Original Article

Unravelling interplay of serum MMP-7 and TGF- β in diabetic nephropathy - A study from a tertiary centre in eastern India

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Abstract

Background: Diabetic Nephropathy (DN) constitutes nearly half of cases of end stage renal disease. Despite decrease in kidney function, eGFR in the early stages may remain unaltered, making diagnosis difficult pointing towards need of more accurate biomarkers for early detection. Altered serum Matrix Metallo-Proteinase-7 (MMP-7) and transforming growth factor- β (TGF-β) has been noted independently in diabetic complications. The role of MMP-7 with TGF-β together has been highlighted in extracellular matrix remodelling in kidneys of diabetic rats. Interaction between MMP-7 with TGF- β in DN cases is scarce. Hence, the objective of present study is to evaluate role of serum MMP-7 and TGF-β in DN. **Methods:** This case control Study included 61 DN cases, 61 diabetes Mellitus controls and 61 healthy controls. After clinical evaluation routine biochemical parameters were estimated along with serum MMP-7 and TGF-β. They were analysed in relation to glycemia and eGFR along with correlation analysis. **Results:** Serum MMP-7 and TGF-β registered significant rise (*P* value-<0.001) in DN cases in comparison to control groups. Their substantial association with each other and with glycaemic status and renal function was noted in the correlational analysis. Diagnostic accuracy of MMP-7 and TGF-β for DN was also noted with significant sensitivity and specificity. Multiple regression analysis documented MMP-7 as an independent determinant for Diabetic nephropathy. **Conclusion:** Serum MMP-7 along with TGF-β play significant role in the pathogenesis of DN. Prospective longitudinal study with future Genetic analysis for their expression is needed to establish their role in disease diagnosis and progression.

Keywords: Diabetic nephropathy, extra cellular matrix remodelling, MMP-7, TGF-β

Introduction

Diabetic kidney disease (DKD), often referred to as diabetic nephropathy (DN), a progressive disorder, remains the commonest cause of end-stage kidney disease (ESKD).[1,2] The process of development of DN involves cellular processes such as Glomerular Basement Membrane (GBM) thickening in the early stage, followed by nodular and subsequently diffuse glomerulosclerosis during late stage.[3,4] As stated by the American Diabetes Association (ADA) and Kidney Disease Improving Global Outcomes (KDIGO) recommendations, the diagnosis of chronic kidney disease in diabetics is based on evidence of increased urine albumin excretion (≥30 mg/g creatinine) or decreased estimated glomerular filtration rate (eGFR) i.e. <60 ml/min/1.73 m^2, which have persisted for more than three months.[5] In the early phase, hyperfiltration can maintain the estimated glomerular filtration rate at a high-normal or even elevated level, which makes it more challenging in diagnosis.

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Early detection of diabetic nephropathy (DN) with more accurate biomarkers of kidney damage is therefore essential for its effective management and retarding its progression with intervention using therapeutic targets.[1,5]

A primary pathologic characteristic of diabetes complications is fibrosis resulting from dysregulated remodelling of extracellular matrix (ECM) in organs, most common being the kidney resulting in its retarded function.[6] MMP-7, the smallest molecule of matrix metalloproteinases (MMPs) well known as Matrilysin plays a vital role in both structure and function of ECM.[7] Previous studies have cited that MMP-7 is hardly expressed in adult healthy kidneys, but it is highly expressed in kidney injuries, both acute kidney injury (AKI) and chronic kidney disease (CKD).[7,8] Increased urinary MMP-7 level has also been documented as a predictor of acute kidney injury after post-cardiac surgery in IgA Nephropathy cases showing raised production of MMP-7 by kidneys.[9]

Li *et al.*[10] have documented that MMP-7 participates in ECM remodelling involving an inflammatory marker TGF-β in STZ-induced diabetic rats. Critical role played by TGF- β in regulating MMP-7 expression has also been cited by others.[7] There exist studies reporting MMP-7 level in different diabetes associated conditions like Diastolic Dysfunction, DKD and Periodontitis.[6,11] However detailed interaction between MMP-7 and TGF-β in diabetes and DN is not reported much. Hence the present study was proposed to evaluate serum MMP-7, TGF- β, and their association with risk of diabetic nephropathy, which may act as a target of therapeutic significance.

