Association of Stromal Cell-derived Factor-1 With Diabetic Kidney Disease in Type 2 Diabetic Patients

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Research

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Abstract

Background: The present study was designed to explore whether serum stromal cell-derived factor-1 (SDF-1) levels were associated with albuminuria, estimated glomerular filtration rate (eGFR) and diabetic kidney disease (DKD), and detect which clinical parameters might affect serum SDF-1 levels in patients with type 2 diabetes (T2D).

Methods: Serum SDF-1 levels were measured by sandwich ELISA. Patients with an eGFR < 60ml/min/1.73m^2 and/or a urinary albumin-to-creatinine ratio (UACR) ≥ 30mg/g who presented with diabetic retinopathy were identified as having DKD.

Results: Serum SDF-1 levels in T2D patients were significantly higher than those in healthy controls ($p < 0.05$). Urinary albumin and UACR were positively correlated with serum SDF-1 levels ($r = 0.216$ and $= 0.276$, respectively, $p < 0.01$), and eGFR was inversely related with serum SDF-1 levels ($r = -0.368$, $p < 0.001$). Moreover, after adjusting for other clinical covariates by multiple linear regression analyses, the serum SDF-1 levels were independently associated with urinary albumin ($\beta = 0.071$, $t = 2.185$, $p < 0.05$), UACR ($\beta = 0.071$, t = 2.077, p < 0.05) and eGFR ($\beta = -3.975$, $t = -3.375$, $p < 0.01$). Furthermore, receiver operating characteristic analysis indicated that the optimal SDF-1 cutoff value for predicting macroalbuminuria was 5.735 ng/mL (its corresponding sensitivity was 50.00% and specificity was 81.46%), for predicting abnormal albuminuria was 4.321 ng/mL (its corresponding sensitivity was 58.46% and specificity was 70.78%) and for predicting DKD was 3.505 ng/mL (its corresponding sensitivity was 83.33% and specificity was 42.86%).

Conclusions: The serum SDF-1 levels were positively associated with urinary albumin, UACR and cystatin C, and negatively associated with eGFR, which indicate that SDF-1 may play a critical role in the onset and progression of DKD.

Background

Diabetic kidney disease (DKD) is one of the most common complications of diabetes and may affect 30% patients with type 1 diabetes (T1D) and 20% patients with type 2 diabetes (T2D) [1]. As the leading cause of end stage renal disease (ESRD) worldwide, DKD presumably accounts for about 45% patients on dialysis [2]. The current management which focused on tight glycemic control and antihypertensive and lipid-lowering failed to prevent the progression of DKD in a large proportion of diabetic patients [3].

Although albuminuria may be the most reliable diagnostic biomarker of DKD, it is not the most perfect one due to various problems [4]. It is possibly widely affected by blood pressure, water intake, infection, fever, recent exercise and so on [5]. Moreover, some patients with normal-albuminuria may suffer advanced renal pathological changes [6]. Therefore, it is of paramount clinical significance to sought new therapeutic targets and markers for DKD.

Stromal cell-derived factor-1 (SDF-1), a member of the CXC chemokine family [7], is ubiquitously expressed in diverse organs and plays multiple function through binding to its receptor CXC chemokine receptor 4 (CXCR4) [8]. SDF-1 is also localized in podocytes and distal tubular cells of human kidney [9], and hyperglycemia can stimulate the secretion of SDF-1 by these cells under diabetic conditions [10]. Elevated SDF-1 can aggregate inflammatory cells to local kidney and regulate the release of inflammatory cytokines, ultimately leading to glomerular sclerosis, loss of podocytes and albuminuria [11]. Hence, SDF-1 is possibly involved in the occurrence and development of DKD. However, few studies revealed the association between serum SDF-1 levels and DKD in Chinese type 2 diabetic patients.

The aim of the present study was to evaluate whether serum SDF-1 levels were related to albuminuria, eGFR and DKD. We also assessed which factors presumably influenced serum SDF-1 levels. Our results demonstrated that serum SDF-1 levels might have the ability to be a therapeutic target and marker for DKD.

Methods

Study design and participants

This study was a cross-sectional study, and a total of 171 type 2 diabetic patients were recruited for this study at the Second Affiliated Hospital of Nantong University between May 2020 and November 2020. During the same period, 42 age and gender matched healthy controls from the Department of Physical Examination Center were enrolled. Patients with T2D diagnosed based on the statement of the American Diabetes Association were eligible for inclusion [13]. The exclusion criteria were as follows: (1) T1D; (2) previous drug uses that affect glycemic metabolism, i.e., steroids; (3) previous and current malignant tumors; (4) chronic hepatitis and heart failure; (5) acute diabetic complications, i.e., diabetic ketoacidosis; and (6) other kidney diseases and urinary tract infection which could affect albumin excretion. All subjects agreed to participate in this study, and the study was approved by the medical research ethics committee of Second Affiliated Hospital of Nantong University.

Basic data collection

Upon enrollment, all subjects completed a questionnaire including parameters on age, sex, weight, height, blood pressure, illness and medical therapy history with the assistance of experienced physicians. Body mass index (BMI) was calculated as the weight/height squared. Blood pressure was measured by a standard mercury sphygmomanometer, and the average of three recordings was recorded.

