Syndecan-1 as a Prognostic Biomarker for Early Diabetic Kidney Disease Progression: A Cohort Study

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Abstract: This study aimed to investigate the role of serum Syndecan-1 levels in the progression of Diabetic kidney disease (DKD) and their predictive value for adverse renal outcomes. Two hundred thirty-eight participants were included in the study cohort, consisting of 90 DKD patients (estimated glomerular filtration rate (eGFR)>60ml/min/1.73m2), 88 diabetes mellitus(DM) patients without kidney disease, and 60 healthy individuals. Baseline levels of Syndecan-1 and relevant clinical indicators were measured for all participants. A 2-year follow-up study defined the primary endpoint as a ≥30% drop in eGFR or an eGFR below 60 mL/min/1.73 m², and the secondary endpoint as a ≥30% rise in proteinuria. Multivariate logistic regression and ROC curve analysis were used. Baseline Syndecan-1 levels differed significantly among the three groups: the DKD group had substantially higher Syndecan-1 levels than the DM group, while the healthy group had the lowest levels. DKD patients were divided into high and low Syndecan-1 expression groups, with the high-expression group experiencing more primary and secondary endpoint events. Multivariate logistic regression analysis confirmed that baseline Syndecan-1 concentration was an independent risk factor for both proteinuria progression and eGFR decline in DKD patients (P<0.05).ROC curve analysis demonstrated that Syndecan-1 had a specific predictive value for DKD progression (AUC = 0.804, P<0.05). Syndecan-1 is highly expressed in DKD patients and is independently associated with adverse renal outcomes. It may serve as a potential biomarker for assessing the risk of DKD progression.

Keywords: Diabetes Mellitus; Diabetic Kidney Disease; Syndecan-1; Progression

1. Introduction

Diabetic kidney disease (DKD) remains one of the most prevalent and devastating microvascular complications of diabetes mellitus (DM), accounting for nearly 50% of end-stage renal disease (ESRD) cases worldwide [1], [2]. With the global epidemic of DM, the incidence of DKD continues to rise, imposing a heavy burden on healthcare systems and severely compromising patients' quality of life. Currently, clinical assessment of DKD progression primarily relies on estimated glomerular filtration rate (eGFR) and proteinuria—two classical but relatively late-stage markers38844018.Current indicators often miss early renal damage and fail to predict disease progression, underscoring the need for better biomarkers for DKD risk assessment and management[3].

Syndecan-1, a transmembrane heparan sulfate proteoglycan, plays a pivotal role in regulating extracellular matrix remodeling, inflammatory responses, and vascular permeability—key pathological processes underlying DKD progression[4] [5]. Emerging evidence has linked abnormal Syndecan-1 expression to renal injury in non-diabetic kidney diseases, such as focal segmental glomerulosclerosis and lupus nephritis[6] [7]. However, the expression pattern of Syndecan-1 in DKD patients relative to those with DM and healthy individuals remains unclear. More importantly, whether Syndecan-1 can predict adverse renal outcomes in patients with DKD has not been systematically validated.

To address these knowledge gaps, the present study enrolled a well-characterized cohort comprising patients with DKD, patients with DM without kidney disease, and healthy controls. Our objectives were to: (1) compare baseline Syndecan-1 levels among three groups; (2) explore the link between Syndecan-1 expression and key renal outcomes (≥30% decline in eGFR and ≥30% increase in proteinuria) in two years; and (3) assess Syndecan-1's independent prognostic value for DKD progression using multivariate and ROC curve analyses. The findings of this study may provide new insights into the pathological mechanisms of DKD and identify a potential biomarker for optimizing DKD risk assessment. In summary, this study aims to address critical gaps in the understanding of DKD by focusing on Syndecan-1 as a potential biomarker for assessing the risk of disease progression.

