Increased Serum VEGF-B Level Is Associated With Renal Function Impairment in Patients With Type 2 Diabetes

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Aims/Introduction: Renal function impairment related to type 2 diabetes (T2DM) presents serious threat to public health. Previous studies suggest that vascular endothelial growth factor-B (VEGF-B) might contribute to renal injury. Therefore, this study investigated the association of serum VEGF-B level with the risk of renal function impairment in T2DM patients.

Materials and Methods: Serum VEGF-B levels were measured in 213 patients with type 2 diabetes and 31 healthy participants. Participants with type 2 diabetes were further divided into a group of 112 participants with eGFR<90 mL/min/1.73m² and 101 participants with eGFR ≥ 90 mL/min/1.73m². Clinical data were collected, and a binary logistic regression model was employed to test the association between potential predictors and eGFR.

Results: Serum VEGF-B levels evaluated in type 2 diabetes patients compared with healthy controls. In patients with type 2 diabetes, serum VEGF-B level was positively correlated with triglyceride, serum creatinine and cystatin C while negatively correlated with HDL-C and eGFR. Binary logistic regression showed that serum VEGF-B level was an independent risk factor of eGFR<90 mL/min/1.73m².

Conclusions: Serum VEGF-B level is associated with renal function impairment in patients with type 2 diabetes and may be a potential drug target for diabetic kidney disease.

Keywords: vascular endothelial growth factor B, type 2 diabetes mellitus, diabetic kidney disease, glomerular filtration rate, cystatin C
INTRODUCTION

With the global prevalence of type 2 diabetes mellitus (T2DM), diabetic kidney disease (DKD) has become the leading cause of end stage renal disease (ESRD), and poses a great burden to diabetes patients and the health care system (1). Progressing renal function impairment characterized by declining glomerular filtration rate (GFR) runs through the course of T2DM, and eventually results in DKD. Multifactorial pathological processes have been proven to be contributors of diabetes-related renal function impairment, including advanced glycation end products (AGEs), ectopic lipid deposition, hemodynamic perturbations and inflammation (2, 3). However, further study is still required to explore the exact mechanisms underlying renal function impairment in T2DM patients.

Vascular endothelial growth factor-B (VEGF-B) is a member of the vascular endothelial growth factor family expressing in multiple organs, such as heart, adipose, muscle, brain, and kidney (4). Different with other members from VEGF family, VEGF-B shows faint angiogenic effect 

Clinical Data Collection

All participants were admitted to the department of endocrinology. Detailed medical history and physical examination data, including gender, age, medicine usage, resting blood pressure, weight and height were obtained upon admission. Venous blood and midstream urine samples were collected at 6:00 a.m. from participants after 12 hours of fasting. The examination of total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL-C), high density lipoprotein (HDLC), fasting blood-glucose (FBG), fasting C peptide (FCP), glycosylated hemoglobin (HbA1c), serum creatinine (Scr), blood urea nitrogen (BUN), Cystatin C (CysC), urine albumin-to-creatinine ratio (UACR) and 24-hour urine total protein (UTP) were performed at laboratory center of the affiliated hospital of Nanjing university of Chinese medicine. Body mass index (BMI) = body weight (kg)/the square of body height (m²). Homeostasis model of assessment for insulin resistance (HOMA-IR) = fasting glucose (mmol/L)×fasting insulin (mU/L)/22.5. Estimated glomerular filtration rate (eGFR) was calculated according to CKD-EPI2012scr-cys.

Methods

Subjects

31 healthy participants were recruited from the health examination center of the affiliated hospital of Nanjing university of Chinese medicine. None of the healthy participants had known metabolic disorders, kidney injury or other kind of diseases. 213 T2DM patients were recruited from the department of endocrinology of the affiliated hospital of Nanjing university of Chinese medicine. All participants with T2DM satisfied the world health organization 1999 criteria when diagnosed (12). This study was approved by the medical research ethics committee of the affiliated hospital of Nanjing university of Chinese medicine and carried out under the principles of the Declaration of Helsinki. Written informed consents were obtained from all participants.

VEGF-B Measurement

Fresh blood samples were stood at room temperature (22°C) for 30min and then centrifuged at 3000rpm for 10 min. The supernatant were collected as serum samples and stored at -80°C. Serum VEGF-B values were determined by human enzyme-linked immunosorbent assay (ELISA) kits (CB5521, Biorbyt, UK).