Laboratory examination and calculation

Fasting blood samples were collected to measure laboratory parameters. We also collected fresh morning first-void urine samples from type 2 diabetic participants for measurement of urinary albumin and urinary creatinine. UACR was calculated as the ratio of urinary albumin and urinary creatinine. According to UACR, normoabluminuria, microalbuminuria and macroalbuminuria were defined as UACR < 30mg/g, UACR: 30-300mg/g and UACR > 300mg/g, respectively [13]. eGFR was calculated based on the CKD-EPI creatinine-cystatin C equation (2012) [14], and DKD was defined as an eGFR < 60ml/min/1.73m2 and/or a UACR ≥ 30mg/g who presented with diabetic retinopathy [15]. All blood samples were centrifuged and stored at −80°C. Serum SDF-1 levels were measured by sandwich ELISA (Human SDF-1/CXCL12 Elisa Kit; Elabscience, Wuhan, China). The intra- and inter-assay coefficients of variation were both less than 10.0%.

Statistical analyses

Clinical variables are shown for normal controls, type 2 diabetic subjects, and for the quartiles of serum SDF-1 levels. The mean ± SD and frequencies (percentages) were adopted to describe normally distributed continuous variables and categorical variables, respectively. Urinary albumin and UACR were log transformed to achieve a normal distribution. We adopted appropriately the one-way analysis of variance (ANOVA) test to compare differences in normally distributed data, the Kruskal–Wallis test to compare differences in skewed distributed data and the chi-square test to compare categorical data among the four subgroups based on the SDF-1 quartiles. The correlations of SDF-1 with lg (urinary albumin), SDF-1 with lg (UACR), SDF-1 with eGFR, and SDF-1 with other clinical parameters were analyzed by pearson's or spearman's bivariate correlation analysis as appropriate. Three multiple stepwise linear regression analyses were used to explore to explore the associations of SDF-1 with lg (urinary albumin), SDF-1 with lg (UACR), and SDF-1 with eGFR, adjusting for age, gender, diabetic duration, blood pressure, BMI, glycosylated hemoglobin A1c (HbA1c), serum lipid and antidiabetic treatment, as these parameters might affect urinary albumin excretion. Furthermore, receiver operating characteristic (ROC) analysis was conducted to analyze the ability of SDF-1 to indicate macroalbuminuria, abnormal albuminuria and DKD cases, and the cutoff values of SDF-1 to indicate macroalbuminuria, abnormal albuminuria and DKD are provided. Data analyses were performed using SPSS statistical software 18.0 (IBM SPSS Inc., USA). A value of $p < 0.05$ was considered to be statistically significant.

Results

Basic characteristics

Table 1 displays the clinical characteristics of the participants. Compared with healthy controls, T2D patients had higher SDF-1 concentrations, HbA1c, adenosine deaminase (ADA), triglycerides (TG), white blood cells (WBC) and neutrophil percentage (NEU) (all $p < 0.05$). The mean SDF-1 levels for the whole T2D group were 4.17(0.53, 9.29), and the quartiles were Q1 (< 2.95), Q2 (2.95 - 3.92), Q3 (3.94 - 5.40), and Q4 (> 5.40). There were prominent differences in age, urinary albumin, UACR, ADA, blood urea nitrogen (BUN), cystatin C, erythrocyte sedimentation rate (ESR), activated partial thromboplastin time (APTT) and D-dimer among the quartiles of SDF-1 (all $p < 0.05$). As shown in figure 1, compared to other quartiles the incidence of microalbumin was higher in the fourth quartile.

Relationships between SDF-1 and clinical parameters in patients with T2D

As illustrated in the table 2, the serum SDF-1 levels were positively associated with lg (urinary albumin), lg (UACR), age, HbA1c, ADA, BUN, cystatin C, DKD incidence, ESR, D-dimer and NEU ($r = 0.216$, $p < 0.01$; $r = 0.276$, $p < 0.001$; $r = 0.256$, $p < 0.01$; $r = 0.179$, $p < 0.05$; $r = 0.262$, $p < 0.01$; $r = 0.353$, $p < 0.001$; $r = 0.330$, $p < 0.001$; $r = 0.186$, $p < 0.05$; $r = 0.262$, $p < 0.01$; $r = 0.217$, $p < 0.05$; $r = 0.196$, $p < 0.05$, respectively) and negatively associated with eGFR and APTT ($r = -0.368$, $p < 0.001$, $r = -0.294$, $p < 0.01$).

Multiple linear regression models displayed independent associations of SDF-1 with albuminuria parameters

Table 2 shows the associations of SDF-1 with urinary albumin, UACR and eGFR based on multiple linear regression analyses. In the basal unadjusted model 0, SDF-1 was significantly associated with lg (urinary albumin) ($\beta = 0.106$, $t = 3.364$, $p < 0.01$, adjusted $R^2 = 0.069$), lg (UACR) ($\beta = 0.112$, $t = 3.582$, $p < 0.001$, adjusted $R^2 = 0.076$) and eGFR ($\beta = -5.732$, $t = -4.661$, $p < 0.001$, adjusted $R^2 = 0.129$). After gradually adding the other clinical covariates in each model, we observed a gradual increase in the adjusted R^2. In the fully adjusted model 3, SDF-1 was still independently associated with lg (urinary albumin) ($\beta = 0.071$, $t = 2.185$, $p < 0.05$, adjusted $R^2 = 0.207$), lg (UACR) ($\beta = 0.071$, $t = 2.077$, $p < 0.05$, adjusted $R^2 = 0.246$) and eGFR ($\beta = -3.975$, $t = -3.375$, $p < 0.01$, adjusted $R^2 = 0.378$). As a result, the serum SDF-1 levels were independently and positively associated with urinary albumin and UACR, and negatively associated with eGFR in type 2 diabetic patients.