2. Methods

2.1 Study Subjects

Patients with diabetes mellitus who visited the Department of Nephrology and the Department of Endocrinology of our hospital from January 2021 to January 2022 were enrolled as the study subjects.The Ethical Committee of the Loudi Central Hospital approved the study protocol (202202).All participants were informed, and signed the informed consent.

Inclusion criteria: (1) Meeting the 1999 World Health Organization (WHO) diagnostic criteria for diabetes mellitus[8]; (2) Estimated glomerular filtration rate (eGFR) > 90 mL/min·1.73m² (calculated using the CKD-EPI formula)[9]; (3) Aged 18–75 years; (4) Voluntarily participating in this study and signing the informed consent form.

Exclusion criteria: (1) Complicating with other kidney diseases (e.g., lupus nephritis, hypertensive renal damage); (2) Having acute infection, cardiovascular and cerebrovascular events (e.g., myocardial infarction, cerebral infarction), or surgery within the past 3 months; (3) Hepatic insufficiency (Child-Pugh class B/C); (4) Malignant tumors or autoimmune diseases; (5) Poor control of blood pressure or blood glucose.Finally, 178 patients with diabetes mellitus were included, including 88 patients in the DM group and 90 patients in the DKD group.

Healthy group: Individuals with normal physical examination results, aged 18–75 years, with normal blood glucose and renal function, and no history of diabetes mellitus/hypertension.

2.2 Detection Indicators

General information: Data, including age, gender, history of hypertension (systolic blood pressure ≥ 140 mmHg/diastolic blood pressure ≥ 90 mmHg or use of antihypertensive drugs), history of cardiovascular and cerebrovascular disease (CCVD), defined as a history of myocardial infarction, stroke, or peripheral arterial disease, were collected. Additionally, 24-hour urinary protein excretion and eGFR (calculated via the CKD-EPI formula) were measured.

Serum Syndecan-1: Serum Syndecan-1 levels were detected using an enzyme-linked immunosorbent assay (ELISA) kit purchased from R&D Systems, and the operation was performed strictly following the manufacturer's instructions.

2.3 Endpoint Events

The 30% reduction of eGFR or eGFR < 60 mL/min/1.73 was defined as a primary end point. The secondary endpoint was a 30% or greater increase from baseline in 24-hour urine protein.

2.4 Statistical Methods

SPSS 26.0 software was used for statistical analysis. Measurement data with normal distribution were expressed as mean ± standard deviation (x±s), while those with non-normal distribution were expressed as median (25th percentile, 75th percentile). An independent samples t-test was used for comparison between two groups with normal distribution, and the Mann-Whitney U test was used for groups with non-normal distribution. One-way analysis of variance (ANOVA) with post-hoc LSD-t test was used for comparison among three groups. Categorical data were expressed as n (%) and compared via the Chi-square test. Pearson correlation assessed correlations, while binary logistic regression was used for multivariate analysis. Receiver Operating Characteristic (ROC) curve analysis determined the area under the curve (AUC). $P < 0.05$ was considered statistically significant.

3. Results

3.1 Baseline Characteristics

Table 1. Baseline Characteristics of Study Participants

Variable	HC(n=60)	DM(n=88)	DKD(n=90)	P Value
Age(y)	54.96±12.85	54.42±14.99	52.8±14.43	0.61
Gender(M /F,n)	35/26	45/43	42/48	0.43
Hypertension(n，%)	-	32(36.4)	71(78.9)	<0.001
CCVD(n,%)	-	11(12.5)	17(18.9)	<0.001
24 hUP(mg/24h)	-	-	1.42(0.78,2.46)	-
eGFR(ml/min/1.73m²)	90.19(74.69,107.46)	95.52(82.66,114.47)	76.04(64.52,94.95)	<0.001
Syndecan-1(ng/ml)	63.61±32.03	92.88±38.22	112.4±50.17	<0.001

No significant age or gender differences were found among the healthy, DM, and DKD groups (all $P > 0.05$), but hypertension and CCVD history were more prevalent in the DKD group than in the DM group ($P < 0.05$). Regarding renal function, the estimated glomerular filtration rate (eGFR) was significantly lower in the DKD group than in the DM group ($P < 0.05$). Additionally, serum Syndecan-1 levels showed a graded increase across the three groups, with the highest concentrations in the DKD group and the lowest in healthy controls, and these differences were statistically significant ($P < 0.001$).

