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Original Research Article

Effects of XueZhiTong capsules on chronic kidney disease patients with dyslipidemia

Ya Feng[1]*, Weichun Liang[2], Wei Liang[3], Xiang Xiao[1], Yalan Zhang[1]
[1]Department of Nephrology, The First Affiliated Hospital of Chengdu Medical College, Chengdu, [2]Beijing Huashi Kangyuan Pharmaceutical Technology Co., Ltd., Beijing, [3]Changchun University of Chinese Medicine, Changchun, China

For correspondence:* ***Email:* *shaojiure33927318@163.com*

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Abstract

Purpose: *To determine the clinical effectiveness of Xuezhitong capsule in chronic kidney disease (CKD) patients with dyslipidemia, and its influence on inflammation and oxidative stress.*
Methods: *Ninety CKD patients with dyslipidemia who were admitted to the Department of Nephrology of our hospital from January 2018 to January 2020 were randomly assigned to group A (treated with Xuezhitong capsules), group B (treated with combination of Xuezhitong capsules and atorvastatin), and group C (treated with atorvastatin), with 30 cases in each group. Renal function, lipid indicators, inflammatory indicators, and degree of oxidative stress were compared among the three groups of patients after 3 consecutive months of treatment.*
Results: *At 3 months after treatment, estimated glomerular filtration rate (eGFR) and urinary albumin creatinine ratio (UACR) were markedly decreased in all three groups ($p < 0.05$). After treatment, the levels of TC, TGs, and LDL-C were decreased markedly and time-dependently in the three groups, with the lowest levels in group B, while HDL-C level was elevated with treatment time, with the highest level in group B ($p < 0.05$). After treatment, the 3 groups exhibited significant decreases in levels of hypersensitive C-reactive protein (hs-CRP), homocysteine (Hcy), and malondialdehyde (MDA), with the lowest levels in group B ($p < 0.05$). Adiponectin level was significantly increased in each of the 3 groups ($p < 0.05$).*
Conclusion: *Xuezhitong capsules exerted lipid-lowering effect and mitigated inflammation and oxidative stress in CKD patients with dyslipidemia, without any adverse effects. This finding provides a new treatment option for elderly CKD patients with dyslipidemia.*

Keywords: *Chronic kidney disease, Dyslipidemia, Atorvastatin, XueZhiTong capsule, Allium macrostemon*

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INTRODUCTION

Chronic kidney disease (CKD) ranks amongst major diseases such as hypertension, diabetes and cardiovascular disease, and its prevalence is on the increase worldwide [1]. Dyslipidemia, which is closely related to kidney disease, is a clinical manifestation of CKD, with incidence of about 30 – 60 % [2]. Dyslipidemia is an independent risk factor for atherosclerosis and

cardiovascular events, and it is considered detrimental to long-term prognosis of patients [3]. Lipid-lowering strategies in patients with CKD involve approaches such as diet, drugs, and dialysis, amongst which statins are the most extensively used [4].

Xuezhitong capsule was derived from the classical formula "Xiebai Gualou Baijiu Decoction" by Zhang Zhongjing, the sage of medicine in Han Dynasty, for the treatment of angina pectoris in coronary heart disease. The capsule is based on the Chinese herbal medicine *Xiebai* (*Allium macrostemon*) which is its major component. *Xuezhitong* capsule exerts blood lipid-lowering, platelet-aggregation inhibitory, anti-thrombotic, and anti-atherosclerotic effects [5]. In this study, combination of *Xuezhitong* capsules and atorvastatin was used in the treatment of elderly CKD patients with dyslipidemia, and the treatment effectiveness was evaluated.

METHODS

General information on patients

Ninety CKD patients with dyslipidemia who were admitted to the Department of Nephrology of The First Affiliated Hospital of Chengdu Medical College from anuary 2018 to January 2020, were randomly assigned to groups A, B and C, with 30 patients in each group. The three groups of patients had no significant differences in baseline data, as shown in Table 1.

Ethical issues

The protocol has been approved by the Medical Science Research Ethics Committee of The First Affiliated Hospital of Chengdu Medical College, with the approved No. of 2019CYFYHEC09301 and followed the international guidelines for human studies [6].

