Association between serum insulin like growth factor-1 (IGF-1) and insulin-like growth factor-binding protein-3 levels and chronic kidney disease in diabetic patients

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ARTICLE INFO

ABSTRACT

Introduction: Insulin-like growth factor-1 (IGF-1) is a potent mitogen for glomerular mesangial cells which can stimulate cell migration and the production of fibronectin, proteoglycan, and type IV collagen, thereby promoting the development of the chronic kidney disease (CKD) in patients with diabetes.

Objectives: The aim of the study was to assess the associations between serum levels of IGF-1 and insulin-like growth factor-binding protein-3 (IGFBP-3) and CKD in diabetic patients.

Patients and Methods: We investigated 102 Belarusian men and women with diabetes type 2 aged 56.67 ± 0.81 years. Control group included 68 healthy people the same age. We estimated GFR with the use of the CKD-EPI creatinine-cystatin C equation to determine eGFRcr_cys. Serum total IGF-1 and IGFBP-3 levels were measured using immunoradiometric assay (IRMA) (Beckman Coulter, Czech Republic s.r.o.).

Results: Patients with diabetes had significantly lower level of IGF-1 than controls. However, IGFBP-3 levels were similar in the two groups. Diabetic patients with CKD had significantly higher levels of IGF-1 and IGFBP-3 than diabetic patients without CKD ($P = 0.0031$). However, according to multivariate analysis, only IGF-1 and cystatin C were associated with renal impairment. In detail, the odds of having eGFR<60 mL/min/1.73 m^2 increased with rising IGF-1 levels (OR: 1.025, [CI 1.002-1.048]).

Conclusion: Our study revealed that higher serum IGF-1 levels were positively associated with CKD in patients with diabetes. We suggest that IGF-1 might be a predictor of CKD in patients with diabetes. Further research is necessary to confirm the observed this association and to detect the causal relations.

Introduction

Diabetes mellitus is the leading cause of chronic kidney disease (CKD) in developed countries. It is recognized as one of the major risk factors for adverse outcomes, including cardiovascular events, end stage renal disease, and death (1-3). In patients with type 1 diabetes (T1DM), screening for nephropathy should start five years after diagnosis of diabetes because it usually takes about 5

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years for this complication to develop. In patients with type 2 diabetes (T2DM), screenings should begin at initial diagnosis since the exact onset of diabetes is unknown in most cases (4). During the last decades, serum creatinine concentration has become the most commonly used marker for estimation of glomerular filtration rate (GFR). However, recently, serum cystatin C has been proposed as a new endogenous marker of kidney function which is less influenced by muscle mass, sex and age (5). Some studies have demonstrated that serum cystatin C concentration is a better indicator of GFR in patients with diabetes and a better predictor of mortality and adverse cardiovascular events than serum creatinine (6,7).

Kidney function estimation is commonly made using serum creatinine, serum cystatin C and urine analysis, since accumulating evidence has shown that these markers are not optimal for detection of kidney disease at early stages (8,9).

It is known that insulin-like growth factor-1 (IGF-1) is a potent mitogen for glomerular mesangial cells which can stimulate cell migration and the production of fibronectin, proteoglycan, laminin, and type IV collagen, thereby promoting the development of CKD in patients with diabetes (10). It has been shown that patients with diabetes and microalbuminuria present with severe alterations in the growth hormone–insulin-like growth factor–insulin-like growth factor binding protein (GH–IGF–IGFBP) system, with increased IGF-1 renal levels and IGF-1 binding protein 3 (IGFBP-3) protease activity, increased excretion of bioactive GH, IGF-1, and IGFBP-3, with a decrease in circulating intact IGFBP-3 levels. At the same time data regarding levels of IGF-1 in diabetic patients have yielded conflicting results. Decreased serum IGF-1 levels have been noted in diabetic subjects with reduced kidney function (11). However, increased IGF-1 and IGFBP-3 levels have been found in adult patients with decreased estimated GFR (12).

Objectives
The aim of this study was to assess the associations between serum levels of IGF-1 and insulin-like growth factor-binding protein-3 (IGFBP-3) and CKD in diabetic patients.

