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Association of insulin-like growth factor-1 and insulin-like growth factor-binding protein-3 with estimated glomerular filtration rate in patients with type 2 diabetes mellitus

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Abstract

Type 2 diabetes mellitus patients often suffer from kidney damage, which is more serious than in ordinary people. The insulin-like growth factor (IGF) system has synergistic effects with other hormonal axes and has an essential role in glucose metabolism and type 2 diabetes. The study aimed to observe the association of IGF-1 and IGF factor-binding protein-3 (IGFBP-3) with estimated glomerular filtration rate (eGFR) in patients with type 2 diabetes mellitus. We recruited 521 patients with type 2 diabetes from the Endocrinology Department of the First Affiliated Hospital of Xinjiang Medical University from March 1, 2021, to December 20, 2021. The clinical data we collected were analyzed to determine the association of IGF-1 and IGFBP-3 with eGFR in patients with type 2 diabetes. Spearman correlation analysis showed that eGFR was positively correlated with IGF-1 and IGFBP-3 in all subjects ($P = 0.044$ and $P = 0.004$, respectively). We developed a linear regression model. In the multiple linear regression model, serum IGF-1 and IGFBP-3 were positively correlated with eGFR ($\beta = 0.03$, 95% CI = 0.01 – 0.06; $P = 0.009$ and $\beta = 1.29$, 95% CI = 0.09 – 2.49; $P = 0.035$). The results of the correlations were further validated. This preliminary study demonstrated positive associations of serum IGF-1 and IGFBP-3 levels with eGFR in patients with type 2 diabetes.

Keywords: Estimated glomerular filtration rate; Insulin-like growth factor-binding protein-3; Insulin-like growth factor-1; Kidney function; Type 2 diabetes mellitus

1. Introduction

Diabetes mellitus, which is a serious global public health problem, is either caused by impaired insulin secretion or disturbed insulin effect, or usually both[1]. More than 90% of diabetic patients are classified under type 2 diabetes mellitus, which is characterized by insulin resistance with or without deficient insulin secretion[2]. It is well known that diabetes is a risk factor for kidney disease, which can lead to proteinuria, decreased renal function, and further development of diabetic nephropathy.

Approximately half of the patients with type 2 diabetes mellitus will develop chronic kidney disease (CKD) as the disease progresses and manifest increased urinary albumin

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excretion[3]. However, this view has been challenged, because many patients with type 2 diabetes mellitus suffer from a decline in glomerular filtration rate (GFR) in the absence of proteinuria, as confirmed by Kramer *et al.*[4], Garg *et al.*[5] and MacIsaac *et al.*[6] Therefore, in many cases, CKD is defined as a continuous decrease in GFR.

Insulin-like growth factors (IGFs) are proteins with multiple functions, including stimulation of cell proliferation, inhibition of apoptosis, and enhancement of cell motility as well as the regulation of cell differentiation and transformation[7]. Among the IGFs, the IGF-1 gene encodes a small protein made up of 70 amino acid residues. IGF-1 is an anabolic hormone and a primary mediator for growth hormone (GH)-related signaling pathways[8]. It also plays a versatile role in regulating many cellular processes, such as cellular metabolism, growth, proliferation, and apoptosis in multiple organs, and promoting the growth, development, and maintenance of cells[9]. The kidney can produce and release IGF-1 and is also the target organ of the GH/IGF-1 axis. Free IGF-1 in the blood is biologically active; more than 90% of IGF-1 binds to the IGF factor-binding protein-3 (IGFBP-3) in plasma. Therefore, IGFBP-3 is the primary regulator of the biological activity of plasma IGF-1[10-12]. In the literature, we can find that the molar ratio of IGF-1/IGFBP-3 is commonly used to reflect the bioactivity of IGF-1[13,14].

A prospective study observed that the serum IGFBP-3 levels were positively correlated with the risk of type 2 diabetes independent of IGF-1 levels[15]. IGF-1 and IGFBP-3 not only are correlated to diabetes but also have specific effects on the kidneys. It has been shown that serum IGF-1 levels are related to GFR[16]. Furthermore, the administration of intravenous recombinant human IGF-1 (rhIGF-1) stimulates the kidney in healthy subjects by increasing GFR and renal plasma flows[17,18]. Nevertheless, few studies have explored the level of IGF-1 in patients with type 2 diabetes and its relationship with kidney disease.