ROC analysis to explore the cutoff SDF-1 value to predict macroalbuminuria and abnormal albuminuria

ROC analysis was further applied to explore the cutoff SDF-1 value to indicate macroalbuminuria, abnormal albuminuria and DKD cases. The optimal cutoff value of SDF-1 to predict macroalbuminuria was 5.735 ng/mL, to predict abnormal albuminuria was 4.321 ng/mL and to predict DKD was 3.505 ng/mL. The corresponding AUC to predict macroalbuminuria was 0.671 (95% CI 0.626–0.816), and its Youden index was 0.315, its sensitivity was 50.00%, and its specificity was 81.46% (Fig. 2). The corresponding AUC to predict abnormal albuminuria was 0.639 (95% CI 0.551–0.726), and its

Youden index was 0.292, its sensitivity was 58.46%, and its specificity was 70.78% (Fig. 3). The corresponding AUC to predict DKD was 0.654 (95% CI 0.536–0.773), and its Youden index was 0.262, its sensitivity was 83.33%, and its specificity was 42.86% (Fig. 4).

Discussion

In the present study, we compared the serum SDF-1 levels between the type 2 diabetic patients and healthy controls, analyzed the associations of serum SDF-1 levels with urinary albumin, UACR and eGFR in Chinese type 2 diabetic patients. The main findings of this study are as follows: first, compared with normal controls, serum SDF-1 levels were higher in patients with T2D; second, urinary albumin, UACR and DKD incidence were positively related with serum SDF-1 levels, while eGFR was negatively related with serum SDF-1 levels; third, serum SDF-1 levels were positively associated with HbA1c, D-dimer, ESR, NEU, and negatively associated with APTT; fourth, after adjusting for other clinical covariates, the serum SDF-1 levels were independently and positively associated with urinary albumin and UACR, and inversely associated with eGFR in patients with T2D; and fifth, the optimal SDF-1 cutoff value for predicting macroalbuminuria was 5.735 ng/mL (its corresponding sensitivity was 50.00% and specificity was 81.46%), for predicting abnormal albuminuria was 4.321 ng/mL (its corresponding sensitivity was 58.46% and specificity was 70.78%) and for predicting DKD was 3.505 ng/mL (its corresponding sensitivity was 83.33% and specificity was 42.86%).

The present study demonstrated that serum SDF-1 levels were significantly higher in type 2 diabetic patients than normal controls, and were positively associated with HbA1c. Similar with our study, R. Derakhshan et al revealed that plasm SDF-1 levels were higher in gestational diabetes mellitus mothers than in normal pregnancy mothers [16], and higher in type 2 diabetic patients than in normal controls [17]. SDF-1 and its receptor CXCR4 are expressed in both islet alpha- and beta- cells [18], and the SDF-1/CXCR4 axis may induce islet inflammation by attracting inflammatory cells to the islet and eventually lead to the occurrence of T2D [19]. Hence, SDF-1 may accelerate the onset and progression of T2D.

T2D is capable to result in chronic inflammation characterized by activated mononuclear phagocyte system and increased secretion of cytokines in vivo [20], and inflammation can promote hypercoagulability through the mechanism that cytokines can stimulate the release and expression of procoagulant molecules and inhibit the expression of anti-coagulant molecules [21]. It was shown that serum SDF-1 levels were positively associated with ESR, NEU, D-dimer and negatively associated with APTT in this study. ESR and NEU are recognized inflammatory biomarkers, while APTT and D-dimer are important indicators of coagulation function. A shorter APTT reflects enhanced endogenous coagulation function [22] and D-dimer is a fibrin degradation product [1]. In patients with disseminated intravascular coagulation (DIC), the coagulation activation was able to contribute to increased levels of the circulating SDF-1, which in turn enhanced platelet aggregation and then promoted coagulation [23]. Given these results, elevated serum levels of SDF-1 presumably reflected the condition of hyperglycemia, inflammation and hypercoagulability in type 2 diabetic patients. As DKD is a result of the interaction of hyperglycemia, hemodynamic alterations, inflammation and oxidative stress [24], SDF-1 may play a critical role in the development and progression of DKD, or at least can serve as a potential predictor of DKD. In support of this conclusion, renal biopsy revealed that SDF-1 significantly increased in kidneys of diabetic rodents and patients with DKD [25], and blockade of SDF-1 by the specific inhibitor NOX-A12 significantly reduced podocyte loss and glomerulosclerosis, thereby reducing proteinuria [26].

In the early stage of DKD, renal alterations are manifested as glomerular hypertrophy, glomerular basement membrane (GBM) thickening, podocyte loss and tubular damage. In advanced DKD, renal morphological changes include glomerulosclerosis and tubulointerstitial fibrosis, and corresponding clinical features include renal filtration function declines with or without albuminuria [27]. Our study showed that serum SDF-1 levels were positively associated with urinary albumin and UACR, and negatively associated with eGFR. UACR, an evaluation index of increased urinary albumin, can reflect damage to the basement membrane and endothelium of glomerular capillaries, and represent early changes of DKD [28]. Based on the CKD-EPI creatinine-cystatin C equation, eGFR can accurately estimate renal function [14]. Thus, serum SDF-1 levels may have the potential to be an evaluation indicator of early and advanced DKD. Recent researches strongly suggest that renal tubular damage is a vital component of early DKD and may precede the occurrence of glomerular injury [29]. Serum cystatin C, a non-glycosylated, low molecular weight and basic protein, is completely removed by glomerular filtration and subsequently reabsorbed and degraded by proximal tubular [30]. In addition to the ability to assess GFR, cystatin C can also reflect renal tubular damage of DKD [31]. In this study, serum SDF-1 levels were significantly associated with cystatin C (r = 0.330, $p < 0.001$). Therefore, serum SDF-1 levels possibly and roundly reflect renal alterations of DKD patients, which is consistent with that SDF-1 is expressed in podocytes and distal tubular cells of human kidney [9].

