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Original Article

Clinical observation of ACEI combined with ARB for treatment of diabetic nephropathy in elderly patients

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Abstract: Objective: The aim of the current study was to evaluate the clinical efficacy of angiotensin converting enzyme inhibitor (ACEI) combined with angiotensin receptor blocker (ARB) for treatment of diabetic nephropathy in elderly patients. Methods: A total of 90 elderly patients with diabetic nephropathy were included in this study. They were treated at Tianjin Fifth Center Hospital from August 2016 to March 2018. The patients were randomly divided into three groups, with 30 cases in each group, including the ACEI group, ARB group, and ACEI combined with ARB group. They were given the routine antihypertensive and oral hypoglycemic drug treatment. Patients in the ACEI group received captopril and placebo for 10 weeks. Patients in the ARB group received ARB treatment for 10 weeks. Patients in the ACEI combined with ARB group received combined treatment of the two drugs for 10 weeks. Levels of 24-hour urinary protein, urinary microprotein (including urinary micro albumin, urinary transferrin, urinary β2 microspheres, urine α1 microspheres, and urine immunoglobulin G), serum creatinine (Scr), and blood urea nitrogen (BUN), before and after treatment, were recorded and compared between the three groups. Results: After 10 weeks of treatment, blood pressure, blood sugar, and blood lipid levels of the three groups were controlled in the normal range. Levels of Scr and BUN were lower than those before treatment in the three groups. Differences were statistically different in the ACEI combined with ARB group ($P<0.05$), but not in the ACEI group ($P>0.05$) and ARB group ($P>0.05$). In addition, levels of 24-hour urinary protein and urinary microalbumin in the three groups were significantly lower than those before treatment. Differences were statistically significant ($P<0.05$). Moreover, levels of 24-hour urinary protein and urinary microprotein in the ACEI combined with ARB group were significantly lower than those in the ACEI group and ARB group. Differences were statistically significant ($P<0.05$). There were no significant differences between the ACEI group and ARB group ($P>0.05$). The clinical efficacy of ACEI combined with ARB was 100%, significantly higher than that in the ACEI group (86.7%) and ARB group (83.3%). Differences were significant ($P<0.05$). However, no significant differences were found between the ACEI group and ARB group ($P>0.05$). Conclusion: The clinical efficacy of ACEI combined with ARB for treatment of diabetic nephropathy is better than that of either drug alone, effectively improving renal function and proteinuria in diabetic nephropathy patients.

Keywords: Diabetic nephropathy, elderly patients, angiotensin converting enzyme inhibitors, angiotensin receptor antagonists, clinical efficacy

Introduction

Diabetes mellitus is a common and frequently-occurring disease, prone to vascular, nervous, kidney, and other tissue and organ complications. The number of diabetic patients in China is nearly 100 million, ranking first in the world [1, 2]. It has been estimated that there will be 200 million people in China suffering from diabetes by 2025, seriously threatening human health [3-5].

Diabetic nephropathy (DN) is a serious complication caused by diabetic microangiopathy. Incidence of DN is 20%-40% in diabetic patients. It can involve renal tubules, glomeruli, and interstitium, leading to chronic renal failure [6, 7]. DN has become one of the main causes of disability and death in diabetic patients, especially in middle-aged and elderly patients. In patients with diabetes, incidence of DN has increased year by year. Once DN occurs, the rate and degree of deterioration will be difficult to control. It is more difficult to reverse when entering the stage of massive proteinuria [8].

In clinical practice, early detection, early prevention, accurate application of drugs, and app-

ropriate intervention can delay occurrence of DN lesions, effectively prevent the deterioration of the disease, prevent development of DN proteinuria into diabetic renal failure and uremia, and fundamentally improve the quality of life of DN patients [9, 10]. Previous studies have shown that ACEI or ARB drugs can effectively reduce urinary microproteins in patients with diabetic nephropathy. However, few clinical studies have been conducted concerning the combined use of ACEI and ARB drugs for treatment of diabetic nephropathy, especially in elderly patients [11, 12].

Therefore, the current study focused on evaluation of the clinical efficacy of ACEI combined with ARB for treatment of diabetic nephropathy. Results showed that the combination of ACEI and ARB was more effective than administration of each drug alone.