Statistical Analysis

Statistical analyses were performed using SPSS 25.0. All data were represented as mean ± standard deviation (SD), median with interquartile range (IQR) or percentage, as appropriate. Data that were not normally distributed, including Diabetes duration, FBG, HbA1c, HOMA-IR, Triglyceride, Total cholesterol, HDL-C, LDL-C, Serum creatinine, Blood urea nitrogen, Cystatin C, UACR, UTP, eGFR, Serum VEGF-B were logarithmically transformed before analysis. ANOVA and Mann-Whitney U tests were used for continuous variables distributed normally and asymmetrically, respectively. Chisquared test ($\chi^2$) was employed for comparisons of categorical variables. The relationships between clinical indicators were examined using Pearson correlation, Spearman correlation or partial correlation. Binary logistic regression analysis was used to test the association between potential
predictors and eGFR. A p-value of <0.05 was indicated statistically significant.

RESULTS

Serum VEGF-B Level Elevates in T2DM Patients

The study recruited 244 eligible participants, including 213 patients explicitly diagnosed with T2DM at baseline and 31 healthy subjects seeking for routine examination. Fasting blood samples were collected from all participants and serum VEGF-B levels were tested. As shown in Figure 1, compared to the healthy controls, a significantly elevated level of serum VEGF-B was observed in T2DM patients (p<0.001).

Baseline Characteristics of Participants With T2DM

Based on the accepted eGFR cutoff value (90 mL/min/1.73m²), we further divided the enrolled T2DM patients into a group of 112 participants with eGFR<90 mL/min/1.73m² and 101 participants with eGFR ≥ 90 mL/min/1.73m² (13). Gender distribution, drinking history, smoking history, BMI, SBP, HbA1c, FPG, HOMA-IR, TC, TG, HDL-C, LDL-C, UCR and UTP were similar between the groups (all p>0.05). However, the eGFR<90 mL/min/1.73m² group had older age (p<0.001), longer diabetes duration (p=0.004), lower DBP (p=0.003), as well as worse renal dysfunction characterized by higher levels of SCR (p<0.001), BUN (p<0.001), CysC (p<0.001) and UACR (p=0.005). Most importantly, eGFR<90 mL/min/1.73m² group also showed a significantly increased level of serum VEGF-B (p=0.002) (Table 1). Upon the usage of medications, no significant difference was observed between 2 groups on the usage of metformin, sulfonylureas, pioglitazone, glucosidase inhibitors, GLP1rA (glucagon-like peptide 1 receptor agonists), DPP4 inhibitors, SGLT2 inhibitors, statins, insulin and ACEI/ARB (all p>0.05). But, a higher percentage of patients using beta-blockers (p=0.007) and Calcium channel blockers (p=0.039) in eGFR<90 mL/min/1.73m² group was showed by Chisquared test (Table 2).

Serum VEGF-B Level Significantly Associates With Renal Function Indicators in T2DM Patients

As shown in Table 3, in T2DM patients, serum VEGF-B level was positively correlated with triglyceride (r=0.172, p=0.013), serum creatinine (r=0.150, p=0.031) and cystatin C (r=0.245, p<0.001) while inversely correlated with HDL-C (r=-0.138, p=0.047) and eGFR (r=-0.205, p=0.003) after adjusting gender, age, smoking history, drinking history, diabetes duration and BMI. However, although partial correlation confirmed that VEGF-B level significantly associates with several renal function indicators (Figures 2A–C), no significant correlation was observed between serum VEGF-B and UACR nor UTP (both p>0.05).

Regression Model of eGFR in T2DM Patients

We further employed binary logistic regression analysis to analyze the associations between serum VEGF-B and the risk of eGFR<90 mL/min/1.73m². We found that serum VEGF-B level (p=0.002) was significant in predicting eGFR<90 mL/min/1.73m², even after controlling age, UACR, diabetes duration and diastolic pressure (based on the results from Table 1). Of the risk factors above, age (p<0.001) showed a significant, positive relationship with eGFR<90 mL/min/1.73m² as well (Table 4 and Figure 3).
DISCUSSION

Diabetic kidney disease is one of the leading complications of type 2 diabetes. Currently, the mechanisms underlying T2DM-related renal function impairment remains unclear, and the strategies of DKD prediction are still limited (14). In this study, we assessed whether serum VEGF-B, a biomarker from vascular endothelial growth factor family, was associated with progression of diabetes-related renal function impairment in 213 patients with established T2DM. Our results showed that elevated level of VEGF-B in T2DM patients was significantly correlated with markers of lipid metabolism and glomerular function. Regression model also indicated that serum VEGF-B was one of the independent risk factors of eGFR<90 mL/min/1.73m² in T2DM patients.

