Renoprotection Provided by Dipeptidyl Peptidase-4 Inhibitors in Combination with Angiotensin Receptor Blockers in Patients with Type 2 Diabetic Nephropathy

Dan-Dan Qiu[1], Jing Liu[2], Jing-Song Shi[1], Yu An[1], Yong-Chun Ge[1], Min-Lin Zhou[1], Song Jiang[1]

[1]National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, Jiangsu 210002, China
[2]Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, Jiangsu 210002, China

Dan-Dan Qiu and Jing Liu contributed equally to this work.

Abstract

Background: Treatment with the dipeptidyl peptidase-4 inhibitors (DPP4i) and angiotensin receptor blockers (ARBs) in patients with type 2 diabetic nephropathy (DN) has not been well characterized. This study aimed to assess the renoprotection of this combined treatment in DN patients.

Methods: A total of 159 type 2 DN patients from 2013 to 2015 were enrolled retrospectively from a prospective DN cohort at the National Clinical Research Center of Kidney Diseases, Jinling Hospital (China). Fifty-seven patients received DPP4i and ARB treatment, and 102 patients were treated with ARBs alone. All patients were followed up for at least 12 months. Statistical analyses were performed using Stata version 12.0.

Results: There were no significant differences at baseline for age, sex, body mass index, duration of diabetes, fasting blood glucose (FBG), hemoglobin A1c (HbA1c), and estimated glomerular filtration rate (eGFR) between the two groups. Antihypertensive and antidiabetic medication use was similar in each group except calcium channel antagonists ($P = 0.032$). No significant changes in FBG and HbA1c were observed in the two groups after treatment. The eGFR decreased slower in the DPP4i + ARB group than in the ARB group at 12 months (Δ12 months: -2.48 ± 13.86 vs. -6.81 ± 12.52 ml·min^{-1}·1.73m^{-2}, $P = 0.044$). In addition, proteinuria was decreased further in the DPP4i + ARB group than in the ARB group after 24 months of treatment (Δ24 months: -0.18 [-1.00, 0.17] vs. 0.32 [-0.35, 0.88], $P = 0.031$). There were 36 patients with an eGFR decrease of more than 30% over 24 months. After adjusting for FBG, HbA1c, and other risk factors, DPP4i + ARB treatment was still associated with a reduced incidence of an eGFR decrease of 20% or 30%.

Conclusions: The combined treatment of DPP4i and ARBs is superior to ARBs alone, as evidenced by the greater proteinuria reduction and lower eGFR decline. In addition, the renoprotection of DPP4i combined with ARBs was independent of glycemic control.

Key words: Angiotensin Receptor Blockers; Diabetic Nephropathy; Dipeptidyl Peptidase-4 Inhibitors

INTRODUCTION

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease (ESRD) worldwide. However, the treatment options available for these patients are currently limited. The most common treatment for type 2 DN is controlling blood glucose and blood pressure levels and decreasing the hyperfiltration of the glomeruli. Dipeptidyl peptidase 4-inhibitor (DPP4i) could prevent the inactivation of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, thus raising plasma concentrations of the intact, active forms of these peptides and thereby improving islet function by increasing α-cell and β-cell sensitivity to glucose.[1] DPP4i has been used widely for blood glucose control. In

Address for correspondence: Dr. Song Jiang,
National Clinical Research Center of Kidney Diseases, Jinling Hospital,
Nanjing University School of Medicine, Nanjing,
Jiangsu 210002, China
E-Mail: js1120@163.com

patients with type 2 diabetes with normal renal function or renal impairment, DPP4i has been proven to be efficacious as a monotherapy and in combination with many other antidiabetic drugs for controlling serum glucose levels.[2] In addition, there is a series of studies demonstrating that DPP4i could reduce proteinuria levels while not impairing renal function in patients with type 2 DN, and these treatment effects were independent of glycemic control.[3-6] These findings indicated that DPP4i may be a potential novel drug class for treating type 2 DN.

However, treatment with DPP4i combined with angiotensin receptor blockers (ARBs) in type 2 DN patients has not been well characterized. Is the efficacy of combined treatment with DPP4i and ARBs superior to ARB treatment alone? Accordingly, this study aimed to assess the renoprotective effects of DPP4i combined with ARBs in patients with type 2 DN whose hyperglycemia was not adequately controlled with insulin alone or in combination with oral antidiabetic agents at baseline.

METHODS

Ethical approval

This study was conducted according to the *Declaration of Helsinki* and approved by the Local Ethics Committee of Jinling Hospital (No. 2013KLY-013). Written informed consent was obtained from all recruited participants.