Materials and methods

Patients enrolled

Inclusion criteria: Patients in accordance with WHO diagnostic criteria for type 2 diabetes in 1999; Patients over 65; DN patients in stage III-IV; Patients with serum creatinine (Scr) continually <265 μmol/L within 3 months; Patients with a history of hypertension; Patients without a history of ACEI or ARB drug use within the first 7 days of admission.

Exclusion criteria: Patients unwilling to cooperate with the treatment and index test; DN patients at stage V; Patients allergic to ACEI and ARB; Patients with primary nephropathy; Patients with secondary glomerular disease caused by hypertensive renal atherosclerosis; Patients with severe heart, liver and hematopoietic system diseases; Patients with neurotic diseases; Patients with ketoacidosis, fevers, heart failure, acute and chronic nephritis, urinary tract infections, and other factors recently affecting urinary protein.

A total of 90 elderly patients diagnosed with diabetic nephropathy were enrolled in this study. They were treated at Tianjin Fifth Center Hospital from August 2016 to March 2018. The patients were randomly divided into three groups, including the ACEI group (30 cases), ARB group (30 cases) and ACEI combined with ARB group (30 cases). Patients in the ACEI group received ACEI treatment. Patients in the ARB group received ARB treatment. Patients in the ACEI combined with ARB group received the two drugs combined. The current study was approved by the Ethics Committee of Tianjin Fifth Center Hospital and all patients provided informed consent.

Treatment

Routine treatment: Patients in all three groups were given routine treatment, including dietary regulation, proper exercise, insulin injections, and oral hypoglycemic drugs to control blood sugar levels. If systolic blood pressure was higher than 130 mmHg or diastolic blood pressure was lower than 80 mmHg, other antihypertensive drugs were added, such as beta-receptor blockers and calcium antagonists. A low salt, low sugar, low phosphorus, and high-quality protein diet was maintained. Blood lipids were controlled. Water, electrolytes, and acid-base imbalances were corrected. Anemia improvements and infection control were maintained.

Based on routine treatment, patients in the ACEI group received captopril and a placebo orally, once a day, at 25 mg/d. This was increased to 100 mg/d after 7 days. In the ARB group, patients received valsartan and a placebo orally, once a day, at 45 mg/d. This was increased to 70 mg/d after 7 days. In the ACEI combined with ARB group, patients received captopril and valsartan, simultaneously, at the same dosage as above. All patients were treated for a total of 10 weeks.

Measurements

Blood pressure, blood sugar, blood lipid, 24-hour urinary protein, urinary microprotein (including urinary microalbumin, urinary transferrin, urinary β2 microglobulin, urinary α1 microglobulin, urinary immunoglobulin G), Scr, and BUN levels were recorded and compared, before and after treatment, in the three groups.

Clinical efficacy was designated at three levels: 1) Marked effectiveness: Conscious symptoms improved or basically disappeared, in accord with one of the following: 24-hour urinary protein and BUN decreased by more than 30% and Scr decreased by more than 30%; 2) Effectiveness: Self-conscious symptoms were

Table 1. General information of the three groups

	ACEI group (n=30)	ARB group (n=30)	ACEI combined with ARB group (n=30)	F/χ^2	P
Gender (Male/Female)	18/12	17/13	15/15	0.630	0.730
Average age (year)	71.9±8.6	70.6±8.3	73.1±8.3	0.810	0.610
Average course of disease (year)	6.6±3.9	7.1±3.6	6.9±3.7	0.791	0.589
BMI (kg/m^2)	26.34±1.91	25.93±1.60	26.12±1.81	0.899	0.710
Scr (μmol/L)	231.31±23.61	229.60±29.13	233.03±28.91	0.810	0.691
DN stage (n)				0.090	0.956
III	16	17	16		
IV	14	13	14		
Complication (n)					
Hyperlipidemia	12	13	12	0.092	0.955
History of medicine (n)					
Oral hypoglycemic drugs	21	19	21	0.407	0.816
Insulin	9	11	9	0.407	0.816
Diuretics	16	13	19	2.411	0.300
Nitrendipine	19	21	18	0.679	0.712
Lipid lowering agents	10	11	9	0.300	0.861

Note: ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; Scr: serum creatinine; DN: diabetic nephropathy.

alleviated, in accord with one of the following: 24-hour urinary protein and BUN decreased by more than 30% and Scr decreased by more than 30%; 3) Ineffectiveness: Conscious symptoms did not improve or were aggravated. Moreover, 24-hour urinary protein, BUN, and Scr did not decrease or increase.

