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Sitagliptin reduces transforming growth factor-β1 and Platelet derived growth factor-BB in regulation of UAER in type 2 diabetic nephropathy stage III patients.

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Abstract

Background: Sitagliptin has been used as oral hypoglycemic agents and widely used for treatment of type 2 diabetes mellitus (T2DM).
Objectives: The study aimed to explore the correlation of transforming growth factor-β1 (TGF-β1) and Platelet derived growth factor-BB (PDGF-BB) in regulation of urinary albumin excretion rate (UAER).
Material and method: 164 patients with type 2 diabetic nephropathy (DN) at stage III admitted in our hospital from June to December 2015 and 160 healthy individuals for physical examination were selected in our study. All patients were treated with metformin before admission and given metformin plus sitagliptin treatment in our hospital. Related clinical parameters, such as, fasting blood glucose (FPG), postprandial blood glucose (PBG), homeostasis model assessment for insulin resistance (HOMA-IR), homeostasis model assessment for insulin secretion index (HOMA-IS), glycosylated hemoglobin (HbA1c), urinary albumin excretion rate (UAER), urinary TGF-β1 and PDGF-BB were measured. Linear regression analysis was carried out among the parameters.
Results: Type 2 DN patients showed poor health status with most parameters significantly higher than in healthy individuals (P<0.01). Sitagliptin application significantly reduced the levels of FPG, PBG, Insulin, HbA1C, HOMA-IR, SBP and TG (P<0.01), and promoted the level of HOMA-IS (P<0.01). Linear regression analysis illustrated that UAER closely correlated with TGF-β1 (r=0.774, P<0.001) and PDGF-BB (r=0.758, P<0.001), which all showed significantly decreased levels after sitagliptin application (P<0.01). TGF-β1 positively correlated with PDGF-BB (r=0.787, P<0.001), as well.
Conclusions: This study provides a preliminary evidence for the management of T2DM. Our findings suggest that sitagliptin may change UAER by regulation of urinary PDGF-BB and TGF-β1 in type 2 DN stage III patients.

Keywords: Sitagliptin, Diabetic nephropathy, Transforming growth factor-β1, Platelet derived growth factor-BB, Urinary albumin excretion rate.

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Introduction

DN is a common complication of T2DM, which has become the leading cause of end-stage renal disease worldwide [1]. Currently, the incidence of T2DM and DN is progressively increasing and more and more patients are experiencing renal disease due to lack of effective treatments [2]. Approximately 40% of all patients with T2DM develop into DN, which accounts for 25 to 42% died of end-stage renal failure [2,3]. Moreover, chronic kidney disease may increase the risk of death and cardiovascular disease [4].

The pathogenesis of DN is multifactorial, including genetic, metabolic (hyperglycemic), and/or hemodynamic factors such as glomerular hypertension and associated renal hypertrophy [2]. Many studies have reported that DN correlated with extracellular matrix (ECM). Excessive accumulation ECM results in renal fibrosis inevitably, which ultimately leads to

end-stage renal failure [5]. ECM proteins were also increased in cultured mesangial cells with high glucose [6]. Transforming growth factor-β1 (TGF–β1) has been reported to be a marker of renal injury applied in DN [7]. TGF–β1 showed a high level in patients with DN, which played a critical role in the renal fibrotic process [5,8]. PDGF-BB with a high express in the kidney plays an important role in the initiation and progression of DN, which has been proved to promote the fibrosis of DN though combining with TGF–β1, as well [9,10]. Moreover, the 24 h urinary albumin excretion rate (UAER) is also an important index of DN, which expresses high in patients with DN. Due to so many progressive factors in patients with type 2 DN, few if any specific treatments based on the mechanisms of disease initiation and progression have been clearly identified.