Patients

The patients in our study were selected retrospectively from a prospective DN cohort at the National Clinical Research Center of Kidney Diseases, Jinling Hospital. The study participants were diagnosed with type 2 DN at our center from 2013 to 2015. Based on *Guidelines of NKF-K/DOQI (2007 edition)* and *Expert Consensus on Prevention and Treatment of Diabetic Nephropathy by Chinese Medical Association (2014 edition)*, type 2 DN was diagnosed if the below criteria were met: (1) having the diagnosis of type 2 diabetes, (2) presence of a ratio of urinary albumin to urinary creatinine of at least 30 mg/g for a first morning specimen on two occasions or by a 24-h urinary protein excretion $\geq$500 mg on two consecutive occasions, (3) presence of diabetic retinopathy but absence of any clinical or laboratory evidence of other kidney or renal tract diseases. In addition to the diagnosis of type 2 DN, the eligibility criteria in this study also included age $\geq$30 years, estimated glomerular filtration rate (eGFR) $\geq$30 ml·min^{-1}·1.73m^{-2}, hemoglobin A1c (HbA1c) level of 7–9%, and follow-up for at least 12 months. Patients were excluded if they had received a diagnosis of type 1 diabetes or nondiabetic renal disease and had an elevated plasma potassium level ($\geq$5.5 mmol/L). A total of 159 patients with type 2 DN were enrolled at last. Among them, 57 patients received combined treatment of DPP4i and ARB (DPP4i + ARB group), and 102 patients were treated with ARBs alone (ARB group) [Figure 1]. Throughout the study, the patients received their conventional antihypertensive medications (calcium channel antagonists, β-blocking agents, diuretics, α-blocking agents, or angiotensin-converting enzyme inhibitors) and antidiabetic medications (sulfonylureas and glucosidase inhibitors). Individuals in both groups received injections of 70/30 mixed human insulin twice daily, before breakfast and supper.

Intervention

ARB treatment was monotherapy with losartan 100 mg/d or valsartan 80 mg/d; DPP4i combined with ARB treatment was sitagliptin (100 mg daily) or saxagliptin (5 mg daily) or vildagliptin (50 mg twice a day) in addition to the ARB treatment. For patients with moderate chronic kidney disease (CKD), DPP4i doses were reduced to half of the daily dose for patients with reserved renal function. During the follow-up, the serum potassium level, blood glucose level, and eGFR were closely monitored, and the dosages of the medications were adjusted appropriately.

Data collection and follow-up

Baseline clinical characteristics were collected, including age, duration of diabetes at the time of admission, sex, systolic blood pressure (SBP), diastolic blood pressure (DBP), weight, height, fasting blood glucose (FBG), HbA1c, 24-h urinary protein, serum creatinine (Scr), cholesterol, low-density lipoprotein-cholesterol (LDL-C), and triglyceride (TG) levels. All biochemistry measurements were performed by the Nanjing Jinling Hospital Biochemistry Laboratory. All patients were followed up for at least 12 months. Among them, 116 patients were followed up for 24 months: 45 patients in the DPP4i + ARB group and 71 patients in the ARB group. Relevant clinical and laboratory data during follow-up were also collected. The eGFR was calculated using the CKD-EPI creatinine equation (2009).[7] The primary outcomes included eGFR decreases of $\geq$20% and 30%.
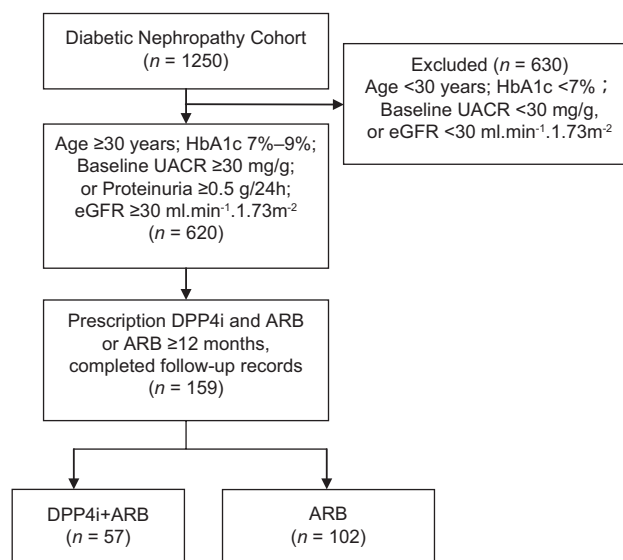

Figure 1: Flowchart for the selection of 159 patients with type 2 diabetic nephropathy.