Inclusion criteria

Patients in the following categories were included in the study: those aged 45 - 75 years, patients who met the diagnostic criteria for CKD, i.e., kidney injury ≥ 3 months with or without decrease in eGFR, or eGFR < 60 mL/min/1.73 m^2), and patients who met the diagnostic criteria for dyslipidemia, i.e., triglycerides (TGs) ≥ 1.70 mmol/L and total cholesterol (TC) ≥ 5.18 mmol/L, LDL-C ≥ 3.37 mmol/L. Moreover, patients with 24 h urine protein values of 0.5 - 1.5 g were included.

Exclusion criteria

The following categories of patients were excluded from the study: patients who discontinued use of proprietary Chinese medicine within 2 weeks of the study; pregnant and lactating women, patients with other diseases which affect renal function such as renal artery stenosis, uncontrolled hypertension, severe infection, urinary tract obstruction, or those on renal injury drugs, and patients with other organ insufficiencies. In addition, patients who had poor compliance and inability to follow regular medication, and patients lost to follow-up, were excluded. Prior to enrollment, all included patients and their family members signed informed consent forms after being fully informed of the purpose and procedures of the study.

Treatments

All patients were given dietary therapy, antihypertensive therapy, and lipid-lowering drug therapy after admission. Dietary therapy included restriction of intake of protein, sodium, and phosphorus, to levels of 0.8 to 1.0 g/kg, < 3 g/day, and < 10 mg/kg, respectively. Angiotensin converting enzyme inhibitor-1 (ACE-I) was used as the first-line antihypertensive drug for antihypertensive therapy.

Table 1: Comparison of baseline data among the three groups of patients (mean ± SD)

Variable	Group A (n=30)	Group B (n=30)	Group C (n=30)	*P*-value
Gender (male/female)	19/11	12/18	14/16	>0.05
Age (years)	54.24±8.56	52.28±9.03	55.19±10.25	>0.05
BMI (kg/m^2)	25.29±2.25	23.18±3.04	24.95±2.42	>0.05
Serum creatine kinase (U/L)	112±15	106±22	110±19	>0.05
Serum creatinine (mg/dL)	1.37±0.33	1.41±0.34	1.34±0.28	>0.05
GFR Stage				>0.05
II	11	9	8	
III	10	13	8	
IV	9	8	14	

If ACE-I control failed to reach the standard blood pressure of 130/80 mmHg, α and β receptor blockers or calcium antagonists were applied in conjunction with ACE-1.

For lipid-lowering therapy, patients in group A were orally administered *Xuezhitong* capsules (Jilin Dongfang Pharmaceutical Co. Ltd, specification: 45 mg x 30s, NMPA approval number: Z10970076), at a dose of 0.9 g 3 times/day. Patients in group C were orally given atorvastatin calcium tablets (Beijing Jialin Pharmaceutical Co. Ltd., specification: 10 mg x 7s, NMPA approval number: H19990258) as a 10-mg tablet once a day. Patients in group B were orally treated with *Xuezhitong* capsules (0.9 g) thrice daily, in combination with atorvastatin calcium tablets (10 mg daily). All patients were treated consecutively for 3 months. Prompt symptomatic treatment and drug changes were performed for side effects such as severe gastrointestinal reactions, rash, hepatic and renal toxicity, and rhabdomyolysis during the treatment period.

Evaluation of indicators

Renal function

Renal function indicators were eGFR and UACR, before and after treatment. The equations for modification of diet in renal disease (MDRD) [7] was used for calculation of eGFR as in Eqs 1 and 2, respectively. *eGFR (male)* was calculated as in Eq 1.

$$eGFR\ (male) = 186\{(bc)^{-1.154} \times (a)^{-0.203} \times (-0.203) \times 1.233\} \ldots\ldots (1)$$

where bc = *blood creatinine*, a = *age*. eGFR (female) was calculated as in Eq 2.

$$eGFR\ (female) = male\ eGFR \times 0.742 \ldots\ldots\ldots (2)$$

Clean morning midstream urine specimens were collected and centrifuged. The urine samples were used to determine urinary microalbumin concentration (mg/L) and urinary creatinine concentration (μmol/L) with the bromocresol green method and the sarcosine oxidase method, respectively. Then, UACR (mg/g) was calculated as shown in Eq 3.

$$UACR\ (mg/g) = \{umc\ (mg/L) \times 10^6 \times 113\ g/mol\}/ucc\ (\mu mol/L) \ldots\ldots (3)$$

where umc = urinary microalbumin concentration, ucc = urinary creatinine concentration.