On the contrary, there are also studies showed that elevated SDF-1 levels may play a role in renal protection via other mechanisms. SDF-1 is critical for the mobilization and migration of endothelial progenitor cells (EPCs), while EPCs can promote endothelial repair and angiogenesis [32]. Therefore, increased SDF-1 may exert a renal protected function by promoting the mobilization and migration of EPCs. SDF-1 is mainly cleaved and inactivated by dipeptidyl peptidase-4 (DPP-4) enzyme in vivo [33]. DPP-4 inhibitors are a class of commonly used oral antidiabetic drugs [34], and clinical studies have shown that short-term administration of DPP-4 inhibitors can significantly increase plasma SDF-1 and EPCs levels in type 2 diabetic patients [35-37]. However, EPCs isolated from diabetic patients are structurally and functionally defective [38]. So even though EPCs level is raised, it fails to promote tissue repair and angiogenesis. Milton Packer summarized several large-scale trials of DPP-4 inhibitors, concluding that DPP-4 inhibitors could improve vascular complications of T2D by upregulating GLP-1 levels, but potentiation of SDF-1 undermined the protective effect [39]. All in all, SDF-1 may contribute to the onset and progression of DKD in patients with T2D.

Several limitations of our study should be addressed. First, the present study could not explain the causal relationship between SDF-1 and albuminuria due to the common problem of cross-sectional studies. Second, on account of the small sample size of this study, the correlation

between DPP-4 inhibitors use and plasma SDF-1 levels could not be verified. Third, all the subjects enrolled in this study were Chinese, which limited the wide applicability of our study. Therefore, further research should be conducted to validate the results of our study and to address the above limitations.

Conclusions

The serum SDF-1 levels were positively associated with urinary albumin, UACR and cystatin C, and negatively associated with eGFR, which indicate that SDF-1 may play a critical role in the onset and progression of DKD.

Abbreviations

SDF-1: stromal cell-derived factor-1, eGFR: estimated glomerular filtration rate (eGFR), DKD: diabetic kidney disease, T2D: type 2 diabetes, UACR: urinary albumin/creatinine ratio, T1D: type 1 diabetes, ERSD: end stage renal disease, CXCR4: CXC chemokine receptor 4, BMI: body mass index, ANOVA: analysis of variance, HbA1c: glycosylated hemoglobin A1c, ROC: receiver operating characteristic, ADA: adenosine deaminase, TG: triglycerides, WBC: white blood cell, NEU: neutrophil percentage, BUN: blood urea nitrogen, ESR: erythrocyte sedimentation rate, APTT: activated partial thromboplastin time, DIC: disseminated intravascular coagulation, GBM: glomerular basement membrane, EPCs: endothelial progenitor cells, DPP-4: dipeptidyl peptidase-4, GLP-1: glucagon-like peptide 1

Declarations

Authors' contributions

CL participated in the design of the study, data collection, analysis of the data, and drafting of the manuscript. JM and XW conceived of the study, participated in its design and revised the manuscript. WL and XG participated in data collection. All authors read and approved the final manuscript.

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Acknowledgements

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Availability of data and materials

The current data are available to all interested researchers upon reasonable request. Requests for access to data should be made to the principal investigators of the study.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The study was approved by the institutional review board of Affiliated Hospital 2 of Nantong University and First People's Hospital of Nantong City, and written informed consent was obtained from all participants.

