diabetes Res Clin Pract. 2005;70(2):119-25.

10. Tjomsland V, Pomianowska E, Aasrum M, Sandnes D, Verbeke CS, Gladhaug IP. Profile of MMP and TIMP expression in human pancreatic stellate cells: regulation by IL-1α and TGFβ and implications for migration of pancreatic cancer cells. Neoplasia. 2016;18(7):447-56.
11. Kobusiak-Prokopowicz M, Krzysztofik J, Kaaz K, Jolda-Mydlowska B, Mysiak A. MMP-2 and TIMP-2 in patients with heart failure and chronic kidney disease. Open Med (Wars). 2018;13:237-46.
12. Catania JM, Chen G, Parrish AR. Role of matrix metalloproteinases in renal pathophysiologies. Am J Physiol Renal Physiol. 2007;292(3):F905-11.
13. Derosa G, Avanzini MA, Geroldi D, Fogari R, Lorini R, De Silvestri A, Tinelli C, Rondini G, d'Annunzio G. Matrix metalloproteinase 2 may be a marker of microangiopathy in children and adolescents with type 1 diabetes mellitus. Diabetes Res Clin Pract. 2005;70(2):119-25.
14. Kim YS, Kim SS, Cho JJ, Choi DH, Hwang O, Lee MS, et al. Matrix metalloproteinase-3: a novel signaling proteinase from apoptotic neuronal cells that activates microglia. J Neurosci. 2005;25(15):3701-11.
15. Brkic M, Balusu S, Libert C, Vandenbroucke RE. Friends or foes: matrix metalloproteinases and their multifaceted roles in neurodegenerative diseases. Mediators Inflamm. 2015;2015:620581.
16. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
17. Rasaratnam N, Salim A, Blackberry I, Cooper ME, Magliano DJ, Van Wijngaarden P, et al. Urine albumin-creatinine ratio variability in people with type 2 diabetes: clinical and research implications. Am J Kidney Dis. 2024;84(1):8-17.e1.
18. Résimont G, Cavalier E, Radermecker R, Delanaye P. Albuminuria in diabetic patients: how to measure it? A narrative review. J Lab Precis Med. 2022;7:1-12.
19. Geva M, Shlomai G, Berkovich A, Tirosh A, Cohen E, Grossman E, et al. The association between fasting plasma glucose and glycated hemoglobin in the prediabetes range and future development of hypertension. Cardiovasc Diabetol. 2019;18(1):53.
20. Jain A, Jain R, Jain S. Determination of blood creatinine. In: Basic techniques in biochemistry, microbiology and molecular biology. Singapore: Springer; 2020. p. 201-3.
21. Kibirige D, Sekitoleko I, Lumu W. Burden and predictors of diabetic kidney disease in an adult Ugandan population with new-onset diabetes. BMC Res Notes. 2023;16(1):234.
22. Jitraknatee J, Ruengorn C, Nochaiwong S. Prevalence and risk factors of chronic kidney disease among type 2 diabetes patients: a cross-sectional study in primary care practice. Sci Rep. 2020;10(1):6205.
23. Tziomalos K, Athyros VG. Diabetic nephropathy: new risk factors and improvements in diagnosis. Rev Diabet Stud. 2015;12(1-2):110-8.
24. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA. 2011;305(24):2532-9.
25. Bilous R. Microvascular disease: what does the UKPDS tell us about diabetic nephropathy? Diabet Med. 2008;25(1):25-9.
26. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. BMJ. 1998;317(7160):703-13.
27. Rossing P, Caramori ML, Chan JC, Heerspink HJ, Hurst C, Khunti K, et al. Clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2022;102(5 Suppl):S1-127.

28. Okuno T, Vansomphone A, Zhang E, Zhou H, Koska J, Reaven P, et al. Association of both short-term and long-term glycemic variability with the development of microalbuminuria in the ACCORD trial. Diabetes. 2023;72(12):1864-72.
29. Cakirca G, Turgut FH. Serum matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1 and matrix metalloproteinase-9/neutrophil gelatinase-associated lipocalin complex levels in patients with early-stage diabetic nephropathy. Iran J Kidney Dis. 2018;12(5):271-7.
30. Shet N, Shetty S, Rao A. Serum MMP-9 levels in early diabetic nephropathy. Int J Pharm Sci Invention. 2014;3(6):1-4.
31. Wang GY. Measure serum matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in patients with type 2 diabetic macroangiopathy. Chin J Diabetes. 2005;13(2):112-6.
32. Papadopoulou-Marketou N, Whiss PA, Eriksson AC, Hyllienmark L, Papassotiriou I, Wahlberg J. Plasma levels of tissue inhibitor of metalloproteinase-1 in patients with type 1 diabetes mellitus associate with early diabetic neuropathy and nephropathy. Diabetes Vasc Dis Res. 2021;18(2):147-54.