Serum stromal cell-derived factor-1 levels are associated with diabetic kidney disease in type 2 diabetic patients

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Abstract. The present study was designed to explore whether serum stromal cell-derived factor-1 (SDF-1) levels were associated with diabetic kidney disease (DKD). Serum SDF-1 levels were measured by sandwich ELISA. Patients with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² or a urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g for 3 months were identified as having DKD. Among the recruited type 2 diabetic patients, 18.71% (n = 32) were found to have DKD, and the serum SDF-1 levels of these patients were higher than those of patients without DKD (p < 0.05). Serum SDF-1 levels were positively correlated with cystatin C levels, the UACR and DKD incidence (r = 0.330, 0.183 and 0.186, respectively, p < 0.05) and inversely related to eGFR (r = –0.368, p < 0.001). After adjusting for other clinical covariates by multivariate logistic regression analyses, serum SDF-1 levels were found to be an independent contributor to DKD, and the odds ratio (95% confidence interval) was 1.438 (1.041–1.986). Furthermore, receiver operating characteristic analysis revealed that the optimal SDF-1 cutoff value for indicating DKD was 5.609 ng/mL (its corresponding sensitivity was 82.00%, and specificity was 46.90%). Our results demonstrated that serum SDF-1 levels were closely associated with DKD and could be considered a potent indicator for DKD in patients with T2D.

Key words: Type 2 diabetes, Stromal cell-derived factor-1, Diabetic kidney disease, Urinary albumin-to-creatinine ratio, Estimated glomerular filtration rate

DIABETIC KIDNEY DISEASE (DKD) is one of the most common complications of diabetes, affecting approximately 20% of patients with type 2 diabetes (T2D) [1]. As the leading cause of end-stage renal disease worldwide, DKD presumably accounts for approximately 45% of patients on dialysis [2]. The current management, focused on strict glycemic control and antihypertensive and lipid-lowering measures, failed to prevent the onset and 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 ideal biomarker [4]. It may be widely affected by blood pressure, water intake, infection, fever and so on [5]. Moreover, some patients with normal albuminuria levels may suffer advanced renal pathological changes [6]. Therefore, it is of paramount clinical significance to seek new therapeutic targets and markers for DKD.

Stromal cell-derived factor-1 (SDF-1), a member of the CXC chemokine family, is ubiquitously expressed in diverse organs and has multiple functions [7]. SDF-1 is also localized in podocytes and distal tubular cells of the human kidney [8], and hyperglycemia can stimulate these cells to secrete SDF-1 under diabetic conditions [9]. Elevated SDF-1 levels can cause inflammatory cells to aggregate in the kidney, which ultimately leads to glomerular sclerosis, loss of podocytes and albuminuria [10]. Hence, SDF-1 may be involved in the occurrence and development of DKD. However, few studies have revealed the association between serum SDF-1 levels and DKD in Chinese type 2 diabetic patients.
Therefore, the aim of the present study was to evaluate whether serum SDF-1 levels are related to DKD in type 2 diabetic patients.

Methods

Study design and participants

This was a cross-sectional study, and 171 type 2 diabetic patients were recruited at the inpatient department of the Second Affiliated Hospital of Nantong University between May 2020 and November 2020. During the same period, 42 age- and sex-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 [11]. The exclusion criteria were as follows: (1) type 1 diabetes (T1D); (2) previous use of drugs 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. All subjects agreed to participate in this study and provided written informed consent. The study was approved by the medical research ethics committee of the Second Affiliated Hospital of Nantong University and complied with the Declaration of Helsinki.

Basic data collection

Upon enrollment, all subjects completed a questionnaire including parameters on age, sex, weight, height, 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, and fresh first-void morning urine samples were also collected for measurement of urinary albumin and urinary creatinine. The UACR was calculated as the ratio of urinary albumin to urinary creatinine. eGFR was calculated based on the CKD-EPI creatinine-cystatin C equation (2012) [12]. DKD was defined as an eGFR <60 mL/min/1.73 m² or a UACR ≥30 mg/g for more than 3 months [13]. Patients with a UACR ≥30 mg/g upon enrollment were reexamined for UACR 3 months later and were diagnosed with DKD if the UACR was still higher than 30 mg/g. All blood samples were 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 5.28% and 3.89%, respectively.