Materials and Methods

This study involved three study groups; one group of cases (diabetic nephropathy) and two control groups (healthy control and Diabetics without nephropathy as Diseased Control). Total 183 participants were enrolled in the study with each group having 61 participants. Sample size was calculated in https://sample-size.net/website taking data from a previous study.[12] Study was approved by institutional ethical committee. Subjects of either sex, age above 18 years, clinically diagnosed with diabetic nephropathy admitted to Department of Nephrology were included as cases, diabetes without complications from NCD clinic were included as diabetic control. Age, sex matched relatives or attenders of patients coming to outpatient department, without history of diabetes were included in the study as healthy control. All participants submitted their consent. Age <18 years, seriously ill patients, pregnant women, patients with previous history of kidney disease (both acute and chronic kidney disease) and cancers were excluded from the study. Diabetic nephropathy cases were staged based on their eGFR. Thirty three patients, with eGFR >60 ml/min/1.73 m^2 were grouped as mild and twenty eight patients with eGFR <60 ml/min/1.73 m^2 were grouped as moderate to severe.[13,14]

5 ml of venous blood sample was collected in plain vial and serum was aliquoted and stored at -20 degree Celsius for further analysis. By using sandwich technique of Enzyme-linked immunosorbent assay (ELISA) serum concentration of MMP-7 and TGF- β was estimated as per manufacturer's protocol (ELK biotechnology). Routine biochemical parameters like fasting plasma glucose or FPS (hexokinase method), glycated hemoglobin or HbA1c (negative immunoturbidimetry), serum creatinine (Jaffe's end point method), serum urea (urease method), serum uric acid (uricase method) were estimated by using Beckman coulter AU5800 autoanalyzer. eGFR was calculated using CKD-EPI Formula.[15] Additional information related to cases was collected from case record of the patient.

Statistical analysis

Descriptive statistics was represented as Mean ± SD for parametric data and as median, range for non-parametric data. ANOVA test with *post hoc* analysis was used to compare parametric data and Kruskal Wallis test for non-parametric data. Chi square test was conducted to compare categorical variables among cases and two control groups. For multiple comparisons Tukey's honestly significant difference (HSD) post-hoc test was performed. Continuous variables between two groups of DN were analyzed using T-test. Spearman's correlation analysis was performed to document the association among the parameters. Diagnostic accuracy of the parameters was assessed by taking area under the curve (AUC) in receiver operating characteristic curve (ROC) analysis. Multiple regression analysis was done to exclude the role of confounders. *P* value less than 0.05 (*P* value < 0.05) was considered significant. Statistical analysis was done using SPSS (version 26).

Results

Present study did not reveal significant difference in age and male to female distribution amongst groups in study population. BMI was found to be significantly higher in DN group as compared to DM controls and healthy controls (Mean ± SD for DN = 28.09 ± 2.6 kg/m^2, DM = 27.55 ± 2.4 kg/m^2, healthy control = 21.76 ± 2.4 kg/m^2, *P* value <0.05). Mean duration was four years and seven years for DM and DN respectively. Marked rise in FPS and HbA1c was observed in the DN group with Mean value of 155.32 mg/dl, 6.93% respectively as compared to healthy control group with Mean value of 90.51 mg/dl, 4.87 respectively (*P* value <0.001). Other routine parameters like serum creatinine, urea and uric acid were also observed to be markedly (*P* value <0.001) raised in DN group compared to DM and healthy controls. Mean eGFR reflecting renal function documented significant (*P* value <0.001) fall in DN group (57.1 ml/min/1.73 m^2) in comparison to DM (91.8 ml/min/1.73 m^2) and healthy controls (111.4 ml/min/1.73 m^2). Glycaemic and renal function parameters were more prominently deranged in DN cases as compared to healthy controls and DM controls in multiple comparisons (*P* value < 0.001, *P* value <0.001, respectively).

Serum MMP-7 and TGF-β levels measured in all the three study groups were represented in box plot [Figure 1] revealing

significantly raised serum value of both the parameters in diabetic nephropathy cases when compared across the groups.

Sixty-one DN cases were divided into two groups based on eGFR i.e., mild (>60 ml/min/1.73 m^2) and moderate to severe (<60 ml/min/1.73 m^2) respectively. Severity of alteration of MMP-7 and TGF-β serum levels was analysed with severity of kidney involvement in DN cases. Both the parameters registered significant rise in moderate to severe cases when compared to mild group of DN [Table 1].