Statistical analysis

The data are expressed as the mean ± standard deviation (SD), with the exception of skewed data, which are expressed as median (25th and 75th percentiles). After testing for data normality (Shapiro–Wilk), baseline comparisons between the DPP4i and ARB or ARB alone groups were evaluated using an unpaired Student's t-test for normal distribution data and Mann–Whitney U-test for skewed data. The Chi-square analysis or Fisher's exact test was also performed for categorical data. For repeated measurement data, random-effects generalized least squares (GLS) regression was performed to analyze the differences in baseline data and changes from baseline to the end of treatment between two groups. The mean change from the baseline (Δchange) was calculated as follows: Δchange = final result − baseline value. The incidence rate of a 20% or 30% decrease in eGFR was assessed using Kaplan–Meier analysis, with the significance based on the log-rank test. The hazard ratio (HR) and 95% confidence intervals (CIs) were calculated for risk factors in a Cox regression analysis by LR forward. Cox regression models were used to analyze the association of DPP4i use with the incidence of a 20% or 30% decrease in eGFR. A value of $P < 0.05$ was considered statistically significant. Stata/SE software version 12.0 (StataCorp, College Station, Texas, USA) was utilized for all analyses.

RESULTS

Baseline parameters

Participants in this study were on average 58.8 ± 11.4 years of age; there were no significant differences at baseline for age, sex, body mass index (BMI), or duration of diabetes. Antihypertensive and antidiabetic medication uses were similar in each group except calcium channel antagonists ($\chi^2 = 4.604$, $P = 0.032$) [Table 1]. No notable differences were found between the two groups for FBG, HbA1c, SBP, DBP, TG, LDL-C, Scr, and eGFR levels.

Glucose and lipid metabolism control

All patients were followed up for at least 12 months. Changes in relative clinical parameters at 12 and 24 months after baseline were evaluated in the two groups. There were no significant differences in FBG, HbA1c, cholesterol, and LDL-C levels before and after treatment between the DPP4i + ARB and ARB alone groups [Table 2 and Figure 2].

Changes in proteinuria and renal function

Baseline and changes in 24-h proteinuria and eGFR were also assessed throughout the follow-up period [Table 2]. Proteinuria was decreased more in the DPP4i + ARB group after 24 months of treatment compared with that in ARB group (Δ24 months: −0.18 [−1.00,

Table 1: Baseline characteristics in the DPP4i + ARB and ARB alone groups

Characteristics	Total (n = 159)	DPP4i + ARBs (n = 57)	ARBs (n = 102)	Statistics	P
Follow-up (months)	18 (12, 20)	18 (13, 21.5)	18 (12, 20)	−1.697*	0.090
Age (years)	58.79 ± 11.42	58.85 ± 10.84	58.76 ± 11.79	−0.049†	0.961
Sex (female/male)	54/105	17/40	37/65	0.678‡	0.410
BMI (kg/m²)	25.08 ± 1.11	25.17 ± 1.08	25.03 ± 1.12	−0.764†	0.446
T2DM duration (months)	80 (34, 140)	80 (35, 144)	78 (30, 136)	−0.775*	0.439
FBG (mmol/L)	9.33 ± 3.42	9.43 ± 3.39	9.27 ± 3.46	−0.272†	0.786
HbA1c (%)	8.04 ± 1.18	8.15 ± 1.22	7.98 ± 1.16	−0.838†	0.403
SBP (mmHg)	138.84 ± 10.99	137.51 ± 11.49	139.59 ± 10.68	1.145†	0.254
DBP (mmHg)	80.84 ± 11.85	81.89 ± 13.00	80.25 ± 11.18	−0.836†	0.405
LDL-C (mmol/L)	3.79 ± 1.67	3.74 ± 1.32	3.82 ± 1.84	0.271†	0.786
TG (mmol/L)	5.86 ± 1.55	5.74 ± 1.32	5.93 ± 1.67	0.743†	0.458
Scr (mg/dl)	1.30 ± 0.57	1.30 ± 0.59	1.32 ± 0.57	0.193†	0.847
Proteinuria (g/24 h)	1.20 (0.59, 2.97)	1.28 (0.66, 2.34)	1.16 (0.53, 3.30)	−0.406*	0.685
eGFR (ml·min⁻¹·1.73m⁻²)	64.12 ± 26.32	65.49 ± 26.17	63.35 ± 26.49	−0.489†	0.625
Conventional antihypertensive medications, n (%)					
Calcium channel antagonists	74 (46.5)	33 (57.9)	41 (40.2)	4.604‡	0.032
ACEi	16 (10.1)	6 (10.5)	10 (9.8)	0.021‡	0.885
α-blockers	11 (6.9)	3 (5.3)	8 (7.8)	0.376‡	0.540
β-blockers	19 (11.9)	7 (12.2)	12 (11.8)	0.009‡	0.923
Diuretics	31 (19.5)	11 (19.3)	20 (19.6)	0.002‡	0.962
Lipid-lowering drugs, n (%)	28 (17.6)	9 (15.8)	19 (18.6)	0.203‡	0.652
Antidiabetic agent					
Sulfonylureas, n (%)	21 (13.2)	7 (12.2)	12 (11.8)	0.009‡	0.923
Glucosidase inhibitor, n (%)	23 (14.5)	7 (12.3)	16 (15.7)	0.343‡	0.558
Dose of insulin (U/d)	22 (12, 36)	24 (14, 36)	22 (12, 34)	−0.136‡	0.260