Patients and Methods
Study participants
We investigated 102 Belarusian men and women with T2DM who consecutively referred to the Republican Research Centre for Radiation Medicine and Human Ecology (Gomel, Republic of Belarus) institution. The inclusion criteria were presence of T2DM, age between 20 and 80 years, and body mass index (BMI) between 18.5 and 40.0 kg/m². All patients were treated with diet and oral antidiabetic drugs. Patients with signs of end stage renal failure, overt infection, pituitary adenomas, severe

liver inflammation, treated with glucocorticoids were excluded. Control group included 68 healthy people the same age. Demographic parameters were evaluated, height and weight were measured, and BMI was calculated.

Biochemical measurements
Fasting blood samples were collected from each patient in the morning after overnight fasting. Serum was separated by centrifugation at 3000 rpm for 15 minutes within 2 hours after sample collection. All the laboratory tests were completed within 8 hours.

Plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDL-cholesterol), and triglyceride (TG) concentrations were assessed using standard enzymatic methods, and low-density lipoprotein cholesterol (LDL-cholesterol) and very low-density lipoprotein cholesterol (VLDL-cholesterol) were calculated by the Friedewald equation. Hemoglobin A_{1c} (HbA$_{1c}$) was assayed using high-performance liquid chromatography.

Kidney function was estimated by serum creatinine (Cr) and cystatin C. All assays were performed in frozen serum specimens that were stored at –70°C. Serum Cr was analyzed using Jaffe method and was traceable to the international standardization with isotope dilution mass spectrometry. Serum cystatin C was assessed by immunoturbidimetric assay (inter-assay and intra-assay coefficients of variation were <3.6% and <2.7%, respectively).

We estimated GFR with the use of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine-cystatin C equation to determine eGFRcr_cys (eGFR = 135 × min (SCr/κ, 1)α × max (SCr/κ, 1) - 0.601 × min (Scys/0.8, 1) - 0.375 × max (Scys/0.8, 1) - 0.711 × 0.995Age × 0.969 [if female]) (13). Urinary albumin creatinine ratio (UACR) was determined from urinary creatinine and albumin measurements from spot midstream urine.

Serum total IGF-1 and IGFBP-3 levels were measured using immunoradiometric assay (IRMA) (Beckman Coulter, Czech Republic s.r.o.). Accurate evaluation of serum levels of IGF-1 and IGFBP-3 was performed in one assay. The sensitivity of IGF-1 assay was 5.0 ng/mL, intra-assay CV was 8.6%, and the inter-assay CV was 10.2%. The sensitivities of IGFBP-3 assay, the intra-assay CV and the inter-assay CV were 1 ng/mL, 1.1%, and 1.8%, respectively.

Ethical issues
Human rights were respected in accordance with the Helsinki Declaration 1975, as revised in 1983. Informed consent was obtained from all patients to conduct this study. The ethical committee of The Republican Research Centre for Radiation Medicine and Human Ecology (Registration Number 134 M 6542) approved this study. This study was supported by the Belarusian Foundation

for Basic Research (research project # M17PM-113; 01.06.2017) and Russian Foundation for Basic Research (Research project #17-54-04080). The informed consent was also obtained from the patients for the publication of this investigation.

Statistical analysis

Data are presented as mean ± standard deviation or median (25th–75th percentile) where appropriate. Spearman rank correlation analysis was performed to evaluate associations of IGF-1 and IGFBP-3 with other existing parameters. For bivariate comparisons the Kruskal-Wallis test was used. Analysis of variance (ANOVA) with adjustment for age and HbA1c was performed to assess the associations between serum IGF-1 or IGFBP-3 and eGFRcr_cys. Multivariate linear regression analysis was also performed to evaluate IGF-1 or IGFBP-3 as potential independent predictors of CKD. P value <0.05 was considered statistically significant. Statistical processing of the obtained data was performed using smStata v 14.2 software (StataCorp, Texas, USA).

Results

Characteristics of the study participants are shown in Table 1. Mean age of patients with diabetes was 59.84 ± 14.03 years, duration of diabetes was 12.88 ± 7.61 years, and HbA1c was 7.82 ± 1.69%. Mean creatinine, cystatin C, eGFRcr_cys, UACR were 87.82 ± 56.93 umol/l, 0.94 ± 0.54 mg/L, 76.78 ± 25.41 ml/min/1.73m^2 and 7.83 ± 12.50 mg/g, respectively. There were significant differences in age, HbA1c, systolic and diastolic blood pressure (BP), triglycerides, VLDL-cholesterol, HDL-

cholesterol levels, creatinine, cystatin C, eGFRcr_cys and UACR between the main and the control groups. Patients with diabetes had a significantly lower level of IGF-1 than controls (98.6 (74.1-163.9) ng/mL versus 185.1 (133-287) ng/mL, $P=0.0127$, respectively). However, IGFBP-3 levels were similar in the two groups (2438 (1639-3004) ng/mL versus 2511 (1008-3099) ng/mL, $P=0.999$).