Due to the defect in insulin resistance and/or insulin secretion, T2DM is often characterized by hypersecretion of glucagon, abnormal gastric emptying, postprandial hyperglycaemia, and, possibly, pancreatic cell dysfunction and the most therapeutic options are incretin-based therapies [11]. Dipeptidyl peptidase IV (DPP-4) inhibitors have been proved to have cytoprotective effects on such organs/tissues, including the heart [12], kidney [13], and retina [14] that are involved in serious T2DM complications. Besides, DPP-4 inhibitors have low risk of hypoglycemia, minimal effects on body weight, and a general lack of gastrointestinal and other side effects, which might preserve and possibly reverse the progressive elimination of pancreatic β-cells and loss of insulin secretory capacity [15]. As one of DPP-4 inhibitors, sitagliptin has been used as an oral hypoglycemic agent widely used for treatment of T2DM [15,16]. Meanwhile, sitagliptin was proved to improve albuminuria and glucose [17]. In this animal model of obese T2DM, sitagliptin prevented β-cell dysfunction and evolution of pancreatic damage, ameliorated the glucose and TGs levels and insulin resistance [18]. However, correlation of TGF-β1 and PDGF-BB in regulation of UAER is inconclusive yet.

We report here the effects of sitagliptin on UAER, TGF-β1, and PDGF-BB and explore possible mechanism as compared with related parameters in DN patients after treated with metformin plus sitagliptin or not for six months.

Materials and Methods

Subjects

164 DN patients at stage III admitted in our hospital were recruited in the study from June to December 2015, who were mean age 60.9 ± 8.49 (41-76) years, diabetes courses 6.01 ± 2.38 years, 47.6% female (78/164). 160 healthy individuals (NGT, normal glucose tolerance) who came to our hospital for routine physical examination were selected as references. Inclusion criteria: 1) All patients are individuals patients with T2DM conformed to China guidelines for T2DM in 2013; 2) All patients are at stage III of DN based on Mogensen standard; 3) Patients have been taking metformin only for more than eight weeks with glycosylated hemoglobin (HbA1c) level of 7% to 10%. Exclusion criteria: 1) Individuals with serious heart disease, severe liver and kidney dysfunction; 2) Individuals with infection, non-diabetic kidney disease and malignant tumors; 3) Individuals who are allergic to sitagliptin. The study was approved by the ethics committee of Sichuan Provincial People's Hospital, performed in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients before enrollment.

Study protocol

Based on the original treatment with metformin (Bristol-Myers Squibb, Shanghai, China, approval number H20090834), all patients were treated with 100 mg sitagliptin (Bristol-Myers Squibb, Shanghai, China) once daily for 6 months. During treatment, patients all kept moderate exercise and balanced diet. Venous blood samples and urinary samples were taken in the morning after an overnight fast for 14h before and after 6-month sitagliptin treatment. Blood samples was centrifuged at 4°C at 5000xg for 10 min. Serum was kept in -70°C refrigerator. The following parameters were measured before and after sitagliptin treatment.

Fasting plasma glucose (FPG) and postprandial 2 hours blood glucose (PBG) were measured by Glucose Assay Kit (Maccura, Chengdu, China). Fasting insulin was measured by chemiluminescence method (Model ARCHITECT i2000 SR, KagamidaNiigata Japan). HbA1c was measured by HPLC (VARIANT II Bio-Rad Laboratories, 4000 Alfred Nobel Drive Hercules, CA). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by Vital Signs monitoring instrument (Model VS-600, Mindray, Shenzhen, China). Lipids were measured using Zhongsheng Beikong Biological Technology Co., LTD., reagents and Abbott Accelerator APS instruments. Triglyceride (TG) was measured by GPO-PAP method. Total cholesterol (TC) was measured by CHOD-PAP method using Triglyceride assay kit (BIOSINO BIO-TEC, Beijing, China). Low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured by direct method of hydrogen peroxide enzyme clearance and surface active agent (BIOSINO BIO-TEC, Beijing, China). Urinary albumin excretion rate (UAER) was measured by immune transmission turbidimetry method using OLYMPUS AU5400 (OLYMPUS, Japan). Urinary TGF-β1 and urinary PDGF-BB were measured using ELISA kit (Senxiong Business company, Shanghai, China). Insulin resistance index (HOMA IR) and Insulin secretion index (HOMA-IS) was calculated as follows:

HOMA-IR = [FPG (mmol/l) × Insulin (uU/ml)] /22.5.]