Values were shown as mean ± SD, medians (25th, 75th) or n (%). *Mann–Whitney U-test; †t-test; ‡Chi-square test. DPP4i: Dipeptidyl peptidase-4 inhibitor; ARBs: Angiotensin receptor blockers; BMI: Body mass index; T2DM: Type 2 diabetes mellitus; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-C: Low-density lipoprotein-cholesterol; TG: Triglyceride; Scr: Serum creatinine; eGFR: Estimated glomerular filtration rate; ACEi: Angiotensin-converting enzyme inhibitors; SD: Standard deviation.

Table 2: Comparison of FBG, HbA1c, proteinuria, and eGFR between the two groups before and after treatment

Variables	DPP4i + ARBs (n = 57/45) (12/24 months)	ARBs (n = 102/71) (12/24 months)	Statistics*	P
FBG (mmol/L)				
Baseline	9.42 ± 3.40	9.27 ± 3.47	0.152	0.696
12 months	7.72 ± 1.52	8.33 ± 2.90	1.703	0.192
24 months	7.25 ± 1.19	8.04 ± 2.48	1.853	0.173
Δ12 months	−1.70 ± 3.60	−0.88 ± 3.65	2.124	0.145
Δ24 months	−2.22 ± 2.88	−2.05 ± 4.19	2.281	0.131
HbA1c (%)				
Baseline	8.15 ± 1.23	7.98 ± 1.16	0.867	0.352
12 months	7.40 ± 0.96	7.45 ± 1.18	0.075	0.784
24 months	7.00 ± 0.55	7.19 ± 0.96	0.754	0.385
Δ12 months	−0.74 ± 1.32	−0.53 ± 1.04	1.535	0.215
Δ24 months	−1.20 ± 1.22	−0.79 ± 1.10	3.077	0.079
eGFR (ml·min^{-1}·1.73m^{-2})				
Baseline	65.49 ± 26.17	63.35 ± 26.49	0.224	0.636
12 months	63.01 ± 24.57	56.54 ± 28.47	2.049	0.152
24 months	57.42 ± 26.02	53.38 ± 31.14	1.274	0.259
Δ12 months	−2.48 ± 13.86	−6.81 ± 12.52	4.060	0.044
Δ24 months	−6.95 ± 13.74	−11.12 ± 15.33	1.677	0.195
Proteinuria (g/24 h)				
Baseline	1.28 (0.66, 2.34)	1.16 (0.53, 3.30)	1.589	0.690
12 months	0.96 (0.57, 1.56)	1.07 (0.58, 2.24)	2.332	0.127
24 months	1.02 (0.52, 2.21)	1.52 (0.86, 2.32)	3.938	0.047
Δ12 months	−0.34 (−1.19, −0.09)	0.03 (−0.68, 0.24)	2.536	0.111
Δ24 months	−0.18 (−1.00, 0.17)	0.32 (−0.35, 0.88)	4.658	0.031

Values were presented as mean ± SD or medians (25th, 75th). *Random-effects GLS regression; Δ12 months: Value at 12 months–value at baseline; Δ24 months: Value at 24 months–value at baseline. DPP4i: Dipeptidyl peptidase-4 inhibitor; ARBs: Angiotensin receptor blockers; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; eGFR: Estimated glomerular filtration rate; SD: Standard deviation; GLS: Generalized least squares.
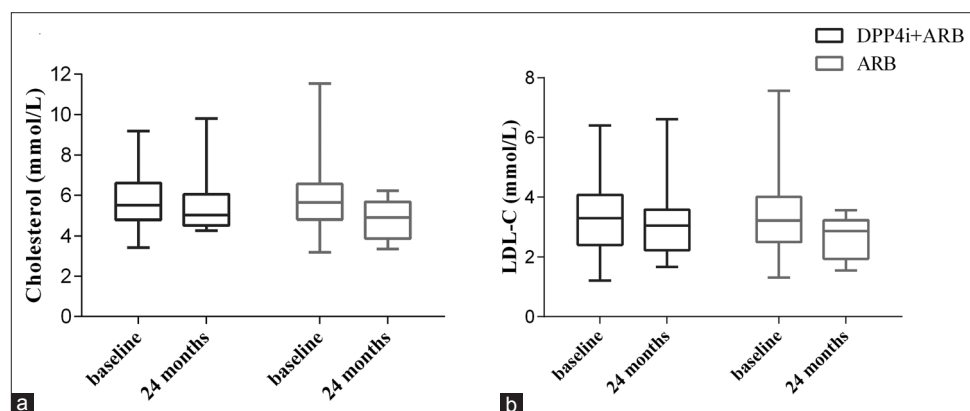