Previously, several studies have observed increased VEGF-B levels in DKD patients compared to healthy controls (10, 11). Our study further proved that, not only in DKD patients, just in T2DM population (only 28 of 213 T2DM patients fitted the diagnostic criteria of DKD), a significantly rising level of serum

### TABLE 1 | Anthropometric characteristics, clinical characteristics and VEGF-B levels.

| Characteristic | eGFR<90 mL/min/1.73m² (n = 112) | eGFR≥ 90 mL/min/1.73m²(n = 101) | p-value |
|---------------|---------------------------------|---------------------------------|---------|
| Female, n (%) | 39 (34.82)                      | 36 (35.64)                      | 0.090²  |
| Age (years)   | 66.00 (57.25, 72.00)            | 53.00 (46.00, 58.50)            | <0.001ⅹ |
| Smoking, n (%)| 25 (22.32)                      | 22 (21.78)                      | 0.925⁵  |
| Drinking, n (%)| 12 (10.71)                     | 20 (19.83)                      | 0.064²  |
| Diabetes duration (years) | 0.99 ± 2.06          | 1.77 ± 1.86                      | 0.004ⅹ  |
| BMI (kg/m²)   | 25.16 ± 3.23                    | 25.42 ± 3.71                    | 0.590⁶  |
| Systolic pressure (mmHg) | 4.88 ± 0.13                 | 4.91 ± 0.14                      | 0.236⁷  |
| Diastolic pressure (mmHg) | 75.46 ± 10.35             | 79.96 ± 11.60                     | 0.003ⅹ  |
| Fasting blood-glucose (mmol/L) | 1.93 ± 0.35               | 1.91 ± 0.37                      | 0.692⁸  |
| HbA1c (%)     | 2.17 ± 0.25                     | 2.16 ± 0.26                      | 0.670⁹  |
| HOMA-IR       | 1.11 ± 0.80                     | 1.20 ± 0.86                      | 0.424ⅹ  |
| Triglyceride (mmol/L) | 0.55 ± 0.64                  | 0.57 ± 0.61                      | 0.281ⅹ  |
| Total cholesterol (mmol/L) | 1.50 ± 0.24                  | 1.47 ± 0.26                      | 0.916ⅹ  |
| HDL-C (mmol/L) | 0.16 ± 0.24                   | 0.13 ± 0.27                      | 0.262⁸  |
| LDL-C (mmol/L) | 1.02 ± 0.32                   | 1.00 ± 0.37                      | 0.544ⅹ  |
| Serum creatinine (umol/L) | 4.03 ± 0.21                  | 4.53 ± 0.33                      | <0.001ⅹ  |
| Blood urea nitrogen (mmol/L) | 1.68 ± 0.27                  | 1.88 ± 0.33                      | <0.001ⅹ  |
| Cystatin C (mg/L) | -0.21 ± 0.13                 | 0.20 ± 0.25                      | <0.001ⅹ  |
| UACR (mg/g)   | 2.36 ± 1.22                     | 2.94 ± 1.88                      | 0.005ⅹ  |
| UTP (mg/24h)  | 4.21 ± 0.98                     | 4.43 ± 1.44                      | 0.465ⅹ  |
| eGFR (mL/min/1.73m²) | 4.66 ± 0.10                  | 4.22 ± 0.34                      | <0.001ⅹ  |
| Serum VEGF-B (pg/mL) | 4.80 ± 0.77                  | 5.16 ± 0.84                      | 0.002ⅹ  |

BMI, body mass index; Fasting blood-glucose; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; UACR, urine albumin-to-creatinine ratio; UTP, 24-hour urine total protein; eGFR, estimated glomerular filtration rate.

Log-transformed before analysis.

*Significance, p < 0.05.

**Student’s t-test.

*Mann-Whitney U test.

χ² test.