Spearman's Correlation analysis [Figure 2] revealed significant positive association between both serum MMP-7 levels and TGF-β (P = <0.001) with a r value of 0.80 pointing towards existence of association between them in Diabetic Nephropathy. Both MMP-7 and TGF-β registered significant positive association (P value < 0.05 with glycemic status and a marked negative relation (P value < 0.05) with renal function as shown with eGFR [Table 2] pointing towards association of raised MMP-7 and TGF-β with fall in renal function.

Figure 3 represents receiver operating characteristic curve (ROC) analysis of serum MMP-7 and TGF-β for diagnostic accuracy for DN, which was noticed significant for both serum MMP-7 and serum TGF-β, as indicated by their high AUC values, i.e., 0.901,0.947 respectively. Serum MMP-7 appeared to have a slightly lower sensitivity but higher specificity compared to serum TGF- β to diagnose DN with cut off value of 8.2 ng/ml and 154.3 pg/ml for MMP-7 and TGF- β, respectively.

Table 1: MMP-7 and TGF-β in DN cases as per staging

	Diabetic Nephropathy		*P*
	Mild (*n*=33) Mean (SD)	Modrate to severe (*n*=28) Mean (SD)	
CKD-EPI eGFR (ml/min/1.73 m^2)	97.1 (19.6)	34.1 (15.4)	0.05
MMP-7 (ng/ml)	4.2 (5.3)	13.4 (8.6)	<0.001
TGF-β (pg/ml)	92.3 (137.9)	299.6 (164.95)	0.03

P<0.05 is considered statistically significant

Multiple regression analysis for determinants in the pathogenesis of DN with Adjusted R^2 of 0.108 revealed that age, BMI, duration of diabetes, glycaemic parameters, and TGF –β were not significantly associated with declined eGFR. Whereas serum MMP-7 documented significant association with eGFR (β = -0.51, P value = 0.03) reflecting its contributory role towards deteriorating renal function [Table 3].

Discussion

The present study was intended to highlight the involvement of MMP-7 and TGF-β in DN which was reported previously in STZ induced diabetic rats showing TGF beta signaling being related to MMP/TIMPs expression.[10]

The classical pathology of DN is glomerulosclerosis with ECM deposition affecting renal function. MMP-7 being an ECM remodelling enzyme and TGF-β as an inflammatory cytokine have been shown as crucial players in the pathogenesis and disease progression of DN individually.[3,16] Current study assessed interrelation of MMP-7, TGF-β and their contributory role in the etiopathogenesis of DN cases as compared to diabetics without Nephropathy and healthy controls.

Elevated expression of MMP-7 associated with poor prognosis has previously been documented in several cancers and fibrotic conditions.[17–22] In addition, MMP-7 has also been linked to plaque rupture and cardiovascular disease.[23,24] It is one of the best studied MMPs in kidney disorders, with prior research demonstrating that it is elevated in renal disorders investigated to date. It was observed that MMP-7 is hardly expressed in healthy human kidneys but in kidney diseases, including polycystic kidney disease, lupus-affected kidneys, diabetic kidney disease, and post-cardiac surgery patients with IgA nephropathy, MMP-7 expression was more than normal.[25,26] Current study also noted overexpression of MMP-7 in DN patients with raised serum levels being positively correlated with hyperglycaemia and deteriorating renal function as reflected by eGFR. Ban *et al.*[6] proposed that the raised serum MMP-7 in diabetic kidney disease may be due accumulation of MMP-7 rather than