This cross-sectional study aimed to assess the association of IGF-1 and IGFBP-3 with indicators of renal function.

2. Materials and methods

2.1. Patients and study design

We reviewed the records of 614 patients who visited and completed type 2 diabetes screening at the Endocrinology Department of the First Affiliated Hospital of Xinjiang Medical University from March 1, 2021, to December 20, 2021. The exclusion criteria are as follows: (i) Patients whose data were incomplete or missing (n = 40); (ii) patients with other types of diabetes (n = 17); (iii) patients with diabetic ketoacidosis (n = 15); (iv) patients with diabetic foot (n = 8); and (v) patients with impaired glucose tolerance (n = 13). Finally, complete data from 521 patients were analyzed (Figure 1). This study was approved by the Ethics Committee of the First Affiliated Hospital of Xinjiang Medical University.

The diagnostic criteria for type 2 diabetes are based on the 1999 World Health Organization criteria: (i) Typical symptoms of diabetes (polydipsia, polyuria, polyphagia, and weight loss); and (ii) random venous plasma blood glucose ≥ 11.1 mmol/L (200 mg/dL) or fasting blood glucose ≥ 7.0 mmol/L (126 mg/dL) or oral glucose tolerance test (OGTT) 2h glucose in venous plasma (for those without diabetic symptoms, repeat the test on another day) ≥ 11.1 mmol/L (200 ng/dL).

2.2. Data collection

Clinical variables that were reviewed from electronic medical records include age, sex, body mass index (BMI), and blood pressure. Height and weight were measured to the nearest 0.5 cm and 0.1 kg, respectively. BMI was calculated as body weight (kg) divided by the square of height (m). Readings of blood pressure (BP) were obtained using a mercury sphygmomanometer from the left arm of patients in supine position, after 5 min of quiet rest. Values were calculated as the average of the last two of three consecutive measurements obtained at 3-min intervals.

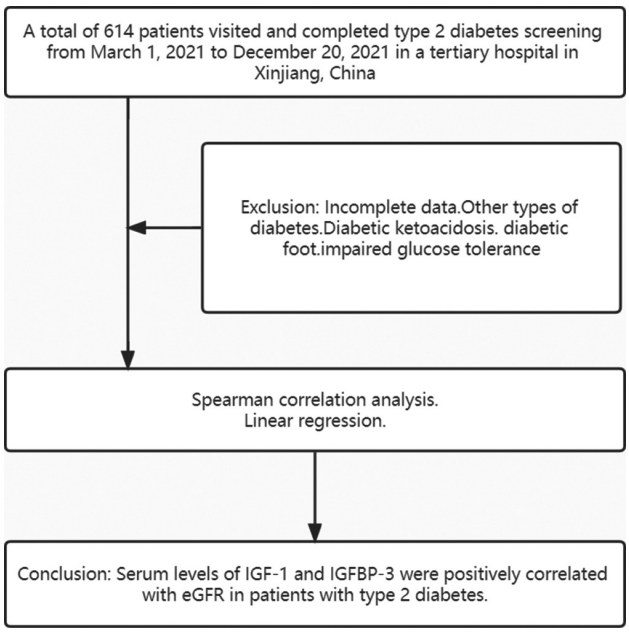

Figure 1. Flow chart of this study.
The relationship between insulin-like growth factor (IGF)-1, IGF factor-binding protein-3, and estimated glomerular filtration rate was clarified by correlation analysis and linear regression.

2.3. Biochemical indicators

Biochemical parameters of the present study include plasma glucose, glycated hemoglobin (HbA1c), serum creatinine, blood urea nitrogen (BUN), and serum cholesterol (total cholesterol [TC]), triglycerides (TG), alanine aminotransferase (ALT), and aspartate transaminase (AST), as determined by Fully Automatic Biochemistry Analyzer (Beckman Coulter).

2.4. Analytical determinations

Serum IGF-1 and IGFBP-3 levels were measured by the chemiluminescence immunometric method (Siemens Healthcare Diagnostics Products Ltd, United Kingdom). Serum creatinine concentration was determined using the Jaffé method. Low-density lipoprotein cholesterol (LDL-c) and high-density lipoprotein cholesterol (HDL-c) were measured by the direct method; TC was determined by enzymatic method; TG was determined by glycerol-3-phosphate (GPO)-peroxidase (POD) method; fasting plasma glucose (FPG) was determined by hexokinase method; and AST and ALT were determined by colorimetry (Fully Automatic Biochemistry Analyzer, Beckman Coulter, Inc., USA).