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Tables

Table 1 Clinical characteristics of the study participants

Variables	Controls	T2D					*P for trend*
		Total	Q1	Q2	Q3	Q4	
SDF-1	2.98±1.36	4.17±1.87***	< 2.95	2.95-3.92	3.94-5.40	> 5.40	
n	42	171	43	44	42	42	
Age (years)	54.38±13.14	55.22±12.37	50.49±14.10	51.98±11.55	59.55±9.73	59.10±11.25	0.000###
Male, n (%)	21(50)	113(66.1)	28(65.1)	33(75.0)	25(59.5)	27(64.3)	0.485
Diabetic duration (years)	N	5.0(0-10.0)	4.0(0-10.0)	4(0.25-10.0)	5.5(0-10)	7.5(1-10)	0.464
BMI (kg/m^2)	24.87±4.40	25.49±4.12	25.22±3.65	25.64±3.91	24.76±4.27	26.29±4.61	0.391
SBP (mmHg)	125(130.5-142.75)	133(124-133)	132(121-146)	133(125-144.50)	134(127.5-150.25)	137(121.5-150.5)	0.617
DBP (mmHg)	80.03±10.40	81.15±11.22	82.86±9.63	81.20±9.62	79.60±11.74	80.90±13.65	0.613
Antidiabetic treatment							
Insulin treatment, n (%)	N	39(22.8)	8(18.6)	11(25.0)	11(26.2)	9(21.4)	0.833
Metformin, n (%)	N	63(36.8)	19(44.2)	15(34.1)	10(23.8)	19(45.2)	0.140
Acarbose, n (%)	N	14(8.2)	5(11.6)	1(2.3)	4(9.5)	4(9.5)	0.403
Insulin-secretagogues, n (%)	N	53(31.0)	13(30.2)	13(29.5)	11(26.2)	16(38.2)	0.683
Insulin-sensitisers, n (%)	N	15(8.8)	2(4.7)	7(15.9)	3(7.1)	3(7.1)	0.262
DPP-4 inhibitors, n (%)	N	4(2.3)	3(7.0)	1(2.3)	0(0)	0(0)	0.109
Lg (Urinary albumin)	N	1.34±0.76	1.27±0.74	1.22±0.65	1.21±0.67	1.65±0.88	0.031#
Lg (UACR)	N	1.47±0.75	1.38±0.68	1.37±0.63	1.34±0.68	1.79±0.92	0.021#
Categories of proteinuria							
Normoalbuminuria, n (%)	N	106(62.0)	31(72.1)	31(70.5)	27(64.3)	17(40.5)	0.029#
Microalbuminuria, n (%)	N	45(26.3)	9(20.9)	9(20.5)	12(28.6)	15(35.7)	0.029#
Macroalbuminuria, n (%)	N	20(11.7)	3(7.0)	4(9.1)	3(7.1)	10(23.8)	0.029#
HbA1c (%)	5.92±0.41	9.38±2.20***	9.06±2.12	8.91±2.18	9.94±2.22	9.64±2.18	0.100
ALT (U/L)	16(12-26)	21(14-31)	17(13-31.5)	24(16.75-32.25)	18(10.5-29.75)	21.5(14-33.75)	0.387
AST (U/L)	18(15-20)	18(14-24)	15.5(13-22)	18(15.5-22.5)	18(13.5-24)	19(14-29)	0.167
ADA (U/L)	9(7-10)	10(8-14)**	10(8-12)	9(8-12)	11(9-15.25)	12(10-16)	0.004##
TG (mmol/L)	1.02(0.85-1.66)	1.66(1.14-3.03)**	1.68(1.19-3.08)	1.81(1.09-2.79)	1.43(0.98-2.48)	1.94(1.21-4.08)	0.504
TC (mmol/L)	4.49±1.23	4.69±1.31	4.63±1.10	4.56±0.92	4.58±0.95	4.96±1.95	0.477
HDL-c (mmol/L)	1.23±0.33	1.19±0.24	1.15±0.24	1.18±0.24	1.24±0.27	1.19±0.21	0.430
LDL-c (mmol/L)	2.72±0.95	2.88±0.86	2.91±0.85	2.85±0.85	2.83±0.83	2.94±0.92	0.935
BUN (mmol/L)	5.08±1.38	5.45±1.82	4.88±1.44	5.24±1.44	5.23±1.55	6.42±2.32	0.001##
Cr (umol/L)	58(47.5-66.5)	56(49.2-67)	54.5(44.25-64.75)	57(50.5-66.75)	54(48.5-65.5)	59(53.5-79.5)	0.077
Serum UA (umol/L)	293.41±88.03	326.6±102.33	318.38±109.59	314.73±95.14	323.23±103.17	350.77±101.05	0.390
Cystatin C (mg/L)	0.71(0.58-0.82)	0.71(0.58-0.86)	0.68(0.53-0.80)	0.64(0.54-0.72)	0.81(0.57-0.98)	0.79(0.69-1.14)	0.000###
eGFR (ml/min/1.73m^2)	115.31±25.47	110.98±28.83	123.84±24.74	117.83±21.65	106.91±28.81	94.98±31.47	0.000###

DKD, n (%)	N	24(14.0)	3(7.0)	5(11.4)	5(11.9)	11(26.2)	0.062
ESR (mm)	5.5(2.25-13.25)	6(3-10)	5.5(2-9.5)	5(2-9)	7(3-14)	7(5-17)	0.029#
CRP (mg/L)	0.12(0.01-1.77)	0.71(0.58-0.86)	0.17(0.05-0.80)	0.24(0.05-1.39)	0.56(0.08-3.18)	0.34(0.11-6.14)	0.382
APTT (s)	29.26±4.87	28.34±2.62	29.12±3.64	28.97±2.30	27.74±2.07	27.69±2.00	0.043#
Fg (g/L)	2.56(2.20-3.19)	2.36(2.18-2.94)	2.34(2.08-2.82)	2.31(2.01-2.80)	2.35(2.23-2.88)	2.61(2.19-3.31)	0.198
D-dimer (ug/L)	243(190-330)	220(190-380)	190(190-462.5)	190(160-265)	220(190-360)	325(195-610)	0.008##
PLT (*10^9/L)	206.5(175.5-259.5)	203.5(169-238.5)	207(170.25-207)	213.5(189.5-239.75)	189(159-233.5)	208.5(163.5-250.75)	0.421
WBC (*10^9/L)	5.84±1.66	6.62±1.90*	6.47±1.84	6.64±1.38	6.22±1.37	7.14±2.65	0.166
NEU (%)	56.48±8/29	60.58±9.51*	59.19±9.34	60.66±9.60	58.70±8.77	63.79±9.78	0.071

Normally distributed values in the table are given as the mean ± SD, skewed distributed values are given as the median (25 and 75% interquartiles), and categorical variables are given as frequency (percentage)

