Curative Effects of Valsartan Alone or Combined with Alpha-lipoic Acid on Inflammatory Cytokines and Renal Function in Early-stage Diabetic Kidney Disease

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Abstract

The aim of this study was to compare curative effects of valsartan alone or combined with alpha-lipoic acid (ALA) on inflammatory cytokine indices including hypersensitive C-reactive protein (hs-CRP), tumor necrosis factor-alpha (TNF-α) and renal function indices including urinary albumin excretion rate (UAER), β_2-microglobulin (β_2-MG) and cystatin C (Cys C) of patients with early-stage diabetic kidney disease (DKD). One hundred and two patients with early-stage DKD were randomly divided into group A and group B, with 51 patients in each group. Group A was administered with valsartan alone, while group B was administered with valsartan combined with ALA. Research showed that 14 days after treatment, group B had significantly lowered hs-CRP, TNF-α, UAER, β_2-MG and Cys C when compared with group A (all $p<0.001$). Compared to valsartan alone, valsartan combined with ALA can reduce level of inflammatory cytokines in serum and improve renal function.

Key Words: *Valsartan, Alpha-lipoic acid (ALA), Diabetic kidney disease (DKD), Inflammatory cytokines, Renal function.*

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Diabetes is a chronic metabolic disease that seriously harms human health. Diabetic kidney disease (DKD) is one of the most common chronic complications of diabetes.[1] The prevalence of diabetes is increasing year by year. About 20-40% of diabetic patients have DKD. Studies have suggested that inflammation caused by disorders of glucose and lipid metabolism in diabetic patients is an important way to cause DKD.[2] Hypersensitive C-reactive protein (hs-CRP) and tumor necrosis factor-alpha (TNF-α) are common inflammatory cytokines, and they both participate in the occurrence and development of DKD. Valsartan is an angiotensin II receptor inhibitor that protects kidney and reduces urine protein. Studies show that valsartan protects against DKD through multiple mechanisms, including decreasing proinflammatory cytokines.[3] Alpha-lipoic acid (ALA) has a strong oxidation capacity and can regulate the body's antioxidant capacity. ALA may have potential benefits in treating various diseases such as diabetes and chronic complications associated with diabetes.[4] Hyperglycemia destroys the body's antioxidant system, resulting in the production of excessive superoxide and affecting the renal function.[5] Urinary albumin excretion rate (UAER), β_2-microglobulin (β_2-MG) and cystatin C (Cys C) sensitively reflect the changes of renal function in early-stage diabetic kidney disease (DKD) patients. So far, there are few reports on the efficacy of valsartan alone or combined with ALA in the treatment of early-stage DKD patients.

The objectives of this study were to compare the curative effects of valsartan alone or combined with ALA on inflammatory cytokines and renal function of patients with early-stage DKD.

This experimental study was carried out in the Department of Endocrinology and Nephropathy, Linyi Third People's Hospital, China, from March 2017 to August 2018. This study was approved by the Hospital Ethics Committee. All patients accepted the study with informed consent. A total of 102 patients with clinically diagnosed DKD were selected as the research object. Inclusion criteria were patients who met the diagnostic criteria of the World Health Organization (WHO) for type II diabetes with early-stage DKD (Mogensen stage 1). Exclusion criteria were patients with urinary tract infections and renal tumors, renal artery stenosis, nephritis and other kidney diseases and a history of taking renal impairment drugs; those with mental illness; those who recently developed acute complications of diabetes, such as hypoglycemia, coma, diabetic ketosis, high glucose hyperosmolar coma, lactic acidosis, *etc.*; those with type I diabetes; and those with poor compliance.

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Table I: Comparison of inflammatory cytokine and renal function indices between two groups.

Indices	Time	Group A (n=51)	Group B (n=51)	p-value
hs-CRP (μg /mL)	Before treatment	4.63 ±0.85	4.65 ±0.92	0.909
	At 14 days after treatment	3.23 ±0.62	2.54 ±0.51	<0.001
TNF-α (ng/L)	Before treatment	54.08 ±7.55	54.12 ±6.96	0.978
	At 14 days after treatment	25.62 ±3.04	22.17 ±2.63	<0.001
UAER (mg/24 h)	Before treatment	137.95 ±16.37	138.02 ±17.54	0.983
	At 14 days after treatment	84.28 ±7.09	63.15 ±5.11	<0.001
β_2-MG (mg/L)	Before treatment	4.12 ±0.86	4.15 ±0.92	0.865
	At 14 days after treatment	2.72 ±0.45	1.97 ±0.38	<0.001
Cys C(mg/L)	Before treatment	2.49 ±0.36	2.51 ±0.41	0.794
	At 14 days after treatment	1.55 ±0.22	1.07 ±0.15	<0.001