Figure 2: Comparison of cholesterol and LDL-C levels between the two groups before and after treatment. There are no significant differences in cholesterol (a) and LDL-C (b) levels at baseline and after 24 months of treatment between the two groups. LDL-C: Low-density lipoprotein cholesterol.

0.17] vs. 0.32 [−0.35, 0.88], χ^2 = 4.658, P = 0.031). Notably, the eGFR decreased more sharply in the ARB group than in the DPP4i + ARB group at 12 months (Δ12 months: −6.81 ± 12.52 vs. −2.48 ± 13.86 ml·min^{-1}·1.73m^{-2}, χ^2 = 4.060, P = 0.044). However, this change disappeared at 24 months (Δ24 months: −11.12 ± 15.33 vs. −6.95 ± 13.74 ml·min^{-1}·1.73m^{-2}, χ^2 = 1.677, P = 0.195).

Risk for incidence of a 20% or 30% decrease in estimated glomerular filtration rate

To further explore the effects of DPP4i on renal function, the incidence rates for a 20% and 30% decrease in eGFR were observed. The cumulative incidence rates for 20% (log-rank χ^2 = 8.519, P = 0.004) and 30% (log-rank χ^2 = 5.432, P = 0.019) decreases in eGFR were significantly higher in the ARB group than in the DPP4i + ARB group [Figure 3]. During the 24-month follow-up period, there were 51 cases with an eGFR decrease of more than 20% (DPP4i + ARB group vs. ARB group = 11 [24.4%] vs. 40 [56.3%], χ^2 = 11.372, P = 0.001). There were 36 cases with an eGFR decrease of more than 30% (DPP4i + ARB group vs. ARB group = 8 (17.8%) vs. 28 (39.4%), χ^2 = 6.037, P = 0.014). These results indicated that DPP4i and ARB use was significantly associated with

a reduced incidence of an eGFR decrease of 20% or 30% over 24 months.

Univariable Cox regression analysis (model 1) showed that DPP4i and ARB use was significantly associated with a reduced incidence of an eGFR decrease of 20% ($HR = 0.40$, 95% CI [0.20–0.79], $P = 0.008$). To rule out the potential confounders that affect DPP4i and ARB efficacy in this study, multivariable Cox regression analysis was employed. After adjusting for demographic characteristics, including age and sex (model 2), the HR was 0.39 (95% CI [0.20–0.77], $P = 0.007$). After adjusting for diabetes-related confounders, including FBG, HbA1c, BMI, and the duration of type 2 diabetes mellitus (T2DM) on the basis of model 2 (model 3), the HR was 0.42 (95% CI [0.21–0.81], $P = 0.011$). DPP4i + ARB treatment was still associated with a reduced incidence of an eGFR decrease of 20% after adjusting for blood pressure and renal function ($HR = 0.42$, 95% CI [0.22–0.83], $P = 0.012$) (model 4). The association of DPP4i + ARBs with a reduced incidence of an eGFR decrease of 30% was similar to that for an eGFR decrease of 20% [Table 3]. These results indicated that a DPP4i in

Figure 3: The cumulative incidences of a 20% or 30% decrease in eGFR in the two groups. (a) The cumulative incidence rate of a 20% decrease in eGFR in the ARB alone group was significantly higher than that in the DPP4i + ARB group (log-rank $\chi^2 = 8.518$, $P = 0.004$). (b) The cumulative incidence rate of a 30% decrease in eGFR in the ARB alone group was also significantly higher than that in the DPP4i + ARB group (log-rank $\chi^2 = 5.431$, $P = 0.019$). eGFR: Estimated glomerular filtration rate; ARBs: Angiotensin receptor blockers; DPP4i: Dipeptidyl peptidase-4 inhibitor.

combination with an ARB had better renoprotective effects than ARBs alone, independent of age, sex, hyperglycemia, blood pressure, and renal function, in patients with type 2 DN.