SDF-1 stromal cell-derived factor-1, BMI body mass index, SBP/DBP systolic/diastolic blood pressure, UACR urine albumin/creatinine ratio, HbA_{1c} glycosylated hemoglobin A1c, ALT alanine transaminase, AST aspartate aminotransferase, ADA adenosine deaminase, TG triglyceride, TC total cholesterol, HDL-c high density lipoprotein cholesterol, LDL-c low density lipoprotein cholesterol, BUN blood urea nitrogen, Cr creatinine, Serum UA serum uric acid, eGFR estimated glomerular filtration rate, DKD diabetic kidney disease, ESR erythrocyte sedimentation rate, CRP C-reactive protein, APTT activated partial thromboplastin time, Fg fibrinogen, PLT platelet, WBC white blood cell count, NEU neutrophil percentage

ANOVA, the Kruskal–Wallis test and the Chi squared test were conducted to determine p values for normally distributed continuous variables, skewed continuous variables and categorical variables, respectively. # P< 0.05, ## P< 0.01, ### P< 0.001

* *P*< 0.05, ** *P*< 0.01, *** *P*< 0.001, the comparison of T2D with Controls

Table 2 Relationship between SDF-1 and clinical parameters in patients with T2D

Variables	*r*	*P* value
Lg (Urinary albumin)	0.262	0.001
Lg (UACR)	0.276	0.000
Age	0.256	0.001
HbA1c	0.179	0.019
ADA	0.262	0.001
BUN	0.353	0.000
Cr	0.154	0.053
Cystatin C	0.330	0.000
eGFR	-0.368	0.000
DKD	0.186	0.015
ESR	0.262	0.003
CRP	0.151	0.131
APTT	-0.294	0.001
Fg	0.114	0.207
D-dimer	0.217	0.015
WBC	0.145	0.067
NEU	0.196	0.013

r pearson's or spearman's correlation coefficient

Table 3 Multiple linear regression models displaying adjusted estimates for SDF-1 for outcomes of albuminuria indexes and eGFR adjusted for the other clinical covariates in each model in patients with T2D

Models	*B* (95% CI)	*t*	*p*	R^2 for model
Lg (Urinary albumin)				
Model 0	0.106 (0.044 to 0.169)	3.364	0.001	0.069
Model 1	0.103 (0.037 to 0.169)	3.099	0.002	0.100
Model 2	0.077 (0.010 to 0.143)	2.283	0.024	0.206
Model 3	0.076 (0.007 to 0.145)	2.185	0.031	0.207
Lg (UACR)				
Model 0	0.112 (0.050 to 0.169)	3.582	0.000	0.076
Model 1	0.092 (0.028 to 0.156)	2.851	0.005	0.136
Model 2	0.068 (0.003 to 0.133)	2.057	0.042	0.242
Model 3	0.071 (0.003 to 0.130)	2.077	0.040	0.246
eGFR				
Model 0	-5.732 (-8.164 to -3.301)	-4.661	0.000	0.129
Model 1	-3.489 (-5.724 to -1.255)	-3.089	0.002	0.356
Model 2	-3.549 (-5.848 to -1.249)	-3.055	0.003	0.368
Model 3	-3.975 (-6.306 to -1.643)	-3.375	0.001	0.378