Statistical analyses

Clinical variables are shown for normal controls, all type 2 diabetic subjects, and for two subgroups with and without DKD. The mean ± SD, median (25 and 75% interquartile) and frequencies (percentages) were adopted to describe normally and skewed distributed continuous variables and categorical variables, respectively. We adopted Student’s t-test to compare differences in normally distributed data, the Mann–Whitney test to compare differences in skewed distributed data and the chi-square test to compare categorical data. The correlations of SDF-1 levels with clinical parameters were analyzed by Pearson’s or Spearman’s bivariate correlation analysis as appropriate. Multivariate logistic regression analyses were performed to explore the impact of serum SDF-1 levels on DKD. Furthermore, receiver operating characteristic (ROC) analysis was conducted to analyze the ability of SDF-1 to indicate DKD cases, and the corresponding cutoff value was provided. Data analyses were performed using SPSS statistical software 18.0 (IBM SPSS Inc., USA). A value of p < 0.05 was considered indicative of statistical significance.

Results

Basic characteristics

Table 1 displays the clinical characteristics of the participants. Compared with healthy controls, T2D patients had higher SDF-1 concentrations, HbA1c levels, triglyceride (TG) levels, white blood cell (WBC) counts and neutrophil percentages (NEU) (all p < 0.05). Among the 171 recruited type 2 diabetic patients, 18.71% had confirmed DKD. Compared to patients without DKD, those with DKD presented with a longer duration of diabetes, higher rate of insulin treatment, and higher UACR, erythrocyte sedimentation rate (ESR), activated partial thromboplastin time (APTT), WBC count, and levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), blood urea nitrogen (BUN), creatinine (Cr), cystatin C, fibrinogen (Fg), D-dimer, and SDF-1 and a lower high-density lipoprotein cholesterol (HDL-c) level and eGFR. There were no differences in age, proportion of males, BMI, systolic/diastolic BP, use of antidiabetic treatments other than insulin, use of antihypertensive treatments, use of statin medications, platelet (PLT) and neutrophil percentages, and levels of HbA1c, TG, serum uric acid, and C-reactive protein (CRP) between patients with and without DKD (p > 0.05).
Table 1  Clinical characteristics of the study participants

| Variables                  | Controls     | Total          | Without DKD    | With DKD       | p value |
|----------------------------|--------------|----------------|----------------|---------------|---------|
| n                          | 42           | 171            | 139            | 32            |         |
| Age (years)                | 54.38 ± 13.14| 55.22 ± 12.37  | 54.01 ± 12.41  | 60.44 ± 10.91 | 0.641   |
| Male, n (%)                | 21 (50.0)    | 113 (66.1)     | 91 (65.5)      | 22 (68.8)     | 0.837   |
| Diabetic duration (years)  | N            | 5.0 (0–10.0)   | 4.0 (0–10.0)   | 10.0 (4.3–20.0)| 0.000   |
| BMI (kg/m²)                | 24.87 ± 4.40 | 25.49 ± 4.12   | 25.34 ± 4.30   | 26.11 ± 3.25  | 0.397   |
| SBP (mmHg)                 | 125 (130.5–142.75) | 133 (124–133) | 133 (124–144) | 139 (125–162) | 0.062   |
| DBP (mmHg)                 | 80.03 ± 10.40| 81.15 ± 11.22  | 81.45 ± 10.54  | 79.84 ± 13.91 | 0.210   |

Antidiabetic treatments

| Insulin treatment, n (%)  | N  | 39 (22.8) | 24 (17.3) | 15 (46.9) | 0.001   |
| Metformin, n (%)          | N  | 63 (36.8) | 49 (35.3) | 14 (43.8) | 0.418   |
| Acarbose, n (%)           | N  | 14 (8.2)  | 10 (7.2)  | 4 (12.5)  | 0.301   |
| Insulin-secretagogues, n (%) | N  | 53 (31.0) | 42 (30.2) | 11 (34.4) | 0.674   |
| Insulin-sensitisers, n (%) | N  | 15 (8.8)  | 12 (8.6)  | 3 (9.4)   | 1.000   |
| DPP-4 inhibitors, n (%)   | N  | 4 (2.3)   | 2 (1.4)   | 2 (6.3)   | 0.159   |

Antihypertensive treatments

| CCB, n (%)                | N  | 43 (25.1) | 32 (23.0) | 11 (34.4) | 0.184   |
| ARB, n (%)                | N  | 32 (18.7) | 24 (17.3) | 8 (25.0)  | 0.321   |
| ACEI, n (%)               | N  | 2 (1.2)   | 2 (1.4)   | 0 (0.0)   | 1.000   |
| β-blockers, n (%)         | N  | 6 (3.5)   | 4 (2.9)   | 2 (6.3)   | 0.313   |
| Diuretics, n (%)          | N  | 12 (7.0)  | 8 (5.8)   | 4 (12.5)  | 0.241   |