Statistical analysis

SPSS 21.0 was used for data analysis. Measurement data are expressed as (mean ± sd) and one-way ANOVA was used to analyze differences among the three groups. Q-test was used for comparisons between the two groups. Paired t-tests were used to analyze intra-group before-after differences. Counting data are expressed as percentages and χ^2 tests were used for comparisons. $P<0.05$ indicates statistical significance.

Results

General information

As shown in **Table 1**, there were no significant differences in sex, age, body mass index (BMI), course of disease, DN stage, complications, and history of medicine among the three groups ($P>0.05$).

Control of blood sugar, blood pressure, and blood lipid levels in the three groups

All patients in the three groups received routine treatment, including blood sugar, blood pressure, and blood lipid control. After 10 weeks of treatment, blood glucose, blood pressure, and blood lipid levels in the three groups were controlled within the normal range: 1) Fasting blood glucose was maintained around 7.5 mmol/L; 2) Postprandial 2-hour blood glucose <10.5 mmol/L; 3) Blood pressure within 130-110 mmHg and 75-80 mmHg; 4) Cholesterol <5.2 mmol/L; and 5) Triglycerides within 0.4-1.86 mmol/L. As shown in **Table 2**, there were no significant differences between the three groups ($P>0.05$).

Comparison of Scr between three groups before and after treatment

As shown in **Figure 1**, there were no statistical differences in Scr levels between the three groups before treatment ($P>0.05$). After treatment, Scr levels in the three groups were lower than those before treatment. Differences were statistically different in the ACEI combined with ARB group ($P<0.05$), but not in the ACEI group ($P>0.05$) and ARB group ($P>0.05$).

Table 2. Control of blood sugar, blood pressure, and blood lipid levels in the three groups

	ACEI group (n=30)	ARB group (n=30)	ACEI combined with ARB group (n=30)	F	P
Fasting blood glucose (mmol/L)	7.31±0.93	7.13±0.61	7.33±1.31	0.391	0.661
Postprandial 2 h blood glucose (mmol/L)	8.34±1.91	8.90±1.13	8.70±1.61	0.599	0.510
Systolic blood pressure (mmHg)	110.92±16.90	117.64±18.32	119.33±15.14	0.709	0.536
Diastolic blood pressure (mmHg)	78.04±1.21	79.13±1.30	78.61±1.30	0.810	0.399
Cholesterol (mmol/L)	5.10±0.61	4.92±0.34	4.93±0.33	0.740	0.600
Triglyceride (mmol/L)	0.93±0.69	1.06±0.81	1.02±0.91	0.330	0.561

Note: ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

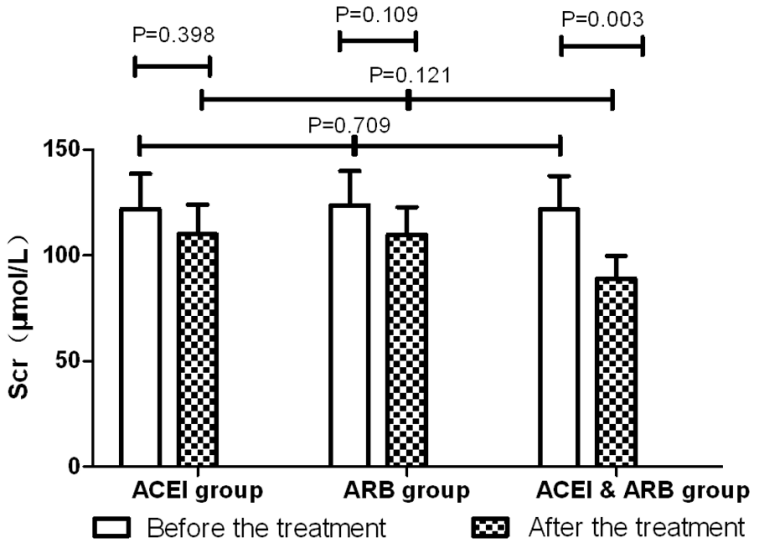

Figure 1. Comparison of Scr between the three groups before and after treatment. Scr: serum creatinine; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