Lipid indicators

The levels of TC, TGs, LDL-C, and HDL-C in fasting venous blood of patients were measured using a Myriad Automatic Biochemistry Analyzer.

Inflammation indicators and oxidative stress indicators

Fasting venous blood was collected from the patients, and the concentrations of hs-CR, Hcy, adiponectin, and MDA were determined using ELISA. Immunoturbidimetric kit (Shanghai Kehua Biological Engineering Co) was used for the determination of hs-CRP concentration, while plasma Hcy concentration was determined with circulating enzyme method, using kits provided by Ningbo Meikang Biotechnology Co. The instruments used were automated Biochemical Analyzers OLYMPVS AV5400. Enzyme-linked immunosorbent assay (ELISA) was used for the determination of adiponectin and MDA, with kits provided by Shenzhen Enogene Biotechnology Co.

Statistical analysis

The SPSS version 23.0 data processing software was used in this research. Counting data are expressed as numbers and percentages [n (%)] and they were compared with χ^2 test. Measurement data are expressed as mean ± SD, and were analyzed with Student's *t*-test. A two-sided test was also employed for analysis. Values of $\alpha < 0.05$ indicated that the difference was statistically significant.

RESULTS

Changes in eGFR and UACR before and after treatment

As shown in Table 2, there were no significant differences in eGFR and UACR among the three groups of patients before treatment, 1 month after treatment, and 3 months after treatment ($p > 0.05$). Within-group comparisons showed marked decreases in eGFR and UACR in all three groups at 1 and at 3 months after treatment ($p < 0.05$).

Changes in blood lipid indicators before and after treatment

As shown in Table 3, before treatment, the three groups had similar levels of TC, TGs, LDL-C, and HDL-C. However, after treatment, the levels of TC, TGs, and LDL-C were decreased markedly with treatment time in the three groups, with the lowest levels recorded in group B, while HDL-C

level was significantly increased with treatment time, with the highest level seen in group B ($p < 0.05$). Groups A and C had comparable levels of TC, TGs, LDL-C and HDL-C at all treatment times.

Levels of hs-CRP and adiponectin

The results in Table 4 demonstrate that there were no significant differences in levels of hs-CRP and adiponectin amongst the three groups before treatment. However, after treatment, hs-CRP levels decreased markedly in the three groups, with the lowest results observed in group B ($p < 0.05$), but there was no significant difference in hs-CRP level between groups A and C. The level of adiponectin was significantly increased in all three groups ($p < 0.05$), but there were no significant differences amongst the three groups.

Oxidative stress indicators

Before treatment, the levels of Hcy and MDA were similar in the three groups. However, after treatment, the levels of the two indicators were significantly decreased in all groups, with the lowest levels seen in group B ($p < 0.05$). There were no significant differences in levels of Hcy and MDA between group A and group C. These results are shown in Table 5.

Table 2: Changes in eGFR and UACR before and after treatment in the three groups of patients (mean ± SD)

Variable	eGFR (mL/min/1.73 m^2)			UACR (mg/g-Cr)		
	Before treatment	***1 months after treatment***	***3 months after treatment***	***Before treatment***	***1 months after treatment***	***3 months after treatment***
Group A (n=30)	40.47±5.94	34.18±4.72*	35.17±4.29*	1014±447	625±206*	637±193*
Group B (n=30)	39.67±4.72	33.87±5.18*	34.84±4.46*	986±392	632±224*	619±216*
Group C (n=30)	38.29±6.34	34.14±5.32*	33.46±5.53*	1012±435	619±221*	624±243*

*Compared with value before treatment

Table 3: Changes in lipid indicators before and after treatment in the three groups of patients (mean ± SD)