Statins medications, n (%)  | N  | 4 (2.3)   | 2 (1.4)   | 2 (6.3)   | 0.159   |

HbA1c (%)  | 5.92 ± 0.41 | 9.38 ± 2.20*** | 9.49 ± 2.20 | 8.90 ± 2.16 | 0.933   |
TG (mmol/L) | 1.02 (0.85–1.16) | 1.66 (1.14–3.03)** | 1.64 (1.03–2.59) | 1.98 (1.29–4.22) | 0.087   |
TC (mmol/L) | 4.49 ± 1.23 | 4.69 ± 1.31 | 4.60 ± 0.92 | 5.05 ± 2.25 | 0.001   |
HDL-c (mmol/L) | 1.23 ± 0.33 | 1.19 ± 0.24 | 1.20 ± 0.25 | 1.15 ± 0.17 | 0.005   |
LDL-c (mmol/L) | 2.72 ± 0.95 | 2.88 ± 0.86 | 2.86 ± 0.79 | 2.99 ± 1.10 | 0.019   |
BUN (mmol/L) | 5.08 ± 1.38 | 5.45 ± 1.82 | 5.09 ± 1.49 | 6.89 ± 2.26 | 0.001   |
Cr (umol/L)  | 58 (47.5–66.5) | 56 (49.2–67) | 54.1 (47.0–63.0) | 74.0 (57.3–107.5) | 0.000   |
Cystatin C (mg/L) | 0.71 (0.58–0.82) | 0.71 (0.58–0.86) | 0.70 (0.56–0.82) | 0.93 (0.66–1.34) | 0.000   |
SDF-1 reflects diabetic kidney injury

| CRP (mg/L)                | 0.12 (0.01–1.77) | 0.71 (0.58–0.86) | 0.33 (0.08–2.49) | 0.40 (0.11–3.29) | 0.613   |
| APPT (s)                  | 29.26 ± 4.87 | 28.34 ± 2.62 | 28.46 ± 2.24 | 27.83 ± 1.97 | 0.045   |
| Fg (g/L)                  | 2.56 (2.20–3.19) | 2.36 (2.18–2.94) | 2.35 (2.12–2.74) | 2.87 (2.30–3.55) | 0.001   |
| D-dimer (ug/L)            | 243 (190–330) | 220 (190–380) | 205 (190–350) | 450 (220–650) | 0.001   |
| PLT (10^9/L)              | 206.5 (175.5–259.5) | 203.5 (169–238.5) | 205.5 (169.3–241.5) | 196.0 (153.3–233.0) | 0.412   |
| WBC (*10^3/L)             | 5.84 ± 1.66 | 6.62 ± 1.90* | 6.39 ± 1.60 | 5.74 ± 2.64 | 0.001   |
| NEU (%)                   | 56.48 ± 8.29 | 60.58 ± 9.51* | 59.77 ± 9.39 | 63.84 ± 9.40 | 0.832   |
| SDF-1 (ng/mL)             | 2.98 ± 1.36 | 4.17 ± 1.87 | 3.92 ± 1.71 | 5.23 ± 2.18 | 0.030   |

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).

DKD, diabetic kidney disease; BMI, body mass index; SBP/DBP, systolic/diastolic blood pressure; Insulin-secretagogues, insulin secretagogues; Insulin-sensitisers insulin sensitizing agents; DPP-4 inhibitors, dipeptidyl peptidase-4 inhibitors; CCB, calcium channel blockers; ARB, angiotensin receptor blockers; ACEI, angiotensin-converting enzyme inhibitors; HbA1c, glycosylated hemoglobin A1c; ALT, alanine transaminase; AST, aspartate aminotransferase; 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; UACR, urine albumin/creatinine ratio; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; APTT, activated partial thromboplastin time; Fg, fibrinogen; PLT, platelet; WBC, white blood cells; NEU, neutrophil percentage; SDF-1, stromal cell-derived factor-1.

* p < 0.05, ** p < 0.01, *** p < 0.001, the comparison of T2D with Controls
relationships between SDF-1 and clinical parameters in patients with T2D

As illustrated in Table 2, serum SDF-1 levels were positively associated with age, HbA1c level, BUN level, cystatin C level, UACR, DKD incidence, ESR, D-dimer level, and NEU (r = 0.256, r = 0.179, r = 0.353, r = 0.330, r = 0.183, r = 0.186, r = 0.262, r = 0.217, r = 0.196, respectively, all p < 0.05) and negatively associated with eGFR and APTT (r = –0.368 and –0.294, both p < 0.05). However, there were no significant correlations between SDF-1 levels and diabetes duration, BMI, systolic/diastolic BP, antidiabetic treatments, antihypertensive treatments, statin medication use, lipid profile, Cr level, BUN level, CRP level, Fg level, PLT percentage or WBC count (all p > 0.05).