Follow-up blood pressures and dosages of insulin used

The insulin dosages slightly decreased for all groups, but no significant difference was found between the DPP4i + ARB group and the ARB group. Furthermore, hypoglycemia and hyperkalemia did not occur in both groups. The SBPs were controlled below 140 mmHg, and the diastolic pressures were stable at about 85 mmHg. No differences in blood pressures were observed between the two groups. No patients presented serious adverse events. The incidence of an increase in any liver function test above the upper limit of normal was not different between the two groups. Hemoglobin levels in the patients remained stable, and no ESRD (eGFR <15 ml·min^{-1}·1.73m^{-2} or needed dialysis) or deaths occurred during the study period.

DISCUSSION

The main findings of this study of a DN cohort were that compared with ARB treatment alone, DPP4i combined with ARBs markedly decreased proteinuria levels and attenuated renal function decline, and the renoprotective effect of the combined therapy was independent of glycemic control.

DPP4i have already become first-line drugs for controlling blood glucose levels in patients with T2DM. The efficacy and safety of DPP4i for glycemic control in diabetes mellitus patients with renal impairment have been well established in the past decade. A series of studies has indicated that DPP4i is a suitable treatment option for patients with advanced type 2 diabetes and impaired renal function who require insulin therapy and present a
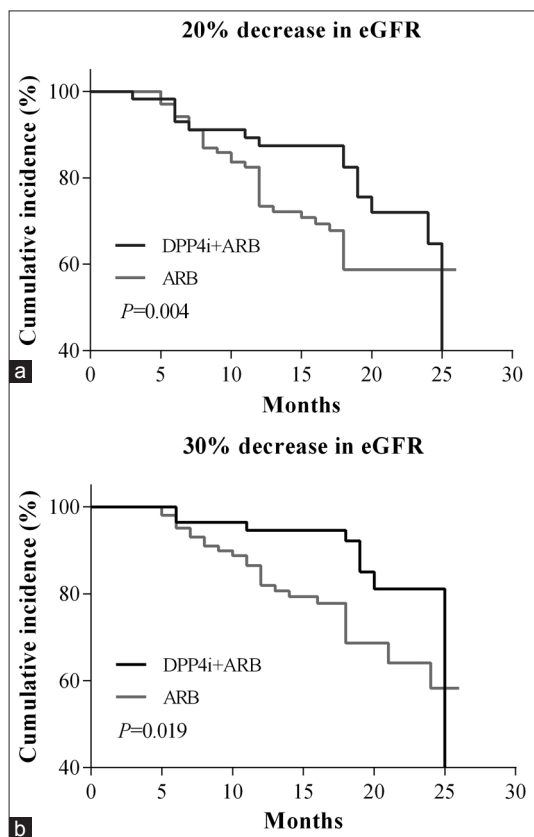
Table 3: Cox regression analysis for eGFR decline according to the baseline variables of the two groups

Variables	ARBs (n = 71)	DPP4i + ARBs (n = 45)	P
		HR, 95% *CI*	
20% decrease in eGFR			
Model 1	Reference 1	0.40 (0.20–0.79)	0.008
Model 2	1	0.39 (0.20–0.77)	0.007
Model 3	1	0.42 (0.21–0.81)	0.011
Model 4	1	0.42 (0.22–0.83)	0.012
30% decrease in eGFR			
Model 1	Reference 1	0.42 (0.19–0.92)	0.029
Model 2	1	0.39 (0.18–0.86)	0.020
Model 3	1	0.41 (0.20–0.92)	0.030
Model 4	1	0.43 (0.19–0.95)	0.038

Model 1: No adjustments; Model 2: Model 1 + age and sex; Model 3: Model 2 + baseline FBG, HbA1c, BMI, and the duration of T2DM; Model 4: Model 3 + baseline Scr, eGFR, and blood pressure. ARBs: Angiotensin receptor blockers; DPP4i: Dipeptidyl peptidase-4 inhibitor; eGFR: Estimated glomerular filtration rate; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; BMI: Body mass index; T2DM: Type 2 diabetes; Scr: Serum creatinine; *CI*: Confidence interval; *HR*: Hazard ratio.

serious therapeutic challenge in clinical practice. Ferreira et al.[8] conducted a 1-year, randomized, double-blind, parallel-arm study and demonstrated that treatment with sitagliptin or glipizide monotherapy was effective and well tolerated in patients with type 2 diabetes and ESRD who were receiving dialysis. Lukashevich et al.[9] employed a 24-week randomized controlled trial (RCT) study, to compare the efficacy and safety of vildagliptin versus placebo in patients with type 2 diabetes and moderate or severe renal impairment. The results showed that 50 mg vildagliptin once daily was efficacious, eliciting HbA1c reductions. These short-term clinical studies demonstrated that DPP4i had better glycemic control efficacy than a placebo, and the tolerance was good.