2.5. Calculations

GFR is estimated using the simplified Modification of Diet in Renal Disease (MDRD) formula:

Estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) = 186.3 × serum creatinine (mg/dL)$^{-1.154}$ × age (years)$^{-0.203}$ × (0.742 for women)[19,20]

2.6. Statistical analysis

Statistical analysis was performed using a statistical computer program for the R (version 4.1.1) project. All the statistical tests were considered significant at the 0.05 probability level. Continuous variables are expressed as mean ± standard deviation (SD) or the median with the interquartile range. We used Shapiro–Wilk tests and Q-Q plot tests to verify the normality of the distribution of continuous variables. For the data of interest in this study, it has no impact on the normality of the distribution. Spearman's rank correlation coefficient was performed to analyze the correlation of IGF-1 and IGFBP-3 with other continuous variables of interest. Then, the univariate and multivariate linear regression analyses were performed to determine the association of circulating IGF-1 and other variables with eGFR in all study subjects. For a standardized coefficient (*B*), we estimated two-tailed probability values and the 95% confidence interval (95% CI). All P-values are two-tailed, and values of less than 0.05 are considered statistically significant.

3. Results

The study population comprised 317 men and 204 women. The mean age of the patients was 56.84 ± 12.38 years. The mean ± SD of IGF-1 was 152.46 ± 57.08 ng/mL, the mean ± SD of IGFBP-3 was 4.03 ± 1.22 μg/mL, and the mean ± SD of eGFR was 94.13 ± 21.08 ml/min/1.73 m^2. Baseline characteristics for the entire cohort are presented in Table 1.

All study subjects were divided into five groups according to eGFR. One-way analysis of variance (ANOVA) was performed for each group, and differences

Table 1. Characteristics of patients

Characteristic	N=521 (mean±SD)
Age (years)	56.84±12.38
Sex (female, %)	204 (39.16%)
SBP (mmHg)	129.18±17.17
DBP (mmHg)	78.54±10.98
Height (cm)	167.69±8.3
Weight (kg)	73.03±12.81
BMI (kg/m^2)	26.02±4.62
IGF-1 (ng/mL)	152.46±57.08
IGFBP-3 (μg/mL)	4.03±1.22
FBG (mmol/L)	7.93±2.67
2H-OGTT (mmol/L)	16.69±4.48
HbA1c (%)	8.75±2.21
eGFR (ml/min/1.73 m^2)	94.13±21.08
Cr (μmol/L)	71.71±24.94
BUN (mmol/L)	5.83±2.13
ALT (U/L)	25.16±31.76
AST (U/L)	21.26±18.48
TG (mmol/L)	2.15±1.97
TC (mmol/L)	4.19±1.21
LDL-c (mmol/L)	2.71±0.96
HDL-c (mmol/L)	0.98±0.27
24H-UP (g/24 h)	0.32±0.99
24H-UM (mg/24 h)	88.89±278.15
UAER (μg/min)	61.73±193.16

Data are presented as mean±standard deviation or as number (percentage) for sex.
Abbreviations: SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, IGF-1: Insulin-like growth factor 1, IGFBP-3: Insulin-like growth factor-binding protein 3, FPG: Fasting plasma glucose, 2H-OGTT: 2 h-oral glucose tolerance test, HbA1c: Glycated hemoglobin, eGFR: estimated Glomerular Filtration Rate, Cr: Creatinine, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TC: Total cholesterol, TG: Triglyceride, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, 24H-UP: 24-h urinary protein, 24H-UM: 24-h urinary microalbumin, UAER: Urinary albumin excretion rate.

Table 2. Comparison of clinical data between groups stratified by glomerular filtration rate