According to the results of univariate linear regression analysis, IGF-1 level was significantly correlated with age (r=-0.36, $P=0.006$), cystatin C (r=0.61, $P=0.0005$), serum creatinine (r=0.40, $P=0.03$) and eGFRcr_cys (r=-0.35, $P=0.0042$), since IGFBP-3 had also similar interrelationships with the same variables. Meanwhile, both IGF-1 and IGFBP-3 were not significantly correlated with age, duration of diabetes, BMI, HbA1c, TC, triglycerides, HDL-C, and LDL-C (Table 2).

We divided the patients into two groups according to presence of CKD with GFR reduction (eGFRcr_cys<60 mL/min/1.73 m^2 versus eGFRcr_cys>60 mL/min/1.73 m^2) (Table 3). CKD and non-CKD groups had significant differences when compared on the basis of triglycerides levels, serum creatinine, and cystatin C, eGFRcr_cys and also UACR. Diabetic patients with CKD had significant higher levels of IGF-1 and IGFBP-3 than diabetic patients without CKD (137.1 (85.0-165.1) ng/mL versus 98.00 (75.0-157.5) ng/mL, $P=0.04$, and 2467 (1700-3001) ng/mL versus 2198 (1753-3025) ng/mL, $P=0.0031$, respectively). Multivariate ANOVA revealed inverse associations of serum IGF-1 and IGFBP-3 with eGFR by using different cut-offs for eGFRcr_cys (60, 50, 40 and 30 mL/min/1.73 m^2, respectively) (Figure 1). However, according to multivariate analysis, only IGF-1 and cystatin C were

Table 1. Baseline characteristics of the study subjects

Variables	Diabetes n=102	Control n=68	P
Age, years	56.67 ± 0.81	48.20 ± 8.10	0.006
Duration of diabetes, years	12.88 ± 7.61	-	-
BMI, kg/m^2	34.03 ± 12.08	34.71 ± 13.87	0.761
Total cholesterol, mmol/L	5.36 ± 1.36	5.27 ± 1.91	0.244
LDL-cholesterol, mmol/L	3.14 ± 1.11	3.18 ± 0.99	0.612
HS-CRP, mg/L	4.49 ± 7.68	2.67 ± 1.91	0.441
HbA1c, %	7.82 ± 1.69	5.24 ± 0.90	<0.0001
Systolic BP, mm Hg	142.61 ± 17.76	125.44 ± 17.46	<0.0001
Diastolic BP, mm Hg	85.77 ± 10.39	80.18 ± 10.53	0.005
Triglycerides, mmol/L	2.19 ± 1.46	1.57 ± 1.96	0.020
VLDL-cholesterol, mmol/L	0.99 ± 0.67	0.77 ± 0.88	<0.0001
HDL-cholesterol, mmol/L	1.24 ± 0.37	1.51 ± 0.42	<0.0001
Creatinine, umol/L	87.82 ± 56.93	69.10 ± 14.18	0.0001
Cystatin C, mg/L	0.94 ± 0.54	0.81 ± 0.22	<0.0001
eGFRcr_cys, ml/min/1.73 m^2	76.78 ± 25.41	94.09 ± 25.02	0.0001
UACR, mg/g	7.83 ± 12.50	4.46 ± 6.34	0.030
IGF-1, ng/mL	98.6 (74.1-163.9)	185.1 (133-287)	0.013
IGFBP-3, ng/mL	2438 (1639-3004)	2511 (1008-3099)	0.999

Values are mean ± standard deviation or median (25th–75th percentile).