### TABLE 2 | Medicine usage of T2DM patients recruited.

| Use of medications | eGFR<90 mL/min/1.73m² (n = 112) | eGFR≥ 90 mL/min/1.73m² (n = 101) | p-value |
|--------------------|---------------------------------|---------------------------------|---------|
| Metformin, %       | 46.08%                          | 44.55%                          | 0.296²  |
| Sulfonylureas, %   | 27.45%                          | 27.72%                          | 0.167⁴  |
| Pioglitazone, %    | 5.88%                           | 5.94%                           | 0.551⁴  |
| Glucosidase inhibitors, % | 24.51%                   | 24.75%                          | 0.440⁴  |
| GLP1rA, %          | 2.94%                           | 2.97%                           | 0.898⁴  |
| DPP4 inhibitors, % | 25.49%                          | 24.75%                          | 0.115⁴  |
| SGLT2i, %          | 11.76%                          | 11.88%                          | 0.741⁴  |
| Statins, %         | 23.53%                          | 23.76%                          | 0.077⁴  |
| Insulin, %         | 65.69%                          | 65.35%                          | 0.911⁴  |
| ACEI/ARB, %        | 27.45%                          | 27.72%                          | 0.129⁴  |
| Beta-blockers, %   | 36.61%                          | 19.80%                          | 0.007⁷  |
| CCB, %             | 35.71%                          | 22.77%                          | 0.039⁷  |
| Diuretics, %       | 3.92%                           | 3.96%                           | 0.095⁷  |

GLP1rA, glucagon-like peptide 1 receptor agonists; SGLT2i, sodium-glucose co-transporter 2 inhibitors; CCB, Calcium Channel Blockers.

*Significance, p < 0.05.
VEGF-B could be marked. This may provide evidence for the hypothesis that VEGF-B might be a cause for T2DM-related renal function impairment rather than a result. A genome-wide association study demonstrated that the up-regulation of *vegf-b* is related to chronic kidney disease, T2DM, hypertension and hyperlipidemia (15). In animal models of diabetes, VEGF-B increment was found in various type of cells, such as choroidal cells and podocytes (10, 16). Furthermore, *vegf-b* overexpression impaired whereas *vegf-b* knockout rescued the insulin sensitivity and blood lipid profile of gene-edited mouse models (7, 17). Hence, we can assume that VEGF-B may be a future drug target of T2DM and the complications related with huge potential. In addition, a cross-sectional study involving 45 patients with newly diagnosed T2DM also showed an elevation of circulating VEGF-B level in newly diagnosed T2DM patients compared with healthy subjects, and the study exhibited a significantly correlation between circulating VEGF-B and markers of glucose metabolism as well (18). However, in our study, no significant correlation between serum VEGF-B and FBP nor HOMA-IR was observed, which may on account of the anti-diabetic drug usage. We will further expand the sample size and refine the groups to see if more evidence could be provided.

By correlation analysis, we also demonstrated that serum VEGF-B in T2DM patients was correlated with triglyceride and HDL-C, besides renal function markers. Consistent with our findings, Ye etc. found that circulating VEGF-B level was

### TABLE 3 | The correlation of serum VEGF-B (log-transformed) with clinical indicators in T2DM patients.

| Serum VEGF-B level | r       | p-value |
|---------------------|---------|---------|
| Gender              | 0.013   | 0.853*  |
| Age                 | 0.070   | 0.308*  |
| Smoking             | -0.080  | 0.248*  |
| Drinking            | -0.003  | 0.962*  |
| △Diabetes duration  | 0.130   | 0.059*  |
| BMI                 | 0.000   | 0.994*  |
| △Systolic pressure  | 0.019   | 0.790*  |
| Diastolic pressure  | 0.056   | 0.422*  |
| △FBG               | 0.098   | 0.160*  |
| △HbA1c             | 0.056   | 0.420*  |
| △HOMA-IR           | 0.050   | 0.472*  |
| △Triglyceride      | 0.172   | 0.013** |
| △Total cholesterol | 0.062   | 0.371*  |
| △HDL-C            | -0.138  | 0.047** |
| △LDL-C            | 0.121   | 0.083*  |
| △Serum creatinine | 0.150   | 0.031** |
| △Blood urea nitrogen | 0.026  | 0.713*  |
| △Cystatin C      | 0.245   | <0.001**|
| △UACR            | 0.025   | 0.721*  |
| △UTP             | -0.030  | 0.688*  |
| △eGFR            | -0.205  | 0.003** |

BMI, body mass index; FBG, fasting blood-glucose; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; UACR, urine albumin-to-creatinine ratio; UTP, 24-hour urine total protein; eGFR, estimated glomerular filtration rate.

*Log-transformed before analysis.

*Significance, p < 0.05.