Parameters	Glomerular filtration rate					*P*
	≥ 120	90 – 119	61 – 89	31 – 60	≤30	
NO	28	312	146	30	5	
Age (years)	35.86±10.53	54.14±10.23	63.84±9.61	69.77±10.77	60.60±12.58	<0.001
Diabetes duration (years)	6.93±7.22	7.93±6.80	10.13±7.49	11.22±9.80	13.60±4.39	0.003
Height (cm)	171.86±6.73	168.44±8.23	165.96±8.13	164.83±8.80	165.60±9.32	<0.001
Weight (kg)	79.86±15.33	73.40±13.16	71.65±11.10	69.45±11.23	73.40±19.89	0.015
BMI (kg/m^2)	27±4.64	26.01±5.11	25.94±3.44	25.50±3.88	26.80±7.69	0.769
SBP (mmHg)	126.93±16.48	128.40±17.69	129.21±15.37	137.43±18.77	140.00±17.58	0.039
DBP (mmHg)	83.61±9.43	79.15±11.39	76.29±9.63	78.80±11.34	75.80±17.41	0.009
IGF-1 (ng/mL)	147.84±39.56	155.06±57.02	148.13±61.25	147.63±53.92	171.80±33.68	0.653
IGFBP-3 (μg/mL)	4.54±1.20	4.06±1.18	3.87±1.24	3.85±1.45	4.64±0.67	0.048
FBG (mmol/L)	9.93±2.82	7.89±2.74	7.64±2.42	8.13±2.43	7.22±1.81	0.001
2H-OGTT (mmol/L)	18.78±3.83	16.56±4.38	16.72±4.83	16.37±3.93	14.49±4.22	0.101
HbA1c (%)	10.46±2.71	8.68±2.16	8.60±2.14	8.60±1.94	8.12±2.09	<0.001
eGFR (ml/min/1.73 m^2)	132.62±17.78	103.43±7.74	78.68±8.30	48.80±9.04	21.47±7.35	<0.001
Cr (μmol/L)	48.89±9.94	63.30±12.31	79.75±12.33	120.22±28.23	192.75±99.69	<0.001
BUN (mmol/L)	4±1.22	5.38±1.37	6.22±2.01	8.85±2.80	14.03±5.91	<0.001
ALT (U/L)	30.44±22.62	24.83±19.32	26.30±51.81	19.89±9.47	14.33±11.11	0.663
AST (U/L)	23.45±19.2	20.24±11.77	23.45±28.96	20.27±6.89	14.26±5.73	0.38
TG (mmol/L)	3.42±3.49	2.06±1.86	2.07±1.69	2.92±2.02	2.28±2.21	0.011
TC (mmol/L)	4.75±1.58	4.15±1.12	4.18±1.25	4.09±1.48	3.90±0.87	0.147
LDL-c (mmol/L)	2.89±0.99	2.70±0.91	2.73±1.01	2.58±1.07	2.00±0.97	0.354
HDL-c (mmol/L)	0.92±0.37	0.99±0.26	0.97±0.24	0.89±0.19	1.14±0.75	0.175
24H-UP (g/24h)	0.12±0.09	0.19±0.49	0.32±0.91	1.53±2.54	2.78±3.45	<0.001
24H-UM (mg/24h)	23.29±41.66	48.35±142.91	95.28±332.05	417.95±547.73	824.55±798.41	<0.001
UAER (μg/min)	16.17±28.93	33.58±99.24	66.17±230.59	290.24±380.37	572.60±554.45	<0.001

Abbreviations: SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, IGF-1: Insulin-like growth factor 1, IGFBP-3: Insulin-like growth factor-binding protein 3, FPG: Fasting plasma glucose, 2H-OGTT: 2h-oral glucose tolerance test, HbA1c: Glycated hemoglobin, eGFR: estimated glomerular filtration rate, Cr: Creatinine, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TC: Total cholesterol, TG: Triglyceride, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, 24H-UP: 24-h urinary protein, 24H-UM: 24-h urinary microalbumin, UAER: Urinary albumin excretion rate

were found in age, duration of diabetes, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), IGFBP-3, FBG, HbA1c, BUN, TG, 24-h urine protein, and urinary albumin (Table 2).

In this study, the Spearman's rank correlation coefficients among IGF-1and IGFBP-3 with the above-mentioned parameters are illustrated in Table 3. Through Spearman correlation analysis, we found that there was a significantly positive correlation between IGF-1 and IGFBP-3 ($P < 0.001$). IGF-1 and IGFBP-3 were positively correlated with eGFR. A correlation heat map was created based on the results of the correlation analysis (Figure 2).

As presented in Table 4, eGFR was negatively correlated with age, diabetes course, SBP, BUN, serum creatinine, 24-h urine protein, 24-h urinary microalbumin and urinary albumin excretion rate, and positively correlated with FPG, HbA1c, IGF-1, and IGFBP-3 in univariate linear regression analysis.