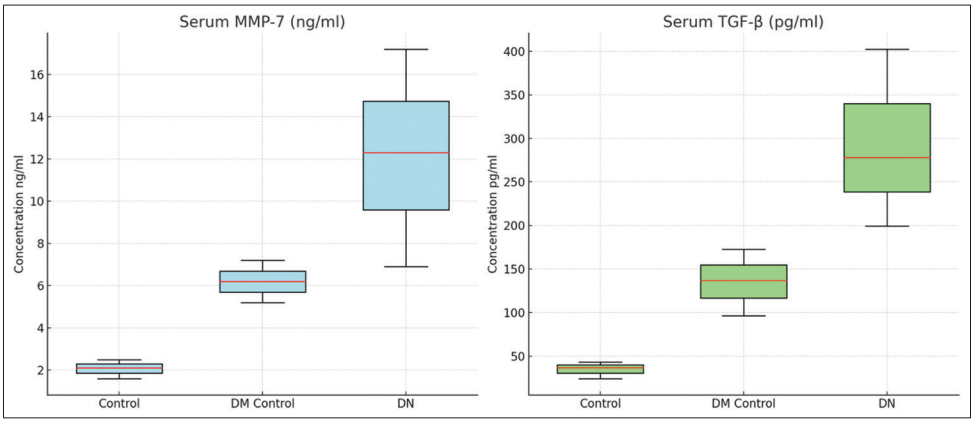

Figure 1: Box plot of serum MMP-7 and serum TGF- β in three study populations

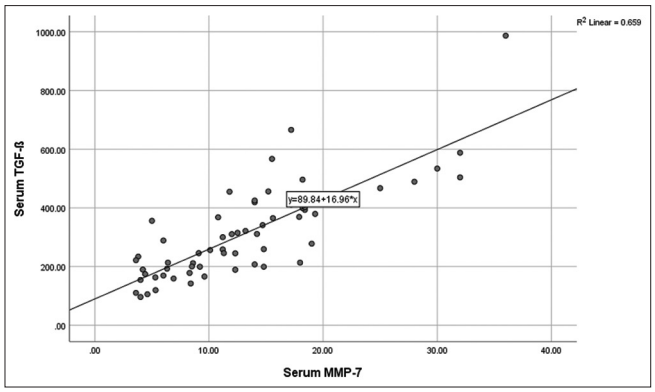

Figure 2: Spearman's Correlation of serum MMP-7 with serum TGF- β. Spearman's correlation coefficient: 0.80 (*P* value = <0.001)

Table 2: Spearman's correlation coefficient (*r*) showing association of MMP-7 and TGF-β with glycaemic status (FBS, HbA1c) and renal function (eGFR)

Parameters	MMP-7 (*r*)	*P*	TGF-β (*r*)	*P*
FPS (mg/dl)	0.33	<0.001	0.37	<0.001
HbA1c (%)	0.38	<0.001	0.35	<0.001
eGFR (ml/min/1.73 m^2)	-0.65	<0.001	-0.49	<0.001

P<0.05 is considered statistically significant

insufficient kidney clearance. Zeidán-Chuliá *et al.*[11] stated that reactive oxygen species along with other MMPs like MMP-2 and MMP-9 facilitates the overexpression of MMP-7 through various signalling pathways in hyperglycaemic conditions as in diabetic periodontitis.

The possible mechanism of MMP-7 mediated kidney damage altering the micro-architecture of the glomerular apparatus is by destroying components of the glomerular ECM.[7,27] Cleavage of Nephrin, a direct substrate of MMP-7 compromises the integrity of the slit diaphragm, hence promoting proteinuria. By degrading E-cadherin MMP-7 disrupts the E-cadherin/β-catenin complex on cell membrane and increases intracellular β-catenin,[8,28] which is then translocated to nucleus increasing the expression of Wnt/β-catenin target genes, one of them being MMP-7.[29,30] Overexpressed MMP-7 further cleaves the E-cadherin and the vicious cycle gets established.[8] In addition to cleaving E-cadherin, degrading collagen IV and laminin in renal basement membrane, and by epithelial to mesenchymal transition (EMT), it subsequently leads to fibrosis in kidney.[7]

Continuous release of TGF-β, a pro inflammatory cytokine from Kidney during injury leads to tubular, interstitial and glomerular fibrosis.[31-33] Study by Mehta *et al.*[34] has shown that plasma TGF-β is independently associated with declined eGFR being negatively co-related with it in kidney disease patients. TGF-β is a critical regulator in Diabetic Nephropathy, being related to hazardous ambient factors like hyperglycaemia, advanced glycation end products, reactive oxygen species, dyslipidaemia, etc.[35,36] Present study also witnessed marked rise of TGF-β in

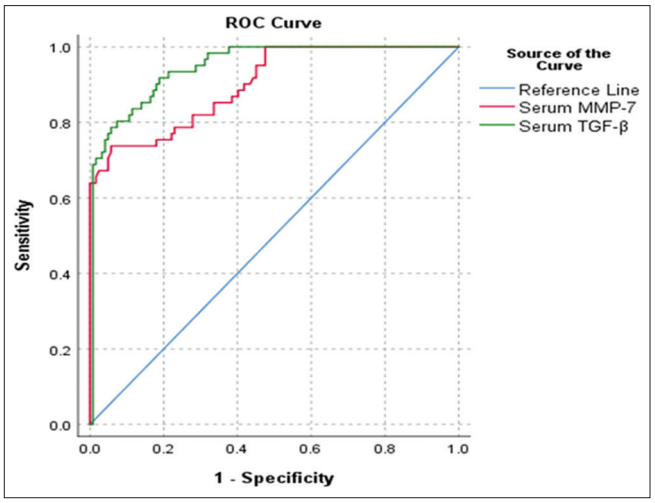

Figure 3: Receiver operating characteristic curve (ROC) analysis of MMP-7 and TGF- β as biomarker to diagnose DN