Group		TC	TG	HDL-C	LDL-C
A (n=30)	Before treatment	4.43±1.14	2.15±0.96	1.34±0.35	2.97±0.59
	1 month of treatment	4.04±1.32*	1.75±0.85*	1.42±0.47*	2.53±0.63*
	3 months of treatment	3.02±1.42*	1.49±0.88*	1.67±0.44*	2.12±0.68*
B (n=30)	Before treatment	4.22±1.44	2.27±1.16	1.36±0.43	2.34±0.71
	1 month of treatment	2.53±1.48*#	1.37±1.24*#	1.56±0.40*#	1.84±0.79*#
	3 months of treatment	2.08±1.36*#	1.28±1.22*#	1.88±0.39*#	1.52±0.87*#
C (n=30)	Before treatment	4.35±1.26	2.16±0.96	1.35±0.41	2.93±0.71
	1 month of treatment	4.15±1.32*	1.62±1.02*	1.46±0.52*	2.55±0.68*
	3 months of treatment	2.91±1.13*	1.51±1.08*	1.69±0.48*	2.18±0.62*

*$P < 0.05$, compared with pretreatment value; #$p<0.05$, compared with groups A and C

Table 4: Comparison of the levels of hs-CRP and adiponectin before and after treatment in the three groups of patients (mean ± SD)

Variable	hs-CRP (mg/L)		Adiponectin (μg/mL)	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
Group A (n=30)	22.29±12.38	7.52±3.48*	5.11±1.83	8.58±2.07*
Group B (n=30)	25.31±15.34	5.19±2.67*#	5.07±2.12	8.38±2.65*
Group C (n=30)	23.13±16.44	7.19±3.21*	5.25±1.99	8.75±2.16*
F	0.332	4.843	0.068	0.193
P-value	0.719	0.010	0.934	0.825

*$P < 0.05$, compared with value before treatment; #$p < 0.05$, compared with groups A and C

Table 5: Comparison of Hcy and MDA before and after treatment in the three groups of patients (mean ± SD, μmol/L)

Variable	Hcy		MDA	
	Before treatment	***After treatment***	***Before treatment***	***After treatment***
Group A (n=30)	18.28±3.25	14.18±2.95*	18.28±4.51	16.67±3.84*
Group B (n=30)	17.95±3.46	11.28±2.62*#	18.41±3.86	13.26±2.51*#
Group C (n=30)	19.02±3.34	15.02±2.31*	19.03±4.31	15.34±3.45*
F	0.802	16.58	0.269	8.069
P-value	0.452	<0.001	0.765	<0.001

*$P < 0.05$, compared with value before treatment; #$p < 0.05$, compared with groups A and C

Table 6: Comparison of adverse events during treatment in the three groups of patients [n, (%)]

Variable	Angina pectoris	Acute myocardial infarction	Stroke	Renal failure	Total incidence
Group A (n=30)	0	1	1	2	4
Group B (n=30)	1	1	0	1	3
Group C (n=30)	1	0	1	0	2
P-value					>0.05

Incidence of adverse reactions

A 1-year follow-up was carried out after treatment. All patients completed the follow-up (100 % follow-up compliance in the three groups). During the follow-up, group A had 1 case of acute myocardial infarction, 1 case of stroke, and 2 cases of renal failure, accounting for 13.33 % (4/30) incidence of adverse effects. Group B had 1 case of angina pectoris, 1 case of acute myocardial infarction, and 1 case of renal failure, resulting in 10 % (3/30) incidence of adverse events. In contrast, group C had 1 case of angina pectoris and 1 case of stroke, accounting for 6.67% (2/30) incidence of adverse reactions. There were no significant differences in incidence of adverse events amongst the 3 groups of patients. These data are presented in Table 6.

DISCUSSION

The morbidity associated with CKD is on the increase worldwide, with a total prevalence of 12.50 % in the Chinese population [8]. Dyslipidemia, a common symptom of CKD, is an independent risk factor for CKD which may contribute to the deterioration of renal function in multiple ways. In addition, dyslipidemia is associated with cardiovascular complications which are frequent causes of death in CKD patients [9].

Studies have shown that correction of abnormal lipid metabolism serves to retard the progression of CKD and drive down the incidence of serious adverse effects. Atorvastatin is a Class IA drug for the treatment of dyslipidemia. It selectively inhibits HMG-CoA reductase activity, resulting in suppression of cholesterol biosynthesis in the liver, thereby lowering serum cholesterol levels and protecting the kidney. Although the exact mechanism underling its renal protection is poorly understood, it has been reported that it is probably related to increased endothelial NO production, reduced vascular resistance, and enhanced renal blood flow [10].

