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Effects of combined use of atorvastatin and losartan in treating patients with diabetic nephropathy

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Abstract

This study is to investigate the effect of atorvastatin combined with losartan on inflammatory factors, vascular endothelial function, and cardiovascular events in patients with diabetic nephropathy. A total of 128 patients with diabetic nephropathy treated in our hospital from January 2014 to December 2015 were selected as the study subjects, and 64 cases were randomly divided into observation group and 64 cases in the control group. The control group was treated with losartan on the basis of routine treatment, and the observation group was treated with atorvastatin on the basis of the control group. The blood lipid, inflammatory factors, changes in vascular endothelial function and cardiovascular events were compared between the two groups. The levels of total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were not significantly different between the two groups before treatment ($P > 0.05$); after treatment, the levels of TC, TG, and LDL-C in the observation group were significantly lower than those of the control group, and the level of HDL-C was significantly higher than that of the control group ($P < 0.05$). The levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6) were not statistically different between the two groups before treatment ($P > 0.05$); after treatment, the levels of hs-CRP, TNF-α, and IL-6 in the observation group were significantly lower than those of the control group ($P < 0.05$), the level of HDL-C was significantly higher than that of the control group ($P < 0.05$). There were no significant differences in the levels of endothelin-1 (ET-1) and nitric oxide (NO) between the two groups before treatment ($P > 0.05$). After treatment, the level of ET-1 in the observation group was significantly lower than that of the control group ($P < 0.05$), and the level of NO was significantly higher than that of the control group ($P < 0.05$). After treatment, all patients were followed up for 2 years, and the incidence of secondary cardiovascular events in the observation group was 12.50% (8/64), which was significantly lower than 29.69% (19/64) of the control group ($P < 0.05$). Combination of atorvastatin and losartan can significantly improve the levels of blood lipid, inflammatory factors, and vascular endothelial function in patients with diabetic nephropathy and can effectively reduce the incidence of cardiovascular events.

Keywords

atorvastatin, cardiovascular events, diabetic nephropathy, inflammatory factors, losartan, vascular endothelial function

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Type 2 diabetes (T2DM) has become one of the primary diseases that threaten people's health. Diabetic nephropathy (DN) is one of the most common serious microvascular complications of diabetes. It is the leading cause of end-stage renal disease in diabetic patients and is the main cause of death in diabetic patients.[1] Diabetic kidney changes include early glomerular ultrafiltration and glomerular hypertrophy, followed by the glomerular basement membrane thickening, mesangial matrix deposition, and the increase in the urinary albumin excretion rate,

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eventually developing into glomerulosclerosis.[2,3] Due to the prevalence of metabolic syndrome and obesity, diabetes has become a major health problem worldwide. DN is one of the most common and most serious chronic complications of diabetes, and the number of patients gradually increases and there will be tremendous social and economic pressure in the future. High glucose levels are closely related to the progression of DN: long-term high glucose leads to chronic metabolic pathways and hemodynamic pathway disorder, both of which lead to abnormal kidney structure and the development of DN by regulating different intracellular signal pathways and cytokines.[4] The pathogenesis of DN is very complicated. Although strict control of blood glucose can delay disease progression, the current therapeutic effect is still not satisfactory. Previous studies have shown that,[5] atorvastatin, as a commonly used lipid regulating drug, has the function of improving arterial endothelial cell function and elasticity, anti-atherosclerosis, it can effectively improve the DN and vascular endothelial function in patients with DN and coronary heart disease features. Losartan is an angiotensin II (AngII) receptor antagonist commonly used for clinical practice. It has the effect of inhibiting oxidation and improving vascular endothelial function in addition to antihypertensive effect.[6] In recent years, there have been few studies on the effects of atorvastatin on inflammatory factors, vascular endothelial function, and cardiovascular events in patients with DN. Therefore, the purpose of this study is to investigate the effect of atorvastatin combined with losartan on inflammatory factors, vascular endothelial function, and cardiovascular events in patients with DN.

Materials and methods

Group

We selected 128 patients with DN from January 2014 to December 2015 in our hospital as subjects. All patients met the World Health Organization (WHO) Type 2 Diabetes and Early DN Diagnostic Criteria (1999) and were all associated with dyslipidemia (serum triglyceride (TG) $\geq$ 1.7 mmoL/L, or total cholesterol (TC) $\geq$ 5.2 mmol/L, or both are elevated). Exclusion criteria: patients had severe heart failure and systolic blood pressure $<$ 90 mm Hg; patients had severe hepatobiliary diseases; patients had infectious diseases, which means the pathogens mainly include bacteria, viruses, and fungi; patients had primary kidney disease; patients who had used angiotensin II type 1 receptor blocker (ARB) or statins in the last 2 weeks; and breast-feeding and gestational female patients. 128 patients were randomly divided into observation group and control group through random number table, with 64 cases in each group. This research was approved by the ethics committee of Huimin People's Hospital.