Model I was developed after screening variables by the Akaike information criterion (AIC was used as a measure of goodness of fit for each model; all combinations of variables were tested, and the best model has the lowest AIC) based on univariate linear regression analysis, and we developed Model II by replacing the independent variable IGF-1 in Model I with IGFBP-3. In Model I, IGF-1 ($\beta = 0.03$, 95% CI = 0.01 – 0.06) was significantly associated

Table 3. Spearman's correlation analysis among IGF-1and IGFBP-3 with other parameters

Variable	IGF-1	IGFBP-3
Age (years)	−0.258 (<0.001)	−0.401 (<0.001)
Duration of diabetes (years)	0.007 (0.882)	−0.019 (0.657)
SBP (mmHg)	−0.013 (0.764)	−0.011 (0.792)
DBP (mmHg)	0.068 (0.119)	0.093 (0.033)
Height (cm)	0.104 (0.017)	0.046 (0.291)
Weight (kg)	0.027 (0.533)	0.047 (0.275)
BMI (kg/m^2)	−0.055 (0.204)	0.002 (0.957)
Glucose metabolism		
FBG (mmol/L)	0.000 (0.992)	0.061 (0.163)
2H-OGTT (mmol/L)	−0.021 (0.631)	−0.005 (0.916)
HbA1c (%)	0.015 (0.719)	0.055 (0.206)
Kidney function		
eGFR (ml/min/1.73 m2)	0.088 (0.044)	0.126 (0.004)
Cr (μmol/L]	0.056 (0.204)	0.002 (0.968)
BUN (mmol/L)	0.072 (0.101)	−0.019 (0.665)
Liver function		
ALT (U/L)	−0.076 (0.082)	−0.026 (0.558)
AST (U/L)	−0.123 (0.005)	−0.081 (0.062)
Blood lipids		
TG (mmol/L)	0.022 (0.615)	0.261 (0.001)
TC (mmol/L)	0.068 (0.122)	0.311 (<0.001)
LDL-c (mmol/L)	0.057 (0.191)	0.238 (<0.001)
HDL-c (mmol/L)	0.064 (0.436)	0.081 (0.301)
Urine protein		
24H-UP (g/24 h)	0.004 (0.926)	−0.019 (0.775)
24H-UM (mg/24 h)	0.016 (0.709)	0.013 (0.775)
UAER (μg/min)	0.016 (0.709)	0.013 (0.775)
IGFs		
IGF-1 (ng/mL)	-	0.550 (<0.001)
IGFBP-3 (μg/mL)	0.550 (<0.001)	-

Data are given as *r* (*P*), *r*: Spearman's correlation coefficient. Statistical correlation is significant at $P<0.05$. Abbreviations: SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, FPG: Fasting plasma glucose, 2H-OGTT: 2h-oral glucose tolerance test, HbA1c: Glycated hemoglobin, eGFR: estimated glomerular filtration rate, Cr: Creatinine, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TG: Triglyceride, TC: Total cholesterol, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, 24H-UP: 24-h urinary protein, 24H-UM: 24-h urinary microalbumin, UAER: Urinary albumin excretion rate, IGF-1: Insulin-like growth factor 1, IGFBP-3: Insulin-like growth factor-binding protein 3.

with eGFR. In Model II, there was no difference in the correlation between each independent variable and eGFR despite the replacement with IGFBP-3. After adjusting for

Table 4. Univariate linear regression analysis of the correlation between eGFR and various parameters in patients with type 2 diabetes mellitus

Characteristic	β	95% CI	*P*
Age (years)	−1.06	−1.17, −0.94	<0.001
Diabetes duration (years)	−0.46	−0.71, −0.21	<0.001
SBP (mmHg)	−0.21	−0.32, −0.11	<0.001
DBP (mmHg)	−0.16	0.00, 0.32	0.057
Height (cm)	0.49	0.27, 0.70	<0.001
Weight (kg)	0.18	0.04, 0.32	0.013
BMI (kg/m^2)	0.03	−0.37, 0.42	0.892
IGF-1 (ng/mL)	0.03	0.01, 0.06	0.044
IGFBP-3 (μg/mL)	2.18	0.71, 3.66	0.004
FPG (mmol/L)	1.05	0.37, 1.72	0.002
2H-OGTT (mmol/L)	0.38	−0.02, 0.78	0.063
HbA1c (%)	1.47	0.66, 2.28	<0.001
Cr (μmol/L)	−0.61	−0.66, −0.56	<0.001
BUN (mmol/L)	−5.32	−6.04, −4.60	<0.001
ALT (U/L)	0.04	−0.02, 0.09	0.222
AST (U/L)	−0.01	−0.11, 0.09	0.816
TG (mmol/L)	0.73	−0.19, 1.65	0.122
TC (mmol/L)	1.26	−0.24, 2.76	0.099
LDL-c (mmol/L)	1.16	−0.74, 3.06	0.231
HDL-c (mmol/L)	0.09	−6.73, 6.91	0.979
24H-UP (g/24 h)	−6.68	−8.43, −4.94	<0.001
24H-UM (mg/24 h)	−0.03	−0.03, −0.02	<0.001
UAER (μg/min)	−0.04	−0.05, −0.02	<0.001