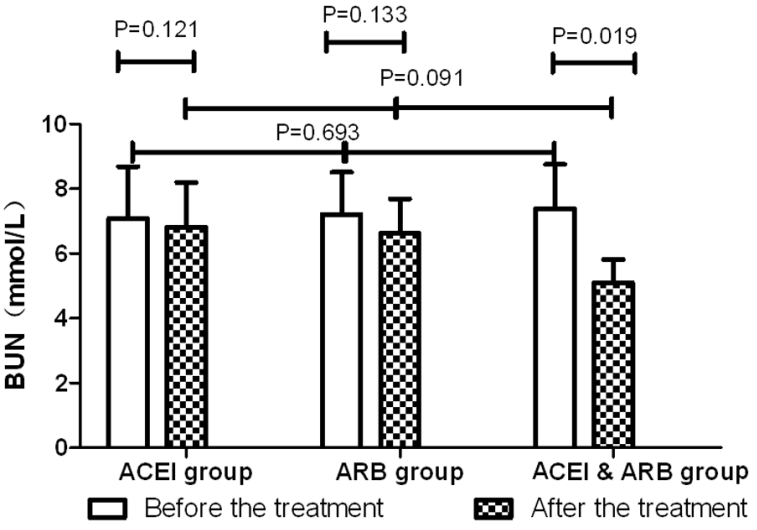

Figure 2. Comparison of BUN between the three groups before and after treatment. BUN: blood urea nitrogen; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Comparison of BUN between the three groups before and after treatment

As shown in **Figure 2**, there were no significant differences in BUN levels between the three groups before treatment (P>0.05). After treatment, BUN levels in the three groups were lower than those before treatment. Differences were statistically different in the ACEI combined with ARB group (P< 0.05), but not in the ACEI group (P>0.05) and ARB group (P> 0.05).

Comparison of urinary protein levels between the three groups before and after treatment

As shown in **Tables 3**-**5**, there were no significant differences in levels of 24-hour urinary protein and urinary microprotein between the three groups before treatment (P>0.05). After treatment, 24-hour urinary protein and urinary microprotein levels in the three groups were significantly lower than those before treatment. Differences were statistically significant (P<0.05). Moreover, 24-hour urinary protein and urinary microprotein levels in the ACEI combined with ARB group were significantly lower than those in the ACEI group or ARB group (P<0.05). There were no signifi-

Table 3. Comparison of 24-hour urinary protein and urinary microprotein between the three groups

	ACEI group (n=30)	ARB group (n=30)	ACEI combined with ARB group (n=30)
24 h urinary protein (g/d)			
Before the treatment	121.93±16.71	123.66±16.31	121.81±15.93
After the treatment	101.06±11.01*,#	103.81±11.06*,#	89.02±10.80*
Urinary microprotein (mg/L)			
Before the treatment	121.91±18.06	119.61±18.33	116.01±17.69
After the treatment	81.66±10.93*,#	82.36±10.91*,#	56.81±6.33*

Note: ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker. *compared with that before the treatment, P<0.05; #compared with ACEI combined with ARB group, P<0.05.

Table 4. Comparison of urinary transferrin and urinary immunoglobulin between the three groups

	ACEI group (n=30)	ARB group (n=30)	ACEI combined with ARB group (n=30)
Urinary transferrin (mg/L)			
Before the treatment	381.91±120.06	371.61±118.33	396.01±121.69
After the treatment	181.66±65.93*,#	202.36±70.91*,#	83.81±41.33*
Urinary immunoglobulin G (mg/L)			
Before the treatment	18.91±2.66	16.61±2.03	16.01±2.16
After the treatment	12.66±1.21*,#	12.36±1.33*,#	9.21±0.80*

Note: ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker. *compared with that before treatment, P<0.05; #compared with ACEI combined with the ARB group, P<0.05.

Table 5. Comparison of urinary α1 microglobulin and urinary β2 microglobulin between the three groups before and after treatment

	ACEI group (n=30)	ARB group (n=30)	ACEI combined with ARB group (n=30)
Urinary α1 microglobulin (mg/L)			
Before the treatment	9.89±1.06	9.31±1.10	9.60±1.21
After the treatment	7.81±0.93*,#	7.36±0.91*,#	6.21±0.63*
Urinary β2 microglobulin (mg/L)			
Before the treatment	0.81±0.12	0.79±0.13	0.81±0.09
After the treatment	0.61±0.06*,#	0.63±0.08*,#	0.46±0.05*

Note: ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker. *compared with that before the treatment, P<0.05; #compared with ACEI combined with ARB group, P<0.05.

cant differences between the ACEI group and ARB group (P>0.05).