HOMA-IS = [20 × Insulin (uU/ml)]/[FPG (mmol/l) - 3.5]

Statistical analysis

Statistical analysis was performed using SPSS (version 21.0). Normally distributed data were expressed as means ± standard deviation (SD) and between-group comparisons were analyzed using t test. Non-normally distributed data were expressed as the median and between-group comparisons were analyzed using wilcoxon test. Relative analysis was performed of DN on continuous variables by spearman correlation analysis and

linear regression. A P value, P<0.05 or P<0.01, was considered as statistically significant.

Results

Basic characteristics measurement in selected subjects

To figure out the health status of patients with DN, we analyzed clinical data of all selected subjects including individuals with normal glucose tolerance and DN patients, in the first 24 h of admission (Table 1). As shown, most parameters in patients with DN were significantly higher than healthy individuals (P<0.05), except DBP, LDL-C, HDL-C. Moreover, there were no significant differences among ages, sex in two groups. Our results illustrated that Metformin monotherapy had poor glycemic control in DN patients.

Table 1. *Measurement of basic characteristics in selected subjects.*

	NGT	DN patients
Total number	160	164
Female/Male	76/84	48/86
Age (years)	59.90 ± 8.61	60.9 ± 8.49
Courses	N/A	6.01 ± 2.38
BMI (kg/m^2)	24.48 ± 2.04	26.29 ± 1.89 **
FPG (mmol/L)	5.21 ± 0.51	10.27 ± 1.01 **
PBG (mmol/L)	6.79 ± 0.59	12.82 ± 1.57 **
Insulin (U/ml)	4.95 (1.90~13.20)	15.30 (7.60~19.60) **
HbA1c (%)	5.47 ± 0.32	8.64 ± 0.65 **
HOMA-IR	1.28 (0.46~3.23)	7.20 (2.84~9.50) **
HOMA-IS	68.37 (16.38~288.31)	43.06 (30.45~64.83) *
SBP (mmHg)	138.63 ± 10.46	145.04 ± 9.31 **
DBP (mmHg)	89.75 ± 10.20	92.01 ± 8.12
TC (mmol/L)	4.61 ± 0.36	5.01 ± 0.31 **
TG (mmol/L)	1.65 ± 0.43	2.69 ± 0.44 **
LDL-C (mmol/L)	2.56 ± 0.60	2.67 ± 0.73
HDL-C (mmol/L)	1.27 ± 0.19	1.17 ± 0.39
UAER (mg/24 h)	86.26 ± 24.36	171.54 ± 81.80 **
TGF-β1 (ng/ml)	114.98 ± 31.92	198.75 ± 53.81 **
PDGF-BB (ng/ml)	1216.23 ± 352.57	1872.29 ± 308.74 **

Note: Individuals with normal glucose tolerance (NGT), Diabetic nephropathy (DN), Body Mass Index (BMI), Fasting blood glucose (FPG), Postprandial blood glucose (PBG), Glycosylated hemoglobin (HbA1c), Homeostasis model assessment for insulin resistance (HOMA-IR), Homeostasis model assessment for insulin secretion index (HOMA-IS), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Total cholesterol (TC), Triglyceride (TG), Low-density lipoprotein cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), Urinary albumin excretion rate (UAER), Transforming growth factor-beta1 (TGF-β1), Platelet derived growth factor-BB (PDGF-BB). *P<0.05 *vs.* NGT, **P<0.01 *vs.* NGT.