Abbreviations: β: Regression coefficient, CI: Confidence interval, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, IGF-1: Insulin-like growth factor 1, IGFBP-3: Insulin-like growth factor-binding protein 3, FPG: Fasting plasma glucose, 2H-OGTT: 2h-oral glucose tolerance test, HbA1c: Glycated hemoglobin, eGFR: estimated glomerular filtration rate, Cr: Creatinine, BUN: Blood urea nitrogen, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, TC: Total cholesterol, TG: Triglyceride, LDL-c: Low-density lipoprotein cholesterol, HDL-c: High-density lipoprotein cholesterol, 24H-UP: 24-h urinary protein, 24H-UM: 24-h urinary microalbumin, UAER: Urinary albumin excretion rate

IGF-1, IGFBP-3 (β = 1.29, 95% CI = 0.09 – 2.49) remained positively correlated with eGFR. In multiple linear regression models, diabetes duration was not associated with eGFR. SBP and BUN were negatively correlated with eGFR, while DBP and FBG were positively correlated with eGFR (Table 5).

4. Discussion

The patients with type 2 diabetes mellitus are a high-risk group of renal insufficiency. It is crucial for

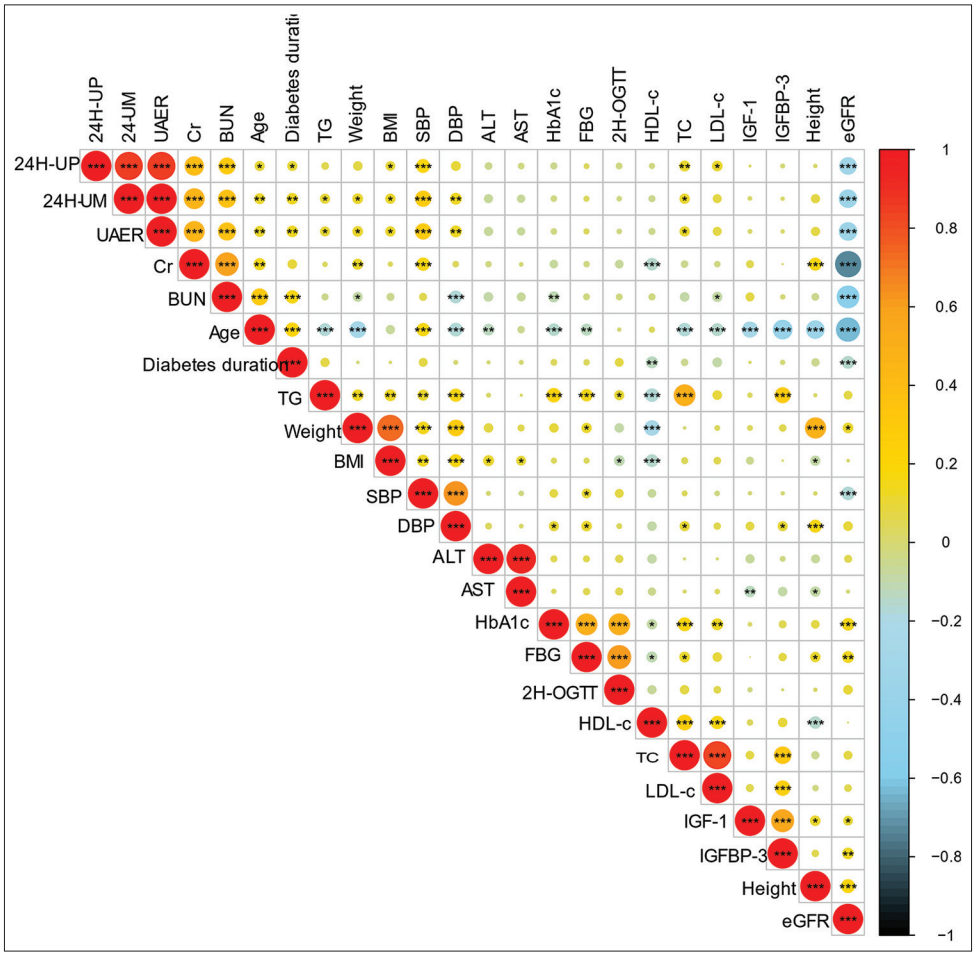

Figure 2. Correlation map reporting Spearman's correlation values for each comparison.
The bar on the right of the map indicates the color legend of the Spearman's correlation values calculated for each couple of samples in the matrix. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 5. Multiple linear regression analysis of the correlation between eGFR and various parameters in patients with type 2 diabetes mellitus

Factors included	Model I		Model II	
	β (95% CI)	*P*	β (95% CI)	*P*
Diabetes duration (years)	−0.15 (−0.35, −0.04)	0.128	−0.15 (−0.35, 0.05)	0.137
SBP (mmHg)	−0.25 (−0.35, −0.04)	<0.001	−0.25 (−0.36, −0.14)	<0.001
DBP (mmHg)	0.25 (0.08, 0.42)	0.005	0.25 (0.08, 0.43)	0.004
FBG (mmol/L)	1.01 (0.48, 1.55)	<0.001	0.98 (0.44, 1.52)	<0.001
BUN (mmol/L)	−4.37 (−5.12, −3.63)	<0.001	−4.29 (−5.03, −3.54)	<0.001
ALT (U/L)	0.23 (0.11, 0.35)	<0.001	0.23 (0.10, 0.35)	<0.001
AST (U/L)	−0.43 (−0.64, −0.21)	<0.001	−0.43(−0.64, −0.22)	<0.001
UAER (μg/min)	−0.02 (−0.03, −0.01)	<0.001	−0.02 (−0.03, −0.01)	<0.001
IGF-1 (ng/mL)	0.03 (0.01, 0.06)	0.009	-	-
IGFBP-3 (μg/mL]	-	-	1.29 (0.09, 2.49)	0.035