Abbreviations: DM, diabetes mellitus; DKD, diabetic nephropathy; eGFR, estimated glomerular filtration rate; CCVD, cardiovascular and cerebrovascular disease (defined as a history of myocardial infarction, stroke, or peripheral arterial disease); 24 hUP, 24-h urine protein.

3.2 Correlations between Serum Syndecan-1 and Renal Parameters

As illustrated in Figure 1, Pearson correlation analysis revealed that serum Syndecan-1 was significantly positively correlated with 24-hour urinary protein excretion (r = 0.394, 95% confidence interval [CI]: 0.20 to 0.56, $P < 0.001$). A weaker but still significant positive correlation was observed between serum Syndecan-1 and eGFR (r = 0.22, 95% CI: 0.02-0.40, P = 0.036).

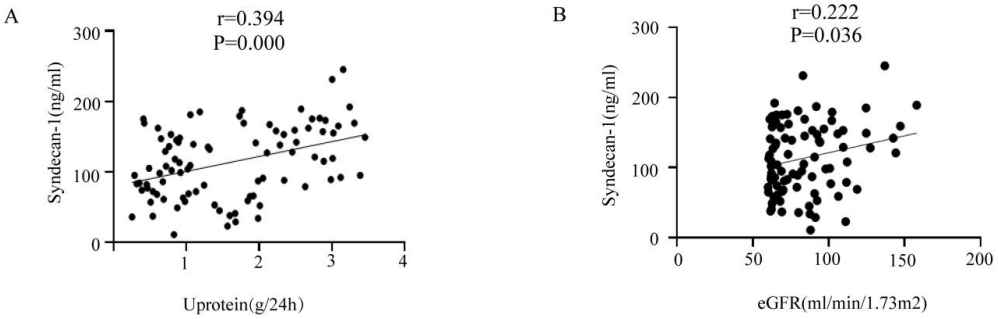

Figure 1. Baseline Characteristics of Study Participants

Abbreviations: DM, diabetes mellitus; DKD, diabetic nephropathy; eGFR, estimated glomerular filtration rate; CCVD, cardiovascular and cerebrovascular disease (defined as a history of myocardial infarction, stroke, or peripheral arterial disease); 24 hUP, 24-h urine protein.

3.3 Subgroup Analysis

Based on Serum Syndecan-1 Levels in DKD Patients. To explore the clinical significance of Syndecan-1 in DKD, patients in the DKD group were stratified into high and low Syndecan-1 subgroups using the median serum level (111 ng/mL) as the cutoff. Compared with the low Syndecan-1 subgroup, the high Syndecan-1 subgroup had significantly higher 24-hour urinary protein excretion and significantly lower eGFR ($P < 0.01$). Moreover, the proportion of patients with a history of CCVD was considerably higher in the high Syndecan-1 subgroup ($P < 0.05$).

Table 2. Clinical Characteristics of DKD Patients Stratified by Serum Syndecan-1 Levels

	Syndecan-1-High (n=45)	Syndecan-1-Low (n=45)	P Value
Primary endpoint(n,%)	17(37.8)	3(6.7)	0.001
Secondary endpoint(n,%)	16(35.6)	6(13.3)	0.014
Hypertension(n,%)	34(75.6)	37(82.2)	0.438
CCVD(n,%)	13(28.9)	4(8.9)	0.029

Age(y)	54.47±16.02	51.13±12.6	0.276
24h-UP(g/24h)	2.15(0.91,2.86)	1.02(0.57,1.86)	0.000
eGFR(ml/min/1.73m^2)	88.96±27.6	78.4±16.98	0.032

Patients with DKD were stratified into two subgroups based on the median serum Syndecan-1 level (111 ng/mL) as the cutoff: a high Syndecan-1 group (≥111 ng/mL) and a low Syndecan-1 group (<111 ng/mL). Abbreviations: eGFR, estimated glomerular filtration rate; CCVD, history of cardiovascular and cerebrovascular disease.