Clinical efficacy of the three groups

As shown in **Table 6**, in the ACEI group, there were 16 patients with marked effectiveness, 10 patients with effectiveness, and 4 patients with ineffectiveness, yielding a clinical efficacy of 86.7%. In the ARB group, there were 13 patients with marked effectiveness, 12 patients with effectiveness, and 5 patients with ineffectiveness, yielding a clinical efficacy of 83.3%. In the ACEI combined with ARB group, there were 21 cases with marked effectiveness and 9 cases with effectiveness, yielding a clinical efficacy of 100%. Clinical efficacy of the ACEI combined with ARB group was significantly higher than either the ACEI group (χ^2=4.286, P=0.038) or ARB group (χ^2=5.455, P=0.020). Differences were statistically significant (P<0.05). There were no significant differences in clinical efficacy between the ACEI group and ARB group (χ^2=0.131, P=0.718).

Discussion

The main pathological change of diabetic nephropathy is glomerulosclerosis, one of the most common complications of diabetes [13]. Clinical manifestations include proteinuria, edema, hypertension, and azotemia. Clinical studies have shown that microalbuminuria can be reversed by early intervention. However, if

Table 6. Clinical efficacy of the three groups

Group	Marked effectiveness (n)	Effectiveness (n)	Ineffectiveness (n)	Clinical efficacy (%)
ACEI group (n=30)	16	10	4	86.7*
ARB group (n=30)	13	12	5	83.3*
ACEI combined with ARB group (n=30)	21	9	0	100.0

Note: ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker. *compared with ACEI combined with ARB group, P<0.05.

treatment is delayed, it can further develop into uremia, causing irreversible damage [14, 15].

Results of this study showed that, after 10 weeks of treatment, blood pressure, blood sugar, and blood lipid levels of the three groups were controlled within the normal range. ACEI combined with ARB can significantly reduce levels of Scr and BUN, while either ACEI alone or ARB alone cannot. In addition, levels of 24-hour urinary protein and urinary microprotein were significantly lower than those before treatment for the three therapeutic modalities. Moreover, combined application of ACEI and ARB can reduce 24-hour urinary protein and urinary microprotein levels more effectively than either ACEI alone or ARB alone. Furthermore, the clinical efficacy of ACEI combined with ARB was 100%, significantly higher than that of ACEI alone (86.7%) or ARB alone (83.3%). Differences were statistically significant. Results of this study suggest that the combination of ACEI and ARB is more effective in improving renal function and alleviating proteinuria in patients with diabetic nephropathy. A previous study also found that ACEI combined with ARB treatment can effectively improve renal function and alleviate proteinuria in patients with diabetic nephropathy [16]. Present results, therefore, are consistent with previous reports.

ACEI has certain protective effects on renal function and delays the decline of renal function, to a certain extent, in diabetic patients [16-18]. Therefore, ACEI was recommended as the first-line drug treatment for diabetic nephropathy in the 2007 Edition of the Chinese Guidelines for the Prevention and Treatment of Type II Diabetes. ARB can play a significant role by blocking receptors and binding exogenous and endogenous angiotensin II. This blocking effect can increase levels of angiotensin II, which will further bind to AT2 receptors. This alleviates further deterioration of renal function [19-21]. It was hypothesized that, when the two drugs are combined, they play a synergistic role in improving renal function, alleviating proteinuria, and delaying renal failure.

There were some limitations to the current study, however. For example, the number of cases included in each group was small, the study period was short, and patients were not followed-up for a long time. In addition, this study did not analyze data by stratifying patients according to DN stage. These factors may have caused statistical bias, affecting the credibility of results. In future studies, the experimental design should be improved, expanding the sample size and carrying out multi-center clinical trials. This will further optimize the clinical treatment of diabetic nephropathy, improving clinical therapeutic efficacy, clinical prognosis, and quality of life for patients.

In conclusion, combined application of ACEI and ARB is significantly better than either drug alone for treatment of diabetic nephropathy. This combination can effectively improve renal function and proteinuria, delaying renal failure in patients with diabetic nephropathy.

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Disclosure of conflict of interest

None.