Methods

The observation group was added losartan (10 mg, qd) plus atorvastatin (50 mg, bid) on the basis of strict acceptance of diabetes diet, reducing protein intake and conventional glucose lowering treatment.

The control group was treated with losartan (10 mg, qd) plus placebo (50 mg, bid), on the basis of strict acceptance of diabetes diet, reducing protein intake and conventional glucose lowering treatment. Both groups were treated for 12 weeks. Patients were blind to the treatments they received. All participants and their families signed informed consent for their participation.

Observation indexes

Blood lipid. At 0 week (before treatment) and 12 weeks (after treatment), after fasting 12 h, 3-mL fasting venous blood was extracted in the dry test tube and self-coagulating at room temperature. The supernatant was taken by centrifugation (4°C, 2000 r/min, 15 min) within 1 h. The serum levels of TC and TG (Elabscience Biotechnology, Wuhan, China) were detected by oxidase method, and serum levels of LDL-C and HDL-C (Elabscience Biotechnology, China) were detected by direct method.

Inflammatory factors. At 0 week (before treatment) and 12 weeks (after treatment), after fasting 12 h, 3-mL fasting venous blood was extracted in the dry test tube and self-coagulating at room temperature. The supernatant was taken by centrifugation (4°C, 2000 r/min, 15 min) within 1 h. The levels of high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6) (Elabscience Biotechnology, Wuhan, China) were measured using an enzyme-linked immunosorbent assay (ELISA) kit.

Vascular endothelial function. At 0 week (before treatment) and 12 weeks (after treatment), after fasting

Table 1. Comparison of general information in the two groups.

Index	Control group (N = 64)	Observation group (N = 64)	*P*
Male	36	37	<0.05
Age (years)	67.05 ± 8.62	66.31 + 9.54	<0.05
Height (cm)	172.1 ± 2.4	171.2 ± 3.7	<0.05
Body mass index (kg/m^2)	24.13 ± 1.34	23.88 ± 1.25	<0.05
Medications			
Aspirin	N = 13	N = 12	<0.05
beta-blockers	N = 21	N = 19	<0.05
Calcium channel blocker	N = 3	N = 5	<0.05

12 h, 3-mL fasting venous blood was extracted in the dry test tube and self-coagulating at room temperature. The supernatant was taken by centrifugation (4°C, 2000 r/min, 15 min) within 1 h. The serum levels of endothelin-1 (ET-1) were determined by radioimmunoassay and the serum levels of nitric oxide (NO) was determined by colorimetry.

Cardiovascular events. Follow-up for 2 years, the number of patients with secondary cardiovascular events was recorded, and the incidence of secondary cardiovascular events was calculated.

Statistical analysis

SPSS 21.0 software was used for statistical data processing. Measured data were expressed as mean ± standard deviation ($\bar{x} \pm s$), the data were analyzed by one-way analysis of variance followed by least significant difference test. Chi-square test was used for count data. $P < 0.05$ was considered statistically significant.

Results

Comparison of general information in the two groups

The observation group included 37 males and 27 females, aged 53 to 76 years, with an average age of 66.31 + 9.54 years and a disease course of 11–46 months, with an average of 24.95 + 7.68 months. The control group included 36 males and 28 females, aged 54–77 years, with an average age of 67.05 ± 8.62 years and a disease course of 12–47 months, with an average of 25.18 ± 6.35 months. There was no significant difference in the general information between the two groups ($P > 0.05$), which was comparable, as shown in Table 1.

Comparison of blood lipid levels in the two groups

The levels of TC, TG, LDL-C and HDL-C were not significantly different between the two groups before treatment ($P > 0.05$); after treatment, the levels of TC, TG, and LDL-C in the observation group were significantly lower than those of the control group, and the level of HDL-C was significantly higher than that of the control group ($P < 0.05$) (Table 2).

Comparison of the levels of inflammatory factors in the two groups

The levels of hs-CRP, TNF-α, and IL-6 were not statistically different between the two groups before treatment ($P > 0.05$); after treatment, the levels of hs-CRP, TNF-α, and IL-6 in the observation group were significantly lower than those of the control group ($P < 0.05$) and the level of HDL-C was significantly higher than that of the control group ($P < 0.05$) (Table 3).

Comparison of vascular endothelial function in two groups

There were no significant differences in the levels of ET-1 and NO between the two groups before treatment ($P > 0.05$). After treatment, the level of ET-1 in the observation group was significantly lower than that of the control group ($P < 0.05$), and the level of NO was significantly higher than that of the control group ($P < 0.05$) (Table 4).