Table 3. Multivariate Regression Analysis in DKD Patients

Variable	Secondary endpoints		Primary endpoints	
	HR(95%CI)	P Value	HR(95%CI)	P Value
Syndecan-1(ng/ml) per 10ng/mL increasel	1.129(1.011-1.261)	0.031	1.319(1.14-1.526)	0.000
CVVD (yes VS no)	3.999(1.224-13.065)	0.022	-	-

Abbreviations: OR, odds ratio; CI, confidence interval; CCVD, cardiovascular and cerebrovascular disease; eGFR, estimated glomerular filtration rate.

3.4 Predictive Values of Syndecan-1 for DKD Progression

DKD progression was determined according to reaching the endpoint. During a 2-year follow-up, the incidence of disease progression was significantly higher in the high Syndecan-1 subgroup than in the low subgroup ($P < 0.01$). Multivariate regression analysis identified serum Syndecan-1 and a history of CCVD as independent risk factors for the progression of proteinuria after adjusting for age, gender, baseline urine protein, and baseline eGFR. In contrast, only serum Syndecan-1 emerged as an independent risk factor for eGFR decline (Table 3).

As shown in Figure 2, ROC curve analysis demonstrated that serum Syndecan-1 had good predictive value for the eGFR decline in DKD, with an AUC of 0.804 (95% CI, 0.698-0.909). This performance was superior to that of urinary protein, which had an AUC of 0.654,95%CI(0.513-0.795)($P < 0.05$).

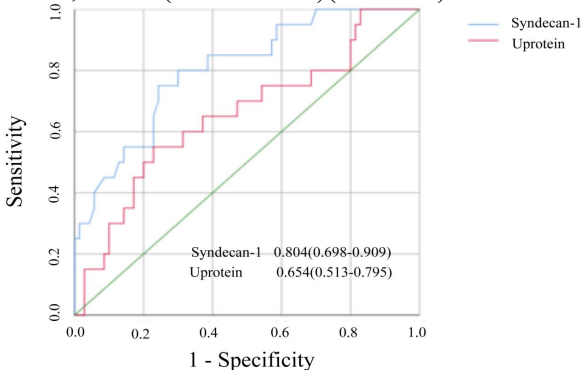

Figure 2. Receiver Operating Characteristic Curve

ROC curves comparing the predictive value of serum Syndecan-1 (blue line) and 24-hour urinary protein (red line) for DKD progression(eGFR decline). Abbreviations: ROC, receiver operating characteristic; AUC, area under the ROC curve; CI, confidence interval.;eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease.

4. Discussion

DKD is a prevalent and severe complication of diabetes mellitus, representing a significant challenge in diabetes management due to its association with increased morbidity and mortality, as well as its substantial economic burden on healthcare systems. The pathophysiology of DKD includes complex interactions between metabolic dysregulation, hemodynamic changes, and inflammation, necessitating early detection and intervention to prevent irreversible kidney damage[10]. Current diagnostic approaches primarily rely on the assessment of urinary albumin excretion and eGFR. Still, these methods often lead to delayed diagnosis and do not effectively capture the early stages of kidney damage, underscoring the urgent need for novel biomarkers to facilitate timely intervention[11, 12].