Using random-number table, the patients were randomly divided into group A and group B, with 51 patients in each group. Both groups were given conventional treatments such as hypoglycemic therapy, hypotensive, lipid regulation, improved circulation and dietary, and exercise intervention. Group A was given oral valsartan treatment at 80 mg/time once a day. Group B was treated with valsartan combined with ALA. That is, group B was intravenously administered with ALA 600 mg plus 0.9% sodium chloride solution 250m once a day, based on the therapy for group A. Both groups kept on the therapies for 14 days.

Before treatment and 14 days after treatment, 5ml of elbow venous blood of the patients was taken. It was centrifuged at 1500 r/min for 5 mins. Then, serum was separated. ELISA was used for the determination and comparison of the levels of serum inflammatory cytokines hs-CRP and TNF-α. Immunoturbidimetry was used to determine and compare the concentration of β_2-MG and Cys C in serum. Meanwhile, 24-hour urine was collected and kept for UAER detection by immuno-turbidimetry. The adverse reactions of the patients were observed during the treatment. Collected data were analysed using independent sample t-test by SPSS version 25. The p-value of less than 0.05 was considered significant.

All patients were the Han people in China. Among the 102 patients, there were 59 (57.84%) males and 43 (42.16%) females. They were aged between 46 and 80 years, with the average of 69.21 ±3.54 years. The course of disease was 5-11 years, with the average of 10.73 ±2.85 years. The glycosylated hemoglobin (HbAlc) was 6.85-10.73%, with the average 8.67 ±1.25%.

Before treatment, there were no significant differences in hs-CRP, TNF-α, UAER, β_2-MG and Cys C between two groups (p=0.909, 0.978, 0.983, 0.865 and 0.794, respectively). At 14 days after treatment, both groups reduced hs-CRP, TNF-α, UAER, β_2-MG and Cys C compared to those before treatment. The levels of hs-CRP, TNF-α, UAER, β_2-MG and Cys C in group B were significantly lower than those in group A (all p<0.001, Table I) . No adverse reactions were observed in either group.

The hs-CRP is correlated to early renal damage. TNF-α acts directly on pancreatic β-cells and induces insulin resistance. Studies have shown that diabetic patients have a micro-inflammatory state, which is characterised by a continuous increase in serum s-CRP, TNF-α and other inflammatory cytokines. This leads to microvascular disease and damage to vital organs.[6] β_2-MG is a β-light chain of the body leukocyte antigen molecule, which has important clinical significance for the diagnosis of renal failure. When the kidney is damaged, the level of β_2-MG in patients will rapidly increase. UEAR is correlated to urinary protein, and is often at a high level in DKD patients. Cys C has received clinical attention as a new endogenous marker for detecting renal function in recent years. Cys C responds well to glomerular filtration rate because renal tubules do not secrete Cys C.

This study found that 14 days after treatment, hs-CRP, TNF-α, UAER, β_2-MG and Cys C were lower than those before treatment, and these indices in group B were significantly lower than those in group A. This shows that valsartan combined with ALA can play a synergistic role in decreasing the level of serum inflammatory cytokines, reducing proteinuria and delaying renal failure in DKD patients. It is worth mentioning that after alpha-lipoic acid (ALA) enters the human body (injected or orally), it is easy to reduce to dihydrolipoic acid in many body tissues. Alpha-lipoic acid or dihydrolipoic acid can play its pharmacological role both in and out of cells. Intravenous injection of alpha-lipoic acid is more effective than oral administration of alpha-lipoic acid. The limitations of study included lack of longer follow-up to demonstrate any lasting effect, cumbersome use of daily intravenous dose and lack of blinding and placebo in group A (control group). Furthermore, whether valsartan combined with ALA can delay the occurrence and development of end-stage DKD remains to be further observed and investigated.

ETHICAL APPROVAL:

Ethical approval from the Ethics Committee of Linyi Third People's Hospital was obtained prior to initiation of the sutdy.

PATIENTS' CONSENT:

Informed consent was accepted by all the patients.

CONFLICT OF INTEREST:
Authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
ZJ: Conception or design of the work; drafting the work.
ZT: Drafting the work; the acquisition, analysis and interpretation of data for the work.
FM: Drafting the work; revising it critically for important intellectual content.
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