Model 0: unadjusted model

Model 1: adjusted for age, male, diabetic duration, BMI

Model 2: additionally adjusted for SBP, DBP, TG, TC, HDL-c, LDL-c

Model 3: additionally adjusted for HbA1c, antidiabetic treatment

Figures

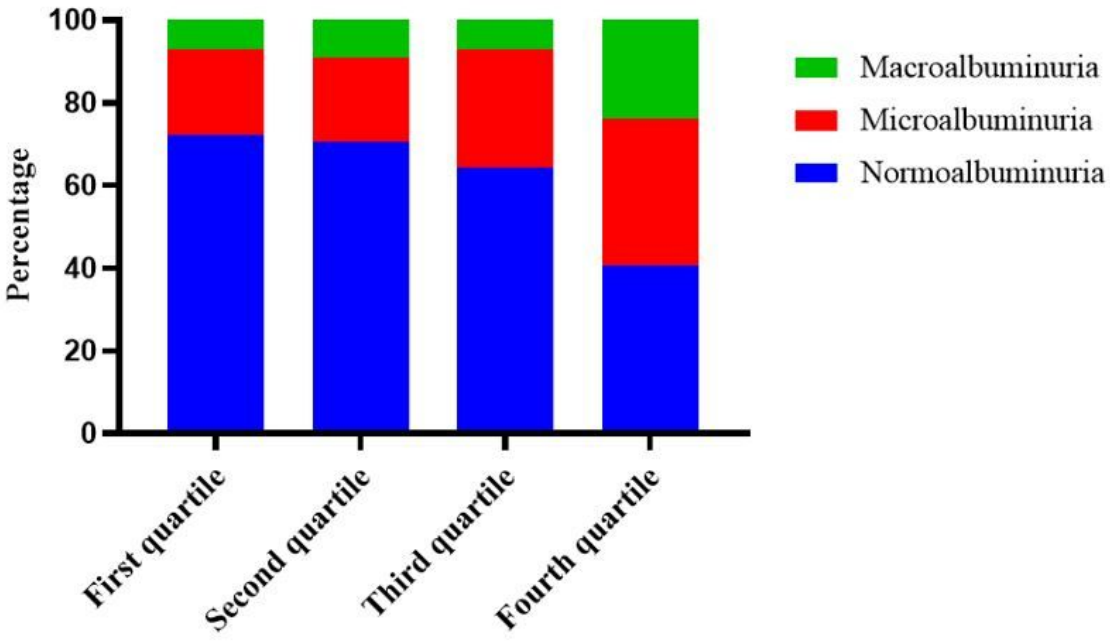

Figure 1

The proportion of albuminuria types stratifed by SDF-1 quartiles

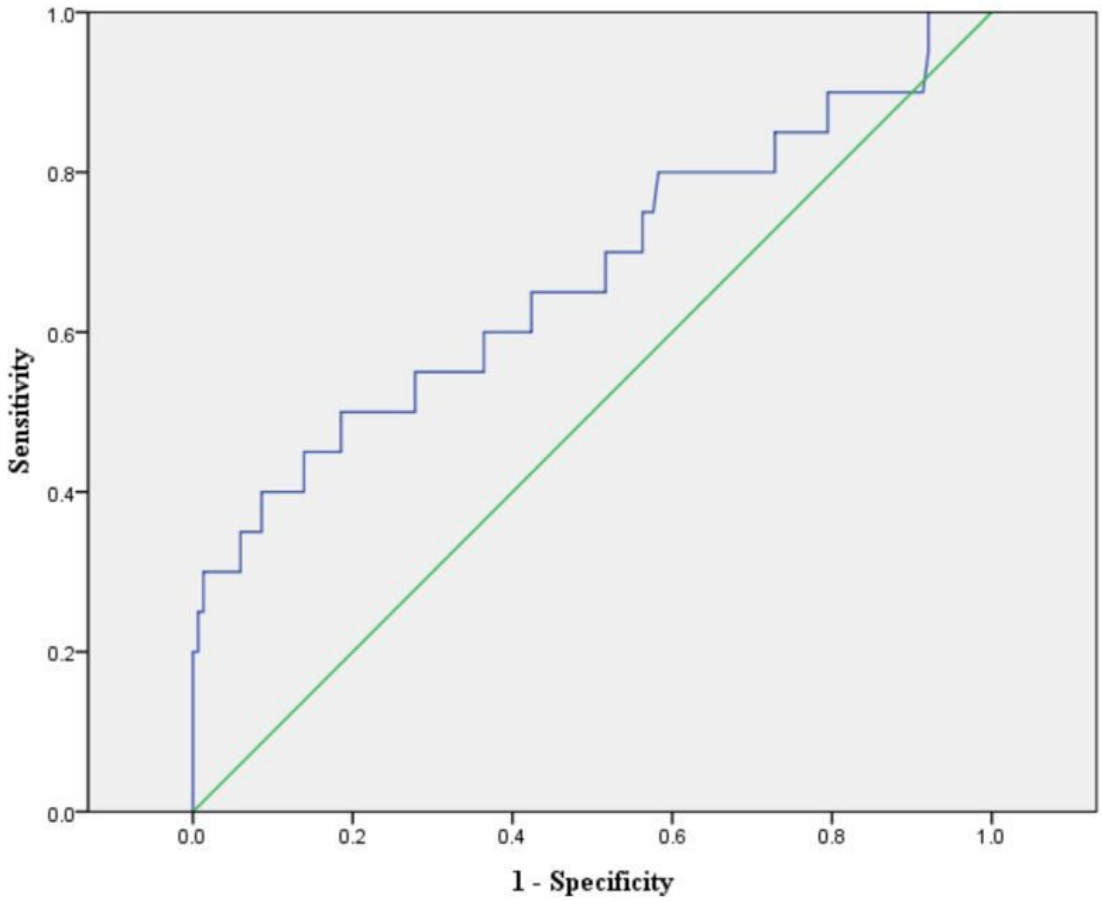

Figure 2

ROC analysis to analyze the ability of SDF-1 to indicate macroalbuminuria AUC of SDF-1 was 0.671 (95% CI 0.626–0.816). Optimal cutof value of SDF-1 was 5.735 to indicate macroalbuminuria; Youden index= 0.315, sensitivity= 50.00% and specifcity= 81.46%