In CKD patients who have dyslipidemia, statin therapy is effective in lowering lipid levels, reducing proteinuria, and delaying deterioration of renal function [11]. However, DYSIS treated 25,317 patients with statins and found that TGs and HDL-C were still poorly controlled in 47.6 % of them, accounting for approximately 74.2% of patients at high risk for coronary heart disease. The strong association between high TG levels and cardiovascular events necessitates the application of appropriate drugs to enhance lipid-lowering effects even when LDL-C levels are well controlled [12].

Xuezhitong capsule is a Chinese patent medicine extracted from *Allium macrostemon*, and it has been associated with lipid-lowering, anti-platelet, and anti-oxidative stress effects [13]. Nonetheless, not much has been reported on its application in patients with CKD complicated with dyslipidemia. In the present study, combined therapy of *Xuezhitong* capsules and atorvastatin was applied in the treatment of CKD complicated with dyslipidemia, and it resulted in promising outcomes.

It is known that UACR and eGFR are major indicators of renal function with high predictive values for terminal renal disease and mortality risk. Moreover, eGFR is negatively correlated with the risk of cardiovascular events, and UACR is used to assess systemic vascular bed status. Moreover, UACR is an effective predictor of the degree of coronary stenosis which is positively correlated with the number of branches involved in the coronary arteries and the Gensini score [14]. In this study, eGFR and UACR were markedly improved in the three groups of patients after treatment, confirming the role of atorvastatin in enhancing renal function and reducing adverse cardiovascular events, which is consistent with the results of previous research [15]. In addition, the efficacy of combination of *Xuezhitong* capsules and atorvastatin was better than that of mono-therapy with either *Xuezhitong* capsules or atorvastatin. *Allium macrostemon* contains a variety of sulfur-containing compounds among which are methylenetrisulfide and methylallyl sulfide. Studies have shown that methylenetrisulfide and methylallyl sulfide enhanced the activity of cholesteryl ester hydrolase by promoting the level of cyclic adenosine phosphate, thereby facilitating the hydrolysis of cholesteryl esters [16].

An animal study showed that *Allium macrostemon* activated the cholesterol metabolic pathway *in vivo* and reduced LDL-C content by upregulating LDLR mRNA expression in the liver tissue of the hyperlipidemic rat models [17]. In addition, it activated the cholesterol reversal pathway and boosted HDL-C concentration, which consequently lowered blood lipids. It has been reported that the stronger TG-lowering effect of *Xuezhitong* capsules, relative to simvastatin, may be related to the activation of the peroxisome proliferator receptor alpha (PPARα) signaling pathway by *Xuezhitong* capsules, thereby upregulating apolipoprotein A5 (apoA5) [18].

Therefore, the combination of *Xuezhitong* capsules with atorvastatin achieved a better lipid-lowering effect, especially for poor control of TGs and HDL-C. The results of this study confirmed that treatment with *Xuezhitong* capsules in combination with atorvastatin markedly improved the levels of hs-CRP, Hcy and MDA. Hs-CRP is an independent risk factor for cardiovascular disease triggered by chronic inflammation, and it plays an important role in the evaluation of the outcome and prognosis of cardiovascular disease. Homocysteine (Hcy) promotes oxidative damage in vascular endothelial cells.

Malondialdehyde (MDA) is a product of lipid peroxidative damage. Thus, Hcy and MDA are major indicators of the oxidative stress response of the body. This study has demonstrated the dual anti-inflammatory and antioxidant effects of *Xuezhitong* capsules. This semi-pure product of *Allium macrostemon* polysaccharide exerts dual effects against hydroxyl radicals and superoxide anions. Furosteroid saponin extracted from *Allium* inhibits platelet activation, while macrostemonoside E and macrostemonoside F suppress ADP-induced platelet aggregation to various degrees [19,20]. Furthermore, the absence of significant differences in incidence of adverse effects among the three groups of patients indicate the safety of the combined use of the two drugs.

The limitations of this study lie in the short follow-up period and the unexamined long-term prognosis of the patients. These limitations mean that the concrete benefit of *Xuezhitong* capsules for the patients should be stated with caution.

CONCLUSION

In CKD patients with dyslipidemia, *Xuezhitong* capsules enhances the lipid-lowering effect of atorvastatin, and mitigates inflammation and oxidative stress. Moreover, it has a good safety profile. Therefore, the combined treatment may provide a new therapeutic option for CKD complicated with dyslipidemia.

DECLARATIONS

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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