Table 2. Univariate correlations between IGF-1, IGFBP-3 and other variables

	IGF-1		IGFBP-3	
	r	P	r	P
Age	-0.35	0.006	-0.11	0.06
Duration of diabetes	-0.19	0.15	-0.14	0.16
Body mass index	-0.13	0.33	0.04	0.70
Hemoglobin A$_{1c}$	-0.11	0.41	-0.01	0.99
Total cholesterol	0.02	0.86	-0.05	0.63
Triglycerides	0.11	0.39	0.17	0.08
HDL-cholesterol	-0.03	0.8	-0.14	0.76
VLDL-cholesterol	0.13	0.33	0.21	0.35
Cystatin C	0.61	0.0005	0.44	0.04
Creatinine	0.40	0.03	0.43	0.03
eGFRcr_cys	-0.35	0.0042	-0.46	0.04

associated with renal impairment. In detail, the odds of having eGFR<60 mL/min/1.73 m^2 increased with rising IGF-1 levels (OR 1.025, [CI 1.002-1.048]) (Table 4).

Discussion

In the present study, we found an association between increased serum IGF-1, IGFBP- 3 and decreased eGFR in patients with diabetes. Elevated levels of IGF-1 and IGFBP-3 were associated with decreased GFR in patients with diabetes. The association remained significant only for IGF-1 after adjustment for age, duration of diabetes, HbA1c, hypertension, triglycerides and serum LDL-cholesterol, in the logistic regression model. Our findings confirm the data from the NHANES III study (14) revealing a positive association between serum level of IGF-1 and the risk of CKD.

In contrast to our results, Frystyk et al showed lower free serum IGF-1 and higher serum IGFBP-3 concentrations in patients with CKD as compared to controls (15). At the same time, total IGF-1 concentrations were slightly but not
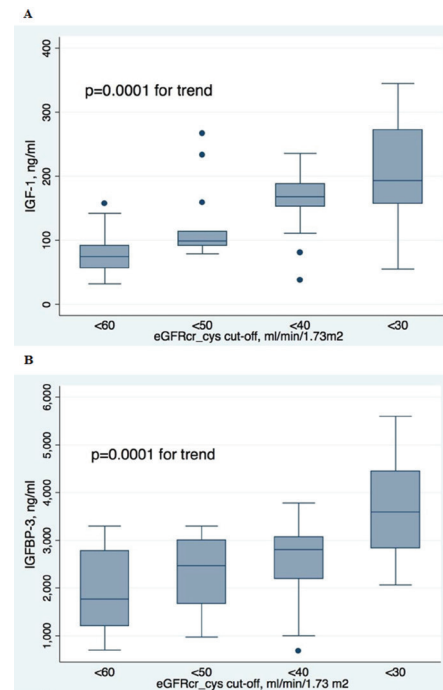

Figure 1. Median IGF-1 (A) and IGFBP-3 (B) levels in diabetic patients by different cut-offs for eGFRcr_cys.

significantly increased in individuals with CKD compared to healthy controls. In another study, hemodialysis patients had significantly higher serum levels of IGF-1 and IGFBP-3 than individuals without CKD (16). Normal serum IGF-1 and elevated serum IGFBP-3 concentrations have been shown in patients with CKD and different types of renal osteodystrophy as compared to healthy control subjects (17).

Previous studies have shown that IGF-1 is associated with cardiovascular disease, hypertension and diabetes, and since these conditions represent major risk factors for CKD, it could be suggested that an increase in serum level

Table 3. Comparison of the clinical characteristics between CKD and non-CKD diabetic patients

Variables	CKD diabetic patients (n=62)	Non-CKD diabetic patients (n=60)	P
Age, years	59.84 ± 9.51	60.04 ± 8.23	0.42
Systolic BP, mm Hg	144.37 ± 19.98	141.65 ± 17.77	0.87
Diastolic BP, mm Hg	86.57 ± 8.34	85.65 ± 14.28	0.68
Hemoglobin A1c, %	7.85 ± 1.53	7.76 ± 1.62	0.95
Total cholesterol, mmol/L	5.27 ± 0.89	5.66 ± 1.59	0.24
Triglycerides, mmol/L	2.09 ± 1.71	2.61 ± 1.59	0.02
LDL-cholesterol, mmol/L	3.11 ± 0.81	3.26 ± 1.35	0.61
Cystatin C, mg/L	0.81 ± 0.22	0.94 ± 0.54	< 0.0001
Creatinine, umol/L	74.18 ± 14.11	130.63 ± 99.42	0.0001
eGFRcr_cys, mL/min/1.73 m^2	85.03 ± 19.07	53.89 ± 25.19	0.0001
UACR, mg/g	1.82 ± 2.49	11.23 ± 15.43	0.03
HS-CRP, mg/L	3.39 ± 1.72	5.93 ± 11.63	0.83
IGF-1, ng/mL	137.1 (85.0-165.1)	98.00 (75.0-157.5)	0.04
IGFBP-3, ng/mL	2467 (1700-3001)	2198 (1753-3025)	0.003

Values are mean ± standard deviation or median (25th–75th percentile).