*Pearson correlation.

*Spearman correlation.

Partial correlation analysis adjusted for gender, age, smoking history, drinking history, diabetes duration and BMI.

![FIGURE 2](https://example.com/figure2.png)

**FIGURE 2 |** Scatter diagrams showing the significant partial correlations between serum VEGF-B levels and renal function indicators in T2DM patients after adjusting for gender, age, smoking history, drinking history, diabetes duration and BMI. (A) The serum VEGF-B level was positively correlated with Cystatin C (r=0.245, p < 0.001); (B) The serum VEGF-B level was positively correlated with Scr (r=0.150, p=0.031); (C) The serum VEGF-B level was negatively correlated with eGFR (r=-0.205, p=0.003). All data was log-transformed before analysis.
positively correlated with HDL-C and negatively correlated with eGFR in patients with non-alcoholic fatty liver disease (19). Disorder of lipid metabolism is an acknowledged contributor of diabetes-related renal function impairment (20). It has been proven that VEGF-B could destroy glomerular filtration barrier by inducing ectopic lipid deposition in podocyte, and VEGF-B antibody injection prevented renal lipotoxicity and further improved the renal function of db/db mice (10). Our results confirmed that serum VEGF-B is positively correlated with triglyceride and HDL-C while negatively correlated with eGFR, which supports the point that VEGF-B affects renal function of T2DM patients at least partially via regulating lipid metabolism.

It is well known that the classic characteristics of DKD are descending GFR and progressing albuminuria. However, epidemiological investigation exhibits a gradually increasing incidence rate of chronic kidney disease with normoalbuminuria in diabetic patients, especially type 2 diabetes, and the disease was recently referred to as normoalbuminuric diabetic kidney disease (NADKD) (21). Our data also showed that after grouping T2DM patients by eGFR, no difference could be seen in UTP between eGFR $\geq$ 90 mL/min/1.73m² group and eGFR<90 mL/min/1.73m² group (the slight decline of UACR in eGFR<90 mL/min/1.73m² group may depend on the increase of creatinine). This could be partially explained by the limited sample size, but also, the phenomenon was consistent with the epidemic of NADKD in T2DM. Moreover, traditionally, albuminuria and diabetic retinopathy are important components of early DKD prediction and diagnosis. But increasing studies point out that substantial numbers of T2DM patients with DKD do not have retinopathy nor abnormal albuminuria, and normoalbuminuric T2DM patients with low GFR (<60 mL/min/1.73m²) are more likely to show diffuse lesions, nodular lesions, tubulointerstitial lesions or vascular lesions compared to those with preserved GFR (≥60 mL/min/1.73m²) (22, 23). And as such, more sensitive indicators are urgently needed for early diagnosis and intervention of DKD. In our research, we found that serum VEGF-B level in T2DM patients was positively correlated with SCr and CysC, while negatively correlated with eGFR and is an independent predictor of eGFR<90 mL/min/1.73m². Interestingly, no significant correlation between serum VEGF-B and UTP nor UACR was observed, which suggested that the relationship between serum VEGF-B level and renal function impairment in T2DM patients was independent of albuminuria, and the VEGF-B up regulation is likely to be a new mechanism underlying NADKD in T2DM patients.

Overall, in this study, we demonstrated that T2DM patients exhibited an elevated serum VEGF-B level, which was associated with renal function impairment. The increased serum VEGF-B level was an independent risk factor of eGFR<90 mL/min/1.73m² in patients with type 2 diabetes and it was irrelevant to albuminuria. However, certain limitations of this study should be noted. Firstly, owing to the difficulty in obtaining renal samples from T2DM patients, VEGF-B levels in serum were tested only, thus we are unable to trace the accurate source of the increasing VEGF-B. Secondly, the persuasiveness as well as the reproducibility of our findings might be blunted by the limited
and to determine the role of VEGF-B in DKD pathology as well as made available by the authors, without undue reservation.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the medical research ethics committee of the affiliated hospital of Nanjing university of Chinese medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

In this study, YW and WS designed the project, YJ performed the data and wrote portions of the manuscript. SH, RZ, PX, LZ, ZZ, YK, XYY, YX, YC, and XW performed the collection of samples and data. YJ, JY and XZY performed the measurement of serum VGEF-B. WS guided the project and wrote portions of the manuscript. All authors are in agreement with the content of the manuscript, and the authors declare no conflict of interest. All authors contributed to the article and approved the submitted version.

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