Association of SDF-1 with DKD in patients with T2D

Table 3 shows the association of SDF-1 with DKD based on multivariate logistic regression analysis. In the basal unadjusted model 0, DKD was significantly associated with SDF-1 [OR (95% CI), 1.456 (1.174–1.804)]. After gradually adding the other clinical covariates in each model, DKD was still independently associated with SDF-1 [OR (95% CI), 1.438 (1.041–1.986)] in the fully adjusted model 3.

ROC analysis to explore the cutoff SDF-1 value to diagnose DKD

ROC analysis was further applied to explore the cutoff SDF-1 value to indicate confirmed DKD cases. The optimal cutoff value of SDF-1 to indicate DKD was 5.609 ng/mL. The corresponding area under the curve (AUC) to indicate DKD was 0.671 (95% CI 0.564–0.778), its Youden index value was 0.289, the sensitivity was 82.0%, and the specificity was 46.9% (Fig. 1).

Discussion

In the current study, we compared SDF-1 levels and investigated the relationship between SDF-1 and DKD among a medium-sized cohort of participants. The main findings of this study are as follows: first, among the recruited type 2 diabetic patients, 18.71% (n = 32) were found to have DKD, and serum SDF-1 levels in these patients were higher than those in patients without DKD (p < 0.05); second, serum SDF-1 levels were positively related to cystatin C levels, the UACR and DKD incidence and inversely associated with eGFR; third, SDF-1 is a significant independent contributor to DKD; each 1 ng/mL increase in SDF-1 levels may lead to a 1.438-fold increased mean risk of DKD, with a 95% CI of 1.041–1.986; and fourth, the optimal SDF-1 cutoff value for diagnosing DKD was 5.609 ng/mL (its corresponding sensitivity was 82.0% and specificity was 46.9%).

T2D pathology is characterized by insulin resistance.

| Variables          | r        | p value |
|--------------------|----------|---------|
| Age                | 0.256    | 0.001   |
| Diabetic duration  | 0.133    | 0.083   |
| BMI                | 0.034    | 0.662   |
| SBP                | 0.095    | 0.217   |
| DBP                | –0.079   | 0.303   |
| Insulin treatment  | 0.023    | 0.761   |
| Metformin          | –0.008   | 0.917   |
| Acarbose           | –0.013   | 0.864   |
| Insulin-secretagogues | 0.045  | 0.558   |
| Insulin-sensitisers| –0.013   | 0.870   |
| DPP-4 inhibitors   | 0.167    | 0.559   |
| CCB                | 0.053    | 0.492   |
| ARB                | –0.064   | 0.406   |
| ACEI               | 0.077    | 0.316   |
| β-blockers         | –0.004   | 0.957   |
| Diuretics          | 0.049    | 0.521   |
| Statins medications| 0.056   | 0.467   |
| HbA1c              | 0.179    | 0.019   |
| TG                 | 0.032    | 0.073   |
| TC                 | 0.073    | 0.359   |
| HDL-c              | 0.104    | 0.190   |
| LDL-c              | –0.006   | 0.942   |
| BUN                | 0.353    | 0.000   |
| Cr                 | 0.154    | 0.053   |
| Cystatin C         | 0.330    | 0.000   |
| eGFR               | –0.368   | 0.000   |
| UACR               | 0.183    | 0.022   |
| 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   |
| PLT                | –0.055   | 0.489   |
| WBC                | 0.145    | 0.067   |
| NEU                | 0.196    | 0.013   |

r: pearson’s or spearman’s correlation coefficient
and β-cell dysfunction. SDF-1 is expressed in both islet α- and β-cells [14] and can induce islet inflammation by attracting inflammatory cells to the islet [15]. Islet inflammation can cause β-cell dysfunction through the mechanism by which islet macrophages secrete interleukin-1β [16]. In addition, Shin J et al. [17] revealed that SDF-1 could aggravate systemic insulin resistance by mediating insulin desensitization in adipocytes. In the present study, serum SDF-1 levels were significantly higher in type 2 diabetic patients than in normal controls and positively associated with HbA1c, suggesting that serum SDF-1 levels might be related to diabetic status. Similar to our study, R. Derakhshan et al. [18] also observed that plasma SDF-1 levels were higher in mothers with gestational diabetes mellitus than in those with normal pregnancy and higher in type 2 diabetic patients than in normal controls [15]. Thus, SDF-1 may be closely correlated with diabetic status.