Comparison of incidence of secondary cardiovascular disease events in two groups

After treatment, all patients were followed up for 2 years, and the incidence of secondary cardiovascular

Table 2. Comparison of blood lipid levels in the two groups.

Group	N	TC (mmol/L)		TG (mmol/L)		LDL-C (mmol/L)		HDL-C (mmol/L)	
		0 week	12 weeks	0 weeks	12 weeks	0 week	12 weeks	0 week	12 weeks
Observation group	64	5.65 ± 0.87	2.79 ± 0.24	2.13 ± 0.17	1.06 ± 0.11	3.86 ± 0.77	2.16 ± 0.13	0.93 ± 0.21	1.69 ± 0.14
Control group	64	5.62 ± 0.41	4.98 ± 0.26	2.11 ± 0.29	1.97 ± 0.13	3.81 ± 0.91	3.37 ± 0.26	0.91 ± 0.17	0.87 ± 012
t		0.662	6.983	0.097	5.441	0.126	6.073	0.334	5.415
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

TC: total cholesterol; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol.

Table 3. Comparison of the levels of inflammatory factors in the two groups.

Group	N	hs-CRP (mg/L)		TNF-α (mg/L)		IL-6 (pg/L)	
		0 week	12 weeks	0 week	12 weeks	0 week	12 weeks
Observation group	64	23.14 ± 2.78	17.12 ± 3.04	58.11 ± 5.22	36.13 ± 5.05	29.13 ± 3.86	16.23 ± 2.15
Control group	64	23.07 ± 3.54	19.16 ± 2.77	59.09 ± 5.14	57.14 ± 6.33	29.08 ± 4.13	26.14 ± 3.92
t		0.415	5.411	0.122	6.159	0.708	5.733
P		>0.05	<0.05	>0.05	<0.05	>0.05	<0.05

hs-CRP: high-sensitivity C-reactive protein; TNF-α: tumor necrosis factor alpha; IL-6: interleukin 6.

Table 4. Comparison of ET-1 and NO levels before and after treatment in the two groups.

Group	N	ET-1 (ng/L)		NO (μmol/L)	
		0 week	12 weeks	0 week	12 weeks
Observation group	64	96.72 ± 9.13	62.84 ± 7.32	16.34 ± 6.25	24.06 ± 7.13
Control group	64	96.31 ± 8.67	90.15 ± 9.24	16.31 ± 7.93	18.19 ± 6.32
t		0.763	5.091	0.456	7.014
P		>0.05	<0.05	>0.05	<0.05

ET-1: endothelin-1; NO: nitric oxide.

events in the observation group was 12.50% (8/64), which was significantly lower than 29.69% (19/64) of the control group ($P < 0.05$).

Discussion

Application of angiotensin converting enzyme inhibitor (ACEI) or ARB drugs still cannot prevent the majority of patients with DN progression to end-stage renal failure even strict control of blood glucose.[7] Also, diabetic patients have fat metabolism disorders. Abnormalities in fat cells activate inflammatory responses. Inflammation is the cause of atherosclerosis and an important predictor of death in patients with end-stage diabetes. Inflammatory factors and inflammation-related immune cells were involved in various stages of DN.[8,9] Inflammatory factors have a high degree of biological activity and play an important role in maintaining the normal structure and function of the kidney under normal conditions.[10] In pathological conditions such as hyperglycemia and hemodynamic disorders, the expression of pro-inflammatory cytokines such as TNF-α, IL-6, and hs-CRP in renal intrinsic cells increased significantly, while the expression of IL-10 decreased significantly. Pro-inflammatory and anti-inflammatory imbalances can amplify the inflammatory response, leading to glomerular sclerosis and renal tubule interstitial fibrosis, resulting in DN. In this study, data showed that atorvastatin in combination with losartan has a better effect of regulating blood lipid and anti-inflammation.

Impaired endothelial function in diabetic patients resulted in ET-1 level increasing and NO level decreasing. Vascular endothelial diastolic function has been impaired before the angiogenesis of DN patients, and impaired vascular endothelial function aggravates atherosclerosis.[11] In this study, results

showed that atorvastatin combined with losartan had a good protective effect on blood vessels, thereby reducing the incidence of cardiovascular events.

Secondary cardiovascular disease has become the first cause of death in diabetic patients, T2DM induces fat metabolic disorder, the dysfunction of fat cells produces a large number of inflammatory cytokines, leading to systemic inflammatory responses in patients, and diabetic patients with dyslipidemia have endothelial dysfunction.[12] These factors have increased the risk of secondary cardiovascular disease. In previous study, follow-up results demonstrated that combination of atorvastatin and losartan can effectively reduce the incidence of cardiovascular events.

Declaration of conflicting interests

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