Table 2. *Comparison of biochemical variables in DN patients before and after sitagliptin application.*

	DN group	
Indexes	Metformin	Sitagliptin
Total number (n)	164	164
BMI (kg/m^2)	26.29 ± 1.89	26.12 ± 1.82
FPG (mmol/l)	10.27 ± 1.01	7.92 ± 0.91 **
PBG (mmol/l)	12.82 ± 1.57	10.26 ± 0.94 **
Insulin (uU/ml)	14.96 ± 2.93	12.32 ± 2.10 **
HbA1c (%)	8.64 ± 0.65	7.86 ± 0.62 **
HOMA-IR	6.90 ± 1.70	4.36 ± 0.98 **
HOMA-IS	44.53 ± 8.44	57.63 ± 13.76 **
SBP (mmHg)	145.04 ± 9.31	139.35 ± 8.47 **
DBP (mmHg)	92.01 ± 8.12	91.43 ± 6.13
TC (mmol/l)	5.01 ± 0.31	4.97 ± 0.35
TG (mmol/l)	2.69 ± 0.44	2.28 ± 0.33 **
LDL-C (mmol/l)	2.67 ± 0.73	2.63 ± 0.67
HDL-C (mmol/l)	1.17 ± 0.39	1.21 ± 0.40
UAER (mg/24 h)	171.54 ± 81.80	89.27 ± 54.16 **
TGF-β1 (ng/ml)	198.75 ± 53.81	150.68 ± 48.55 **
PDGF-BB (ng/ml)	1872.29 ± 308.74	1568.54 ± 223.00 **

Note: Individuals with normal glucose tolerance (NGT), Diabetic nephropathy (DN), Body Mass Index (BMI), Fasting blood glucose (FPG), Postprandial blood glucose (PBG), Glycosylated hemoglobin (HbA1c), Homeostasis model assessment for insulin resistance (HOMA-IR), Homeostasis model assessment for insulin secretion index (HOMA-IS), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Total cholesterol (TC), Triglyceride (TG), Low-density lipoprotein cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), Urinary albumin excretion rate (UAER), Transforming growth factor-beta1 (TGF-β1), Platelet derived growth factor-BB (PDGF-BB). **P<0.01 *vs.* Metformin.

Comparison of biochemical variables in DN patients before and after sitagliptin application

Compared with Metformin treatment, levels of BMI, FPG, PBG, HbA1c, SBP, and TG were all significantly decreased (P<0.01) after sitagliptin treatment for six months (Table 2). Islet function indexes showed different results after sitagliptin treatment, with a significant decrease in HOMA-IR (P<0.01) and a significant increase in HOMA-IS (P<0.01). Sitagliptin addition had no significant effect on DBP, TC, LDL-C and HDL-C (P>0.05). Moreover, pro-sclerotic growth factors, TGF-β1 and PDGF-BB were also significantly decreased in DN patients after sitagliptin application than before treated with only Metformin (P<0.01). After sitagliptin treatment, UAER in DN patients decreased by 48% than treated with only Metformin (P<0.01).

Spearman correlation analysis

As shown in Table 3, spearman correlation analysis among the parameters in DN patients was carried out. Our results showed that UAER had positive correlation with disease courses (r=0.560, P<0.001), FPG (r=0.236, P=0.033), PBG (r=0.431, P<0.001), HbA1c (r=0.552, P<0.001), especially TGF-β1 (r=0.774, P<0.001) and PDGF-BB (r=0.758, P<0.001). Moreover, TGF-β1 showed positive correlation with disease courses (r=0.622, P<0.001), FPG (r=0.271, P=0.014), PBG (r=0.480, P<0.001). PDGF-BB showed positive correlation with disease courses (r=0.502, P<0.001), PBG (r=0.436, P<0.001). A significant correlation existed between TGF-β1 and PDGF-BB (r=0.787, P<0.001), as well.