In addition to the good tolerance and hyperglycemic control, some studies also observed reduced levels of proteinuria or microalbuminuria after DPP4i treatment in patients with type 2 DN. Hattori[3] investigated the inhibitory effect of sitagliptin (50 mg daily) on albuminuria in 36 patients with type 2 diabetes whose HbA1c was higher than 6.5%. After 6 months of treatment, the mean urinary albumin-to-creatinine ratio (UACR) decreased 702 mg in the macroalbuminuria patients. In addition, another small sample pilot study[4] showed that vildagliptin 50 mg bid for 8 weeks significantly decreased the UACR by 44.6%. Mosenzon et al.[6] also reported that saxagliptin (5 mg or 2.5 mg daily) could improve the UACR independent of glycemic control in 16,492 patients with type 2 diabetes, even for those in the normoalbuminuric range. All of these findings suggested that DPP4i may be a potential novel drug for treating type 2 DN.

Most of the studies have compared DPP4i with a placebo; the efficacy of combined treatment with DPP4i and ARBs has not been well characterized. In a previous study,[5] the ability of linagliptin (5 mg/d) to lower albuminuria in addition to inhibiting the renin–angiotensin–aldosterone system (RAAS) in humans was analyzed by pooling data from four similarly designed, 24-week, randomized, double-blind, placebo-controlled, Phase III trials.[10-13] The results showed that the UACR at week 24 was reduced by 32% in the patients treated with linagliptin and RAAS inhibition, compared with 6% treated with placebo and RAAS inhibition. Similarly, our study indicated that the decrease in proteinuria levels at 24 months in the DPP4i + ARB group was higher than that in ARB group. The results demonstrated that compared with the ARB treatment alone, the combined treatment had a better efficacy for attenuating proteinuria in type 2 DN patients.

Although several studies reported that DPP4i had albuminuria-lowering effects in patients with type 2 DN, there are few studies assessing the effect of DPP4i on renal function due to the short-term follow-up. To assess the renoprotective effect of the combined therapy, we estimated the eGFR decline over 2 years. We observed that the eGFR declined slower in the DPP4i + ARB group than in the ARB group at 12 months. During the 24-month follow-up, the percentages of a 20% or 30% decrease in eGFR in the

DPP4i + ARB group were lower than those in the ARB alone group. In a multivariate Cox regression analysis, the DPP4i + ARB treatment was still associated with a reduced incidence of an eGFR decrease of 20% or 30% after adjusting for baseline FBG, HbA1c, blood pressure, BMI, eGFR, Scr, and the duration of T2DM. The results demonstrated that the long-term renal outcome of the DN patients was significantly improved in the DPP4i and ARB treatment group, compared with that in the ARB treatment alone group.

DPP4 is a highly conserved peptidase with high selectivity for dipeptides with a proline or alanine at the second NH2-terminal position, thus altering their biological activities.[14] DPP4 is highly expressed on epithelial cells, such as renal proximal tubules, as well as endothelial cells. Furthermore, DPP4 interacts with extracellular matrix components, such as fibronectin and collagen.[15] High DPP4 expression in the kidney also has been documented in DN.[16,17] However, the exact molecular mechanisms through which DPP4i reduces proteinuria and improves renal function in type 2 DN are not fully clear.

Some studies have indicated that the renoprotective effects of DPP4i might be associated with the attenuation of kidney fibrosis and podocyte injury. Kanasaki et al.[18] found that linagliptin-treated diabetic CD-1 mice exhibited microRNA 29s restoration and kidney fibrosis amelioration associated with endothelial-to-mesenchymal transition inhibition. Shi et al.[19] showed that linagliptin could also inhibit the interaction of DPP4 and integrin-β1 in endothelial cells to alleviate renal fibrosis in the same mouse model. DPP4i could also attenuate podocyte injury. A study proved that gemigliptin, a novel DPP4i, could reduce podocyte apoptosis by suppressing oxidative damage in db/db mice.[20] In 2017, Chang et al.[21] demonstrated that saxagliptin could prevent podocyte epithelial-to-mesenchymal transition through inhibiting SDF-1α cleavage in diabetic rats.