B: Regression coefficient, CI: Confidence interval, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BUN: Blood urea nitrogen, TC: Total cholesterol, LDL-c: Low-density lipoprotein, HbA1c: Glycated hemoglobin, FPG: Fasting plasma glucose, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, UAER: Urinary albumin excretion rate, IGF-1: Insulin-like growth factor-1, IGFBP-3: Insulin-like growth factor-binding protein-3

clinicians to focus on the effects of IGF-1 and IGFBP-3 on renal function in patients with type 2 diabetes and to understand the association of IGF-1 and IGFBP-3 with eGFR, which might be important for renal function assessment and early diagnosis. By observing the indicators of all patients, serum IGF-1 and IGFBP-3 were positively correlated with eGFR. This suggests that serum IGF-1 and IGFBP-3 play a key role in renal function.

The relationship between serum IGF-1 and GFR is unclear. So far, only one study has been conducted to investigate the correlation between serum IGF-1, IGFBP-3, and GFR in patients with type 2 diabetes, showing that the levels of these two proteins are not related to GFR in all patients[21]. In addition, another study found that serum IGF-1 reduction was associated with lower eGFR in insulin-resistant obese patients[22]. On the contrary, in 4028 (2048 women) subjects between the age of 20 and 81 years, IGF-1 was inversely correlated with BMI, presence of diabetes, and GFR[23,24]. Hence, the association between IGF-1 and eGFR in patients with type 2 diabetes is not yet understood. In this study, we studied 521 Chinese patients with type 2 diabetes. Spearman correlation analysis found that both serum IGF-1 and IGFBP-3 are positively linked with eGFR. Then, we established the linear regression model of IGF-1and the linear regression model of IGFBP-3. Interestingly, IGF-1and IGFBP-3 were still related to eGFR. In summary, we speculate that serum IGF-1and IGFBP-3 may be factors that affect the level of eGFR in type 2 diabetes.

This study shows that IGF-1 and IGFBP-3 are positively correlated with eGFR. The physiological link between IGF-1 levels and renal disease in type 2 diabetes is not fully understood; however, it is generally believed that the GH/IGF-1 axis affects renal function[25,26].