Table 3. *Spearman correlation analysis among clinical parameters.*

	UAER	Age	Courses	BMI	FPG	PBG	Insulin	TGF-β1	PDGF-BB
UAER	1								
Age	0.05	1							
Courses	0.56**	0.19	1						
BMI	-0.04	-0.08	0.07	1					
FPG	0.24*	0	0.22	0.1	1				
PBG	0.43**	0.13	0.47**	0.13	0.45**	1			
Insulin	0.1	-0.05	0.14	0.38**	0.45**	0.12	1		
TGF-β1	0.77**	0.17	0.62**	0.01	0.27*	0.48**	0.13	1	
PDGF-BB	0.76**	0.18	0.50**	0.08	0.21	0.44**	0.22	0.79**	1
HbA1c	0.55**	0.05	0.43**	0.16	0.55**	0.67**	0.25*	0.68**	0.56**
SBP	-0.12	0	-0.07	0.03	-0.02	0.1	-0.03	-0.1	-0.02
DBP	-0.06	0.05	0	-0.11	0	0.1	-0.04	0.02	0.08
TG	0.06	0.1	-0.04	0.02	-0.03	-0.02	0.09	0.15	0.16
TC	-0.06	0.05	-0.04	-0.02	-0.01	0.08	-0.03	-0.04	-0.02
LDL-C	-0.09	0.15	-0.04	0.06	-0.04	0.07	-0.08	-0.05	-0.04
HDL-C	0.07	0.02	0.05	0.01	0.01	0	0	0.08	0.04

Note: Urinary albumin excretion rate (UAER), Individuals with normal glucose tolerance (NGT), Diabetic nephropathy (DN), Body Mass Index (BMI), Fasting blood glucose (FPG), Postprandial blood glucose (PBG), Glycosylated hemoglobin (HbA1c), Homeostasis model assessment for insulin resistance (HOMA-IR), Homeostasis model assessment for insulin secretion index (HOMA-IS), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Total cholesterol (TC), Triglyceride (TG), Low-density lipoprotein cholesterol (LDL-C), High-density lipoprotein cholesterol (HDL-C), Transforming growth factor-beta 1 (TGF-β1), Platelet derived growth factor-BB (PDGF-BB). **P<0.01 *vs.* Metformin.

Multiple linear regression analysis

To further figure out correlation of TGF-β1, PDGF-BB with other parameters, especially UAER, multiple linear-regression analysis was performed (Table 4). And UAER was used as a dependent variable. As shown, our finding illustrated that TGF-β1, PDGF-BB were independently associated with levels of UAER, respectively. UAER was positively correlated with TGF-β1, PDGF-BB, but was not correlated with age, BMI, FPG, PBG, Insulin, HbA1c, SBP, DBP, TC, TG, HDL-C, and LDL-C.

Table 4. *Multiple linear regression analysis.*

Model	B	t	Sig.	95.0% Confidence Interval for B	
				Lower Bound	Upper Bound
TGF-β1	0.87	5.65	<0.001	0.56	1.17
PDGF-BB	0.08	2.93	0.004	0.03	0.13

Note: Transforming growth factor-beta1 (TGF-β1), Platelet derived growth factor-BB (PDGF-BB).

Discussion

Sitagliptin, an orally administered DPP-4 inhibitor with good glycemic control, could reduce the risk of diabetes-related microvascular complications in the patients with T2DM [19]. Some studies illustrated that sitagliptin could inhibit the degradation and inactivation of the incretins, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), by inhibiting their breakdown [17,20]. GLP-1 and its receptor are also expressed in the glomerulus of the kidney and target the islet, where the hormone stimulates insulin secretion. Studies have shown that GLP-1 directly decreases blood glucose, reduces the glycation end products