Syndecan-1, a key transmembrane proteoglycan of the endothelial glycocalyx, exhibits distinct expression patterns across renal compartments with critical implications for renal physiology and pathology. Numerous studies have demonstrated that increased levels of Syndecan-1, a heparan sulfate proteoglycan expressed on endothelial and epithelial cells, in blood or urine indicate acute endothelial injury[13]. In acute kidney injury, Syndecan-1 is shed from the surface of epithelial cells, accompanied by the loss of polarity and increased apoptosis of renal tubular epithelial cells [14]. However, whether Syndecan-1 undergoes similar changes in DKD remains unclear. Our findings highlight

serum Syndecan-1 as a promising biomarker associated with the presence and progression of DKD, providing new insights into its potential role in disease pathogenesis and clinical management. First, baseline analyses revealed that serum Syndecan-1 levels were significantly elevated in patients with DKD compared to those with DM alone and healthy controls. This result aligns with emerging evidence that Syndecan-1 is released during cellular injury or inflammation, processes central to DKD progression[15]. The graded increase across study groups (healthy < DM < DN) further supports Syndecan-1 as a marker of renal damage severity, consistent with prior work linking Syndecan-1 to albuminuria and glomerular dysfunction in diabetic models.

The positive correlations between serum Syndecan-1 and 24-hour urinary proteinuria, alongside its association with lower eGFR in DN patients, reinforce its link to renal functional decline. The moderate correlation with proteinuria ($r = 0.394$) suggests that Syndecan-1 may contribute to the breakdown of the glomerular filtration barrier, promoting protein leakage. Serum Syndecan-1 levels were found to exhibit a weak positive correlation with eGFR. This correlation may be attributed to the hyperperfusion and hyperfiltration characteristics typically observed in the early stage of DKD. Notably, this weak positive association further suggests the potential of Syndecan-1 as a biomarker for early-stage renal injury in DKD. Subgroup analyses corroborated these associations: patients with DKD and high Syndecan-1 levels exhibited more severe proteinuria, lower eGFR, and a higher burden of CCVD—a comorbidity strongly linked to DKD progression—underscoring Syndecan-1 as a marker of both renal and systemic vascular injury in diabetes. Notably, our 2-year follow-up data demonstrated that high Syndecan-1 levels independently predicted adverse renal outcomes, including proteinuria progression and eGFR decline, even after adjusting for confounders such as a history of CCVD. This result contributes to the growing evidence that Syndecan-1 may actively participate in disease progression—possibly by disrupting endothelial integrity. Its superior performance over urinary protein in predicting early DKD progression (AUC = 0.804 vs. 0.654) is particularly striking. While urinary protein remains widely used, it often lags behind early renal damage, making Syndecan-1 a potential earlier and more sensitive marker for identifying high-risk DKD patients who could benefit from intensive intervention. Multivariate regression results, which identified Syndecan-1 as an independent risk factor for both proteinuria and eGFR progression, further support its clinical utility.

Limitations of our study include its single-center design, which may limit generalizability, and the lack of mechanistic experiments to confirm Syndecan-1's causal role in DKD. Additionally, using a median cutoff for Syndecan-1, while pragmatic, may not capture optimal clinical thresholds, warranting validation in larger cohorts. Future work should explore whether targeting Syndecan-1-related pathways (e.g., inhibiting its shedding or restoring endothelial function) could mitigate DKD progression and validate its predictive value in multi-ethnic populations.

In conclusion, our data indicate that serum Syndecan-1 is a strong predictor of DKD progression, with potential to improve risk stratification and guide early intervention in diabetic patients at risk of renal decline.

Acknowledgments

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Doubao, a generative AI tool developed by ByteDance, was utilized in the drafting and revision of this manuscript. Specifically, it provided assistance with creating the initial drafts of the Introduction and Discussion sections, as well as polishing sentence expressions to enhance the manuscript's readability. All content generated with AI support was thoroughly reviewed, edited, and finalized by the authors, who confirm that the core scientific content, data interpretation, and conclusions are entirely the result of their own independent work. The authors assume full responsibility for the accuracy, originality, and scientific rigor of the final manuscript, and confirm compliance with the journal's guidelines on AI use.

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