IGF-1 promotes the division of mesangial cell in glomeruli[27], and it can inhibit the apoptosis of mesangial and podocyte cells[28]. IGF-1 may increase glomerular perfusion by reducing the resistance of the arterioles[29,30]. It is worth noting that micro-puncture studies have also shown that IGF-1 increases single nephron GFR and blood flow by expanding the ultrafiltration coefficient and reducing the resistance of the efferent arterioles[26]. Furthermore, IGF-1 can increase extracellular volume and plasma volume[31,32], which also helps increase glomerular filtration. In most patients with decreased renal function, the expression of growth hormone receptor and IGF-1 gene in the kidney is diminished, which is a cause of reduced GFR[33,34].

Similarly, Jorgensen *et al.*[35] found that the reduction of renal plasma flow and glomerular filtration was related to the lack of IGF-1 and growth hormone. The role of IGF-1 in a high glucose environment induces mesangial cells to produce nitric oxide, which, further, leads to changes in renal hemodynamics. In addition, IGF-1 can interact with the renin-angiotensin system to cause changes in glomerular hemodynamics[36,37].

There are inconsistent results reported on the relationship between serum IGF-1, IGFBP-3, and diabetes risk. In a study that included normoglycemic patients between the ages of 45 and 65 years, it was observed that serum IGF-1 was associated with a reduced risk of type 2 diabetes after a glucose tolerance test[38]. In contrast, it has also been found that serum IGF-1or IGFBP-3 was not associated with diabetes risk[39]. In our study, serum IGF-1 and IGFBP-3 levels were not correlated with FBG, 2-h OGTT and HbA1c, which is consistent with previous reports[40,41]. However, in univariate regression analysis, FPG and HbA1c were significantly positively correlated with eGFR.

In comparison, only FPG was statistically significant in multivariate regression analysis. Weil *et al.* found that GFR was positively associated with fasting glucose and glycated hemoglobin in patients with type 2 diabetes[42]. Hyperglycemia may cause hyperfiltration in diabetic patients when they do not develop the end-stage renal disease in the early stages of diabetes.

Dyslipidemia is the basis of cardiovascular disease. The concentration of serum HDL-c is inversely correlated with the risk of coronary heart disease[43,44]. Each 1 mg/dL increase in HDL-c reduces the risk of coronary heart disease by approximately 2 – 3%[45]. It was previously reported that IGF-1 is a protective factor for coronary heart disease in patients with type 2 diabetes[46].

Song *et al.*[47] showed that serum IGF-1 was positively correlated with HDL-c. Our study showed a positive correlation between serum IGFBP-3 and TG, TC, and LDL-c in correlation analysis. However, no correlation was found in linear regression. Further studies need to confirm the role of serum IGFBP-3 on lipid metabolism in type 2 diabetic patients.

Although there are overlaps in the current findings with previous epidemiological and laboratory data, the present study has several limitations that must be considered in the interpretation of its findings. First, the small sample size does not allow for a comprehensive assessment of the entire population, and the findings may be biased. This bias may be reflected in the correlation between IGF-1 and eGFR, and large-scale population data are needed to confirm our results in the future. Furthermore, nutrition is an essential factor in the regulation of IGF-1. Another limitation of this study may be the lack of data concerning nutritional status[48]. In addition, we need to include more patients with eGFR of < 60 ml/min/1.73 m^2, and then conduct a

longitudinal subgroup analysis to clarify further the trend of IGF-1 changes in patients with severe renal impairment.

5. Conclusions

Serum IGF-1 and IGFBP-3 were positively correlated with eGFR in patients with T2DM. Although there has been an increased understanding of the function of IGF-1and IGFBP-3, there are still many unanswered questions about their effects on renal function in patients with T2DM. Therefore, whether serum IGF-1 can be used for the measurement and assessment of renal function requires further evaluation in prospective large-scale studies.

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Conflict of interest

The authors report no conflicts of interest in this work.

Author contributions

Conceptualization: Sheng Jiang
Formal analysis: Sheng Jiang, Jing Yang
Investigation: Jing Yang
Writing – original draft: Sheng Jiang, Jing Yang
Writing – review & editing: Jing Yang

Ethics approval and consent to participate

The study was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and was reviewed and approved by the Human Research Ethics Committee of the Affiliated Hospital of Xinjiang Medical University (K202205-11), and informed consent was obtained from all patients with type 2 diabetes mellitus before their participation.

Consent for publication

Not applicable.

Availability of data

The data used to support the findings of this study are available from the corresponding author on request.

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