DN cases with significant association with hyperglycaemia and deteriorating renal function in agreement to above.

However studies regarding the complex relation of MMP-7 and TGF-β in DN are scarce which has been explored in the present study. Which also documented positive association between both MMP-7 and TGF-β themselves as well as with hyperglycaemia and worsened kidney function having significant diagnostic accuracy towards DN pointing to the fact that they may act in a synergistic way. Further when DN patients were staged in to mild and moderate to severe group based on eGFR. Severity of renal damage was found to be linked with elevated levels of both serum MMP-7 and TGF-β, giving clue about existence of cross talk between them contributing towards renal damage. MMP-7 facilitates the dissociation of the TGF-β–latency-associated peptide (LAP) activating TGF-β which is majorly acts via TGF-β/Smad signalling pathway.[35] The Smad component attaches itself directly to gene promoters to trigger the transcription of pro-fibrotic molecules, such as collagen I, α-smooth muscle actin (α-SMA), and tissue inhibitor of matrix metalloproteinases (TIMP), which cause the activation of myofibroblasts and the deposition of matrix ultimately leading to fibrosis.[36,37] Smad-4, an intracellular signal transducer, and transcriptional activator of MMP-7 leads to MMP-7 overexpression. This may be a probable interaction of TGF-β increasing expression of MMP-7. Additionally TGF-β binding to its receptor can also induce β-catenin in cytoplasm which is a transcriptional activator of MMP-7.[7]

The regression analysis observation excluding expected multiple confounders like age, BMI, duration of DM and glycaemic parameters revealed significant contributory role (β = -0.51, *P* value = 0.03) of MMP-7 in etiopathogenesis of deteriorating renal function that indicates probably MMP-7 dominates over TGF-β for causing kidney damage in DN.

Thus, the present study revealed synergistic interaction of MMP-7 and TGF-β in etiopathogenesis of renal fibrosis with

Table 3: Multiple regression analysis showing association of determinants with kidney function (eGFR)

Determinants	Unstandardized Coefficients		Standardized Coefficients Beta	95.0% Confidence Interval for B		*P*
	B	Std. Error		Lower Bound	Upper Bound	
Age	0.30	0.36	0.10	-0.42	1.02	0.40
BMI	-1.38	1.21	-0.14	-3.82	1.05	0.25
Duration of diabetes	-1.81	3.06	-0.10	-7.96	4.33	0.55
HbA1c (%)	-3.43	3.04	-0.24	-9.53	2.67	0.26
FPS (mg/dl)	0.03	0.07	0.07	-0.12	0.18	0.69
MMP-7(ng/ml)	-1.74	0.78	-0.51	-3.31	-0.16	0.03
TGF-β(pg/ml)	0.06	0.03	0.39	-0.01	0.14	0.10

Dependent variable: CKD EPI eGFR, Adjusted R^2=0.108

declining kidney function in diabetic nephropathy. Targeting MMP-7, individually as well as together with TGF-β may help in retarding further progression of renal damage with resultant better long-term outcome in Diabetic cases, an approach important in primary care set up.

Conclusion

The significant association of raised MMP-7 and TGF-β with glycaemic status and renal function along with their diagnostic predictability in patients of Diabetic Nephropathy indicates towards their critical role in disease process. MMP-7 registered to be an independent determinant of kidney function in DN. Highlighting contribution of both MMP-7, an extracellular enzyme and pro-inflammatory cytokine TGF-β in diabetic nephropathy indeed, is the strength of the present study. However, the complex bidirectional relationship of MMP-7 and TGF-β with Smad signalling needs to be further explored. Elucidating the molecular mechanisms like MMP-7 promoter site polymorphisms influencing its expression in Diabetic Nephropathy would give more insight to the above observation.

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Conflicts of interest

There are no conflicts of interest.

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