Previous studies indicated that DPP4i played an important role in blood pressure regulation. Animal studies have shown that DPP4i improved endothelium-dependent relaxation in renal arteries, restored renal blood flow, and reduced SBP in spontaneously hypertensive rats by increasing cAMP and eNOS levels.[22] Some clinical data also demonstrate a modest blood pressure reducing effect of DPP4i.[23,24] However, the effects of DPP4i on blood pressure remain controversial. It has been reported that DPP4i might sustain NPY (1–36) capacity, which is released by sympathetic renal fibers and is an agonist of the Y1 receptor, to increase the hypertensive response to angiotensin II.[25,26] ARB use in combined treatment might inhibit the effect of DPP4i on increasing blood pressure. In our study, blood pressure was not significantly different between the two groups during the follow-up, may be due to the relatively lower baseline blood pressures and the use of other antihypertensive drugs.

In addition, several studies showed that DPP4i had anti-inflammatory and antioxidative stress effects. DPP4i could induce a significant reduction in CD40, ICAM-1,

MCP-1, and tumor necrosis factor-α to inhibit the inflammatory response.[27] Furthermore, sitagliptin was proven to ameliorate renal oxidative stress by activating the miR-200a/Keap-1/Nrf2 antioxidant pathway in diabetic GK rats.[28] These effects of DPP4i might provide additional benefits for patients with type 2 DN. However, the abovementioned studies were limited to animal models and need further confirmation in clinical studies.

The strengths of our study include that we utilized a 24-month long cohort and observed eGFR decline over 2 years, which allowed us to evaluate the effects of DPP4i on the renal outcome. In addition, we employed a multivariate Cox regression analysis and adjusted for a variety of confounders that might affect the evaluation of the association between DPP4i treatment and renoprotection. We confirmed that DPP4i treatment could have added benefits in type 2 DN patients beyond glycemic control.

There were several limitations in our study. First, the patients were selected from a single-center cohort study. Although we used a Cox regression to adjust for the confounders that might affect the estimation of the efficacy of the treatment, the influence of confounders might not be completely eliminated. Second, DPP4i and ARB treatment in this study included several different drugs and it was hard to determine which drugs might have the greatest influence on these results. Finally, this study was conducted in a Chinese Han population, and the results may not be extended to other races. Therefore, we still need a large sample RCT study that enrolls different race patients to further confirm the benefits of combined DPP4i and ARB treatment for patients with type 2 DN.

In conclusion, combined DPP4i and ARB treatment is superior to ARB treatment alone, as evidenced by the higher reduction in proteinuria and lower eGFR decline over 2 years. In addition, the renoprotective effects of a DPP4i combined with ARBs were independent of glycemic control. The effect of this combined treatment on the risk of ESRD and mortality in type 2 DN patients still needs further RCT studies.

Financial support and sponsorship

Conflicts of interest

There are no conflicts of interest.

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二肽基肽酶4抑制剂联合血管紧张素受体阻断剂治疗2型糖尿病肾病的疗效

摘要

背景： 目前尚无研究报道二肽基肽酶4抑制剂（DPP4i）联合血管紧张素受体阻断剂（ARBs）对2型糖尿病肾病（DN）的治疗效果。本研究旨在分析与单用ARBs相比，DPP4i与ARBs两种药物联用对DN患者是否存在肾脏保护作用。

方法： 回顾性纳入2013年至2015年南京军区南京总医院，国家肾脏疾病临床医学研究中心DN前瞻性队列中159例2型DN患者。其中57例患者接受DPP4i和ARBs联合治疗（DPP4i+ARBs组），102例患者接受ARBs单药治疗（ARBs组）。所有患者至少随访12个月。使用Stata软件（版本12）进行统计学分析。

结果： 两组患者的基线年龄、性别、体质指数、糖尿病病程、空腹血糖（FBG）、糖化血红蛋白（HbA1c）以及估算的肾小球滤过率（eGFR）没有统计学差异。此外，除钙通道拮抗剂外（P=0.032），两组间降压药和降糖药使用情况类似。在治疗12和24个月后，两组中FBG和HbA1c水平无显著差异。在治疗12个月后，DPP4i+ARBs组中eGFR的下降幅度低于ARBs组（Δ12个月：-2.48±13.86 vs. -6.81±12.52 ml/min/1.73 m², P=0.044）。此外，治疗24个月后，DPP4i+ARBs组患者蛋白尿定量水平较ARBs组亦出现明显下降 [Δ24个月：-0.18(-1.00,0.17) vs. 0.32(-0.35,0.88), P=0.031]。在随访过程中有36例患者出现eGFR下降超过30%。校正FBG、HbA1c及其他混杂因素后，DPP4i+ARBs联合治疗仍然与eGFR下降20%或30%降低的风险相关。

结论： 与ARBs单药治疗相比，DPP4i与ARBs联合治疗可以更大程度地降低蛋白尿以及延缓肾功能进展。此外，DPP4i与ARBs联合治疗具有独立于降糖作用的肾脏保护作用。