As DKD is a multifactorial disease, glucose and lipid metabolism disorders and alterations in hemodynamics, inflammation and oxidative stress are all involved in its progression [19]. Consistent with this view, the current study showed that patients with DKD had a longer diabetes duration and higher ESR, WBC count and levels of TC, LDL-c, Fg and D-dimer and a lower HDL-c level and APTT than patients without DKD. These pathological changes cause renal morphological and functional alterations in patients with T2D. In the early stage of DKD, renal alterations manifest as glomerular hypertrophy, glomerular basement membrane (GBM) thickening, podocyte loss and tubular damage [20]. The UACR, an evaluation index of increased urinary albumin, can reflect damage to the GBM and the endothelium of glomerular capillaries and represent early changes in DKD [21]. Unlike in the past, recent studies strongly suggest that tubular damage may precede the occurrence of glomerular injury, and serum cystatin C is a reliable indicator of renal tubular damage [22]. In advanced DKD, renal morphological changes include glomerulosclerosis and tubulointerstitial fibrosis, and corresponding clinical features include a decline in renal filtration function with or without albuminuria [20]. The UACR, cystatin C level and eGFR are all important indicators for the evaluation of DKD. In this study, SDF-1 levels were positively associated with the UACR and cystatin C levels and negatively associated with eGFR, suggesting that SDF-1 might be an important risk factor for DKD.

Under inflammatory and ischemic conditions, SDF-1 is induced by hypoxia-inducible factor-1 and produced by systemic tissues, including the heart and kidney [23]. Renal biopsy revealed that SDF-1 levels significantly increased in the kidneys of diabetic rodents and patients with DKD [3]. In acute kidney injury, elevated SDF-1 levels could promote leukocyte infiltration and the expression of proinflammatory chemokines/cytokines [24]. These cytokines can stimulate the release and expression of procoagulant molecules and inhibit the expression of anticoagulant molecules, eventually
aggravating kidney injury by affecting renal hemodynamics [25]. Therefore, elevated serum SDF-1 levels may reflect inflammation and hypercoagulability. Consistent with these results, the present study found that SDF-1 levels were positively associated with ESR, D-dimer levels, and the NEU percentage and negatively associated with APTT. Multiple studies have shown that increases in SDF-1 levels can result in glomerular and tubular damage, podocyte loss and proteinuria [10, 26] and that blockade of SDF-1 with the specific inhibitor NOX-A12 significantly reduces podocyte loss, glomerulosclerosis and proteinuria [27]. In patients with coronary artery disease, high levels of SDF-1 could predict eGFR decline during 24 months of follow-up [28]. In the Chronic Renal Insufficiency Cohort (CRIC) Study, SDF-1 was identified as a risk factor for chronic kidney disease among diabetic patients [29]. These data are agreement with our study. In the present study, we demonstrated that each 1 ng/mL increase in SDF-1 levels may lead to a 1.438-fold increased mean risk of DKD. We also used ROC analysis to determine that the optimal cutoff value of SDF-1 to indicate DKD was 5.609 ng/mL.

In contrast, there are also studies showing that elevated SDF-1 levels may play a role in renal protection via other mechanisms. Increased SDF-1 levels may exert a renal protective function by promoting the mobilization and migration of endothelial progenitor cells (EPCs) [30]. However, EPCs isolated from diabetic patients are structurally and functionally defective [31], so an increase in the number of EPCs fails to promote tissue repair. SDF-1 is mainly cleaved and inactivated by the dipeptidyl peptidase-4 (DPP-4) enzyme in vivo [32], and clinical studies have shown that short-term administration of DPP-4 inhibitors, a class of commonly used oral antidiabetic drugs, can significantly increase plasma SDF-1 levels and EPC numbers in type 2 diabetic patients [33, 34]. Milton Packer summarized several large-scale trials of DPP-4 inhibitors, concluding that DPP-4 inhibitors could improve vascular complications of T2D by upregulating glucagon-like peptide-1 (GLP-1) levels but that potentiation of SDF-1 undermined the protective effect of DPP-4 inhibitors [35].

Several limitations of our study should be addressed. First, the present study could not explain the causal relationship due to the common problem of cross-sectional studies. Second, on account of the small sample size, the correlation between DPP-4 inhibitor use and plasma SDF-1 levels could not be verified. Third, all the subjects enrolled in this study were Chinese, which limited the generalizability of our study. Therefore, further research should be conducted to validate the results of our study and address the above limitations.

In summary, serum SDF-1 levels were closely associated with DKD and could be considered a potent indicator of DKD in patients with T2D.

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CL participated in the design of the study, data collection, analysis of the data, and drafting of the manuscript. JM, JS 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.

Disclosure Statement

The authors declare that they have no competing interests.

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