Table 4. Logistic regression model for the presence of CKD

CKD	OR	95% CI	P
Age	0.978	0.904-1.059	0.586
Duration	0.984	0.881-1.098	0.768
SBP	0.979	0.929-1.032	0.439
IGF-1	1.025	1.002-1.048	0.033
IGFBP-3	0.999	0.998-1.000	0.192
HbA1c	0.599	0.317-1.131	0.114
Cystatin C	1.002	1.000-1.062	0.001
Triglycerides	0.523	0.191-1.435	0.208
LDL-cholesterol	1.677	0.619-4.547	0.309

CI, confidence interval; OR, odds ratio; SBP, systolic blood pressure.

of IGF-1 would be associated with development of CKD and thus might be a predictor of CKD.

It has been shown that both low and high IGF-1 serum concentrations are associated with an increased risk of mortality in the general population (18). In patients with mild or moderate renal impairment, serum IGF-1 concentrations may be elevated due to increased IGF-1 half-life and may become clinically relevant in patients with severe or end-stage CKD. However, we did not measure free IGF-1 which would provide a more accurate view on the association between GH- IGF axis and renal function in patients with diabetes. It could also be argued that there is no more risk on top of diabetes risk and probably IGF-1 is not specific for impaired renal function in patients with diabetes.

Most studies (19-21) evaluating the interconnections between the GH-IGF axis and lipid metabolism included patients with pituitary diseases. In detail, patients with GH deficiency demonstrated higher triglyceride levels, while HDL levels were lower as compared to healthy controls. Interestingly, GH replacement therapy led to an improvement in lipid profile by increasing HDL, as well as decreasing total cholesterol, LDL-cholesterol and triglyceride levels in GH deficient patients (22,23). In contrast to the above data, population-based studies (24, 25) yielded conflicting results regarding the associations of IGF-1 or IGFBP-3 levels with parameters of lipid metabolism. Filipsson Nyström et al (26) found an inverse relationship between IGF-1 and cholesterol levels in 202 individuals. The currently largest population-based study with 3977 subjects showed similar results demonstrating inverse associations between IGF-1 and total or HDL cholesterol, as well as positive relationships of IGFBP-3 levels with HDL-C and triglycerides (27). Thus, a positive association between IGFBP-3 and triglycerides detected in our study is consistent with the results of other studies. However, additional investigations have to be done to further explain the link between IGF-1 axis and triglycerides.

Conclusion

In conclusion, our study revealed that higher serum IGF-1 levels were positively associated with CKD in patients with DM. Thus, the odds of having eGFR<60 mL/min/1.73 m^2 increased with rising IGF-1 levels (OR 1.025, [CI 1.002-1.048]). Our results suggest that IGF-1 might be a predictor of CKD in patients with diabetes. Further studies are necessary to confirm the observed association and to detect the causal relations.

Limitations of the study

Our study had several limitations. First, this study was limited by the relatively small sample size. In addition, a restricted number of variables were analyzed. Inclusion of other potential confounders, such as IGFBP-1, free IGF-1 and IGF-2, could have an impact on the conclusions. Future studies investigating all these parameters together are needed. Furthermore, we did not evaluate new markers of impaired renal function or injury and used a single cystatin C assay. However, it has been shown that the use of serum cystatin C-based GFR is more accurate for early diagnosis of CKD. Additionally, retrieval of data on potential confounders such as concomitant medication and smoking status was not possible. Further studies are needed to clarify the prognostic value of serum IGF-1 level in patients with DM.

Authors' contribution

VKB and EPN searched the data and prepared the draft of the manuscript. EPN, LEK and NAF collected the data and did much of the analysis. TVM made some critical comments on the manuscript. VNV, IYP and TVM conducted the final check, final editing and finalized the paper. All authors read and signed the final manuscript.

Conflicts of interest

All authors declare that they do not have a conflict of interest with the contents of this paper.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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