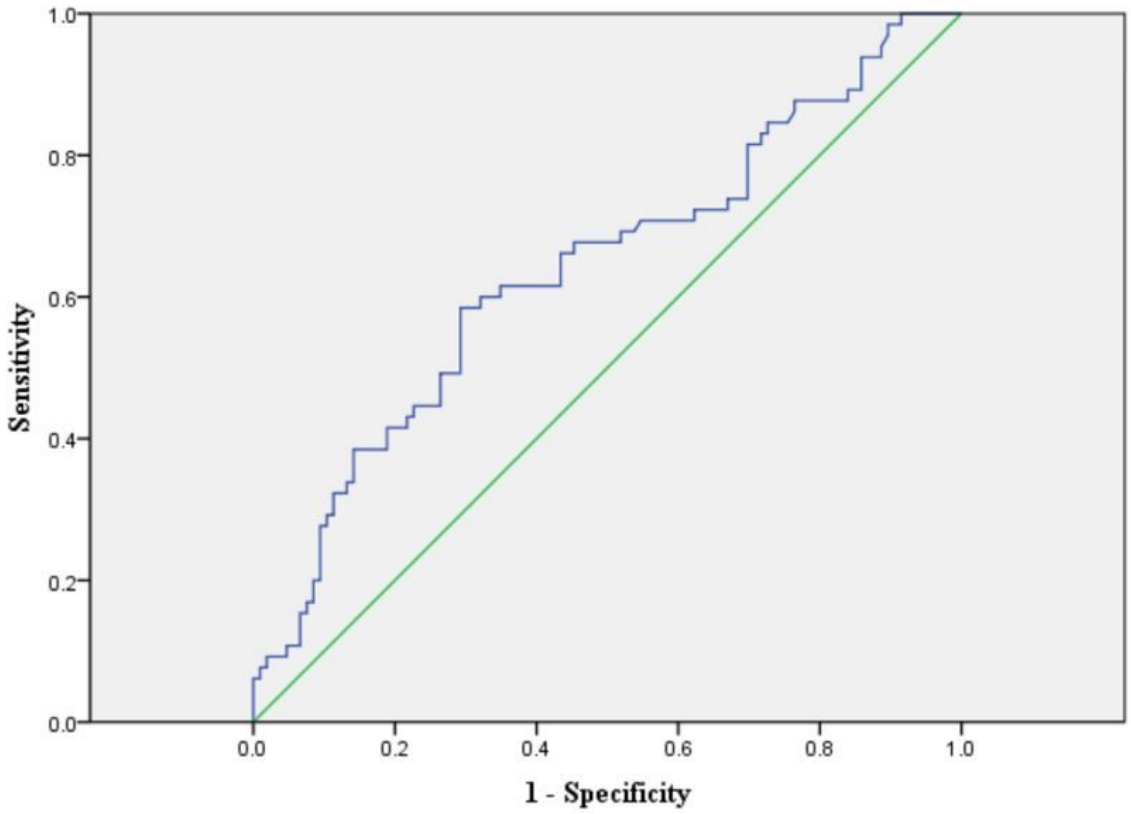

Figure 3

ROC analysis to analyze the ability of SDF-1 to indicate abnormal albuminuria AUC of SDF-1 was 0.639 (95% CI 0.551–0.726). Optimal cutof value of SDF-1 was 4.321 to indicate abnormal albuminuria; Youden index= 0.292, sensitivity= 58.46% and specifcity= 70.78%

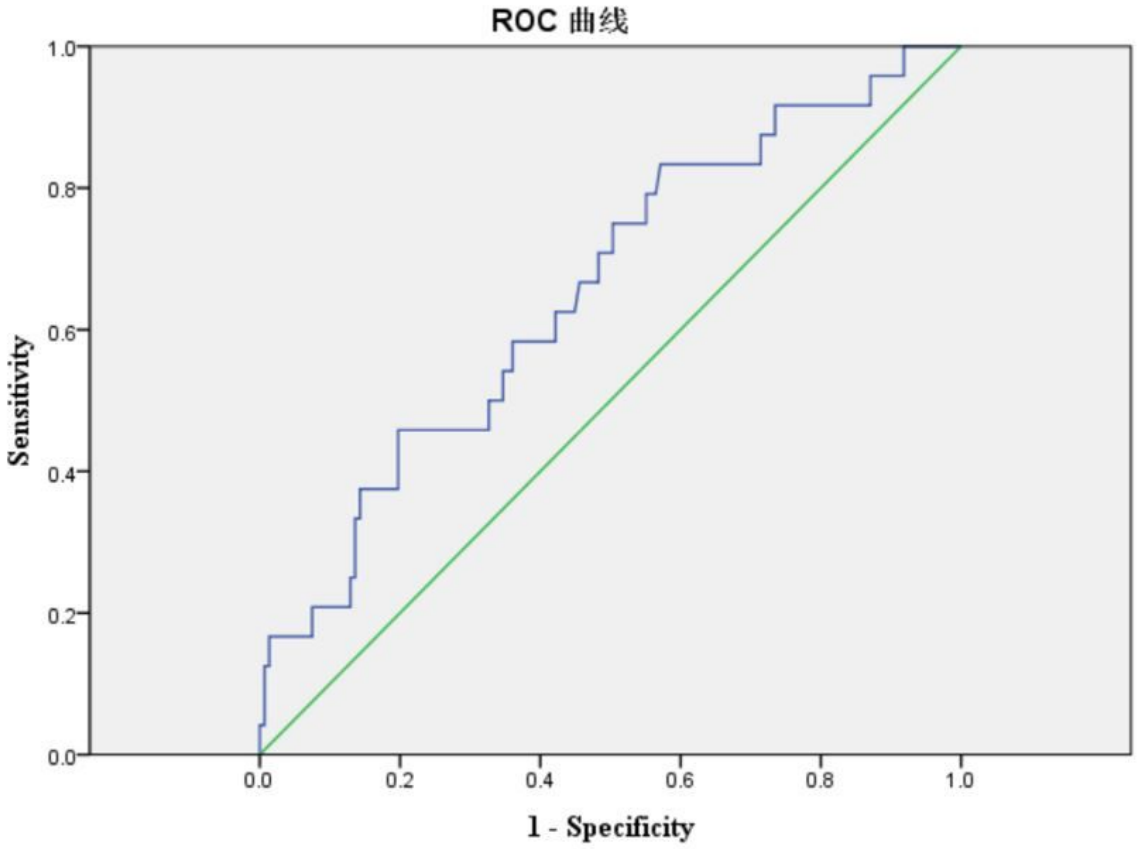

Figure 4

ROC analysis to analyze the ability of SDF-1 to indicate DKD AUC of SDF-1 was 0.654 (95% CI 0.536–0.773). Optimal cutof value of SDF-1 was 3.505 to indicate DKD; Youden index= 0.262, sensitivity= 83.33% and specifcity= 42.86%