level, and down-regulates TGF-β1 levels in mesangial cells [21]. The above may be explained by p38/ERK MAPK, a downstream effector of the TGF-β/Smad signaling pathway, activated by TGF-β1 [22,23]. TGF-β-induced epithelial-to-mesenchymal cell transformation is a key contributor to fibrotic scar formation in DN [24]. Moreover, the efficacy for the management of diabetic kidney is well studied in animal models. Sitagliptin has proved to have protective effects against inflammation and proapoptotic state in the kidney of diabetic rats with decreasing GLP-1 and other cell factors [25]. In rat model of type 1 diabetes, sitagliptin was able to alleviate kidney injury and renal dysfunction via anti-inflammation mechanism [26,27]. In rat model of type 2 diabetes, chronic low-dose sitagliptin could also ameliorate DN by correcting the glycaemic dysmetabolism, hypertriglyceridaemia, inflammation, and hypertension [28,29].

Sitagliptin can prevent progression of DN by reducing the severity of proteinuria and albuminuria in Japanese patients with T2DM [15,17]. Our results showed a significant decrease in TGF-β1 levels than in patients treated with metformin plus sitagliptin, thus illustrating sitagliptin may inhibit renal fibrosis. TGF-β1 significantly correlated with HbA1c, HDL-C and UAER, which illustrated that sitagliptin significantly affected hemodynamic change in patients with type 2 DN. Decreasing HbA1c, HDL-C, UAER and TGF-β1 levels were consistent with decreasing blood glucose. The renoprotective mechanism of sitagliptin may be due to inhibition of TGF-β1 signaling pathway. In addition, albuminuria can be affected by such factors as weight loss [30], blood pressure and blood glucose reduction [31]. HbA1c used to be a biomarker in diabetes, which is helpful for diagnosis of DN [32]. Our findings also showed that sitagliptin improved other blood glucose related indexes, such as BMI, FPG, PBG, HbA1c, SBP and TG, which is consistent with previous studies [15,33].

As we previously described, PDGF-BB expresses higher in patients with DN than normal human and plays a very important role in the initiation and progression of DN [9,10]. PDGF-BB was significantly decreased after treatment with sitagliptin for six months in our study. PDGF induces a variety of cellular responses that may be relevant to the pathology of renal disease, including matrix production, chemotaxis and cell proliferation [9]. As an important factor in histologically early glomerular lesions of DN, PDGF-BB can be the indicator for the early structural change of DN as urinary albumin [10]. The risk of DN in patients with UAER of 20 to 200 μg/min have proved 10 to 20 times higher than that of patients with normal albuminuria [34]. Our results showed a significant correlation between PDGF-BB and UAER, which was consistent with previous study [10]. To be different, PDGF-BB had no significance correlation with triglyceride (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). In addition, a significant correlation existed between TGF-β1 and PDGF-BB ($r=0.787$, $P<0.001$), which both correlated with UAER. TGF–β1 was reported to be a marker of renal injury applied in DN [7], which played a vital role in renal fibrotic process [5,8]. High expressed PDGF-BB combining with TGF–β1 has proved to play an important role in the initiation and progression of DN and promote the fibrosis of DN [9,10]. Overall, it is suggested that PDGF-BB may modulate the level of TGF-β1 or the TGF-β/Smad signaling pathway, thus regulating levels of UAER. Further study is needed to explore correlation between PDGF-BB and TGF-β1.

In addition, sample size in the present study was relatively small. Indexes such as glycated albumin and urinary albumin-to-creatinine ratio reflecting kidney function in DN patients were not measured. The study did not evaluate a warm that continued only on metformin therapy. Further studies are necessary to precisely identify specific organs like pancreas, kidney for TGF-β1 and PDGF levels. In addition, the subjects mainly focus on type 2 DN stage III patients with sitagliptin medication of 6-month. A cohort study with different populations and long-term follow-up must be taken into consideration to explore the latent mechanism. In conclusion, the present study provided a preliminary evidence that sitagliptin may prevent progression of DN by decreasing TGF-β1 and PDGF-BB in regulation of UAER. Coupling metformin with sitagliptin was able to ameliorate DN, which represented a key step forward in the management of T2DM and this serious complication.

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