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References

[1] Wu H, Jackson CA, Wild SH, Jian W, Dong J and Gasevic D. Socioeconomic status and self-re-

ported, screen-detected and total diabetes prevalence in Chinese men and women in 2011-2012: a nationwide cross-sectional study. J Glob Health 2018; 8: 020501.
[2] Zhang G, Chen H, Chen W and Zhang M. Prevalence and risk factors for diabetic retinopathy in China: a multi-hospital-based cross-sectional study. Br J Ophthalmol 2017; 101: 1591-1595.
[3] Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, Zimmet P and Son HY. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006; 368: 1681-1688.
[4] Amin F, Fatima SS, Islam N and Gilani AH. Prevalence of obesity and overweight, its clinical markers and associated factors in a high risk South-Asian population. BMC Obes 2015; 2: 16.
[5] Pan Q, Guo L, Shen Y, Xiao C, Chen G, Li S, Yan H, Endocrinology DO and Hospital B. Prevalence of overweight and obesity and its associated factors among residents aged 15 years old and above in Hubei Province. Beijing Medical Journal 2016.
[6] Shi WX, Li XY. Prevalence of chronic complications and related factors in diabetic patients. Chinese Journal of Epidemiology 2004; 25: 60-64.
[7] Wang L, Zhang WH, Liu H. Prevalence and risk factors of chronic complications of patients with type 2 diabetes. China Modern Doctor 2014; 52: 31-33.
[8] Guo K, Zhang L, Zhao F, Lu J, Pan P, Yu H, Bao Y, Chen H and Jia W. Prevalence of chronic kidney disease and associated factors in Chinese individuals with type 2 diabetes: cross-sectional study. J Diabetes Complications 2016; 30: 803-810.
[9] Wu D, Xuan Y, Ruan Y, Feng X, Zhu Y, Jia C, Liu J, Li H, Li L and Dong X. Prevalence of macro- and microvascular complications in patients with type 2 diabetes and kidney disease with or without albuminuria in a single Chinese diabetes centre. Diab Vasc Dis Res 2016; 13: 21-30.
[10] Du GM. Study on the effect of combined Chinese and western medicine on the treatment of diabetic nephropathy. Chinese Community Doctors 2018; 108-109.
[11] Ruiz-Ortega M, Lorenzo O, Ruperez M and Egido J. ACE inhibitors and AT(1) receptor antagonists-beyond the haemodynamic effect. Nephrol Dial Transplant 2000; 15: 561-565.
[12] Staszkow M and Mieczkowski M. Management of diabetic kidney disease: a summary of European Recommendations 2015. Wiad Lek 2016; 69: 732-735.
[13] Kahn CR. Joslin Diabetes. Pan CY translated. Beijing: People's Health Publishing House 2007; 842-843.
[14] Ma LJ. Clinical observation of valsartan combined with benazepril in the treatment of diabetic nephropathy. China Continuing Medical Education 2016; 8: 182-183.
[15] Xu BK, Zhu GH. Therapeutic effects of benazepril combined with valsartan on blood glucose, blood lipid and kidney function in the treatment of senile diabetic nephropathy. Journal of Clinical Research 2017; 34: 2303-2305.
[16] Liu GJ. Clinical efficacy of enalapril combined with alprostadil in the treatment of diabetic nephropathy. Laboratory Medicine and Clinic 2016; 13: 2039-2041.
[17] Yuan S, Zhou B. Clinical efficacy of ARB and ACEI alone or combined in the treatment of elderly patients with early diabetic nephropathy. Shaanxi Medical Journal 2014; 902-904.
[18] Ye JZ, Xie L, Yu AH. Effects on urinary albumin excretion rate of early diabetic nephropathy in patients with ACEI and ARB spironolactone in combination. Chinese and Foreign Medical Research 2014; 1: 15-16.
[19] Chai DL, Pang T. Effects of rosuvastatin combined with benazepril on serum myohepatic and urea ammonia levels in elderly patients with diabetic nephropathy. Chinese Remedies & Clinics 2018.
[20] Morisco C, Trimarco B. Angiotensin converting enzyme inhibitors and AT1 antagonists for treatment of hypertension. Springer International Publishing 2015; 5: 1-39.
[21] Stanton RC. Combination use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers in diabetic kidney disease. Curr Diab Rep 2013; 13: 567-573.