Risk Factors for Development of PAD in PD Patients

Xiaoyue Wang,[1] Qian Teng,[2] Lin Zhu[1]

[1]Department of nephropathy, Qingdao Traditional Chinese Medicine Hospital, Qingdao, Shandong, China
[2]Department of Nutrition, Qingdao Traditional Chinese Medicine Hospital, Qingdao, Shandong, China

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Original Paper

Introduction. To explore the risk factors for development of peripheral arterial disease (PAD) in patients with maintenance peritoneal dialysis and the relationship between osteoprotegerin (OPG) and PAD.

Methods. In China, 108 patients with PD were selected as the research subjects. General information such as age, gender, height, weight, BMI, blood pressure, and smoking history were collected. Serum albumin, fasting glucose, calcium, phosphorus, blood urea nitrogen, creatinine, total cholesterol, triglyceride, LDL-c, HDL-c and CRP, OPG levels were detected. Urea clearance index (Kt/V) and ankle brachial index (ABI) were measured.

Results. There were 19 patients with PAD, accounting for 17.60%. Compared with the non-PAD group, the PAD group was older, female, lower BMI, a longer duration of PD, a higher proportion of diabetic patients, lower albumin and creatinine levels, lower Kt/V (renal), and higher CRP and OPG levels ($P < .05$); Multivariate Logistic regression analysis showed that elderly (OR = 1.262, 95% CI: 1.021 to 2.015), patients with diabetes (OR = 1.710, 95% CI: 1.054 to 2.651), low serum albumin (OR = 0.786, 95% CI: 0.651 to 0.962) and Kt/V (renal) (OR = 0.547, 95% CI: 0.366 to 0.812), high levels of CRP (OR = 1.303, 95% CI: 1.028 to 2.052) and OPG (OR = 1.125, 95% CI: 1.011 to 1.386)were independent risk factors for PAD in patients with PD; Pearson correlation analysis showed a negative correlation between OPG level and ABI (r = -0.267, $P < .01$).

Conclusion. Old age, malnutrition, high levels of CRP and OPG, and lower Kt/V are related to the occurrence of PAD in peritoneal dialysis patients. OPG levels may be predictive indicators of PAD.

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INTRODUCTION

Peripheral arterial disorder (PAD) is an atherosclerotic cardiovascular disease that occurs in the aorta and its branches other than coronary arteries, PAD can increase cardiovascular and cerebrovascular events incidence, such as myocardial infarction, stroke, and death.[1] The incidence of PAD in patients with end stage renal disease has increased significantly.[2] Previous studies have shown that the prevalence of PAD in patients receiving continuous ambulatory peritoneal dialysis (CAPD) was 27.4%, and was 45% in elderly patients.[3] Osteoprotegerin (OPG) belongs to tumor necrosis factor receptor superfamily and produced by various organs such as lung, intestine, kidney, bone, heart, and blood vessel.[4] Studies have shown that serum OPG levels were significantly associated with the occurrence and severity of atherosclerosis.[5] In patients with chronic kidney disease (CKD), as renal function deteriorates, serum OPG levels gradually increased and was positively correlated with carotid intima-media thickness.[6] However, there are few studies explore the relationship between serum OPG level and PAD in peritoneal dialysis (PD) patients. The present study aims to explore the risk factors for the development of PAD in patients with peritoneal

dialysis and to further explore the role of OPG in the development of PAD.

MATERIALS AND METHODS

Study Design

108 patients who received peritoneal dialysis in Qingdao Hospital of Traditional Chinese Medicine from January 2018 to December 2019 were selected as the research subjects. Inclusion criteria: 1) The duration of peritoneal dialysis > 3 months; 2) Age > 18 years old; 3) Dialysis method was CAPD or automatic peritoneal dialysis. Exclusion criteria: 1) Presence of severe congestive heart failure (New York Heart Association: Class III–IV); 2) Peritonitis occurred within 11 months; 3) Presence of persistent hypotension (systolic blood pressure [SBP] < 90 mmHg or diastolic blood pressure [DBP] < 60 mmHg) after drug treatment; 4) Malignant tumor. The ethics committee of Qingdao Traditional Chinese Medicine Hospital approved the study protocol.

Laboratory Parameters and Definitions

1) general information about patients were collected, including gender, age, height, weight, BMI, smoking history, blood pressure, and whether they had hypertension, diabetes, and medication history.

2) After overnight fasting for 8-10 hours, blood samples were collected early in the morning before dialysis exchange, then centrifuged at 3000 g for 10 min and stored at 4°C. The automatic biochemical analyzer (Siemens ADVIA1800, Germany) was used to detect serum albumin, fasting glucose, total calcium, phosphorus, blood urea nitrogen(BUN), creatinine, total cholesterol (TC), triglyceride (TG), low density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c); Immunoturbidimetric method was used to determine the level of C-reactive protein (CRP); Nichols immunoradiometric method was used to determine serum intact parathyroid hormone (iPTH); Enzyme-linked immunosorbent assay was used to determine the serum OPG level; Blood sample, urine sample and dialysate sample were collected to calculate the average total urea clearance index (Kt/V). The total Kt/V was the sum of peritoneal dialysis Kt/V and the residual kidney Kt/V.

3) After the patients had emptied the dialysate and were lying on his back for at least 15 minutes, the ankle brachial index (ABI) was measured by VP-1000 automated PWV/ABI analyzer (Colin CO. Ltd., Komaki, Japan). The ABI was the ratio of the SBP of the ankle to the SBP of the brachial artery on each side, a lower value was chosen for the analysis. PAD was defined as ABI $\leq$ 0.9.

Statistical Analyses

SPSS 22.0 was used for data analysis. The Kolmogorov–Smirnov method was used for normality test. Continuous data that conformed to the normal distribution were represented as mean ± standard deviation (SD), and t test was used for comparison between two groups; The measurement data of non-normal distribution was expressed as median(interquartile range), and the Mann-Whitney U test was used. Categorical data was expressed by the number of cases (%), and χ^2 test was used. Logistic regression analysis and OR (95% confidence interval) was used to analyze the influencing factors of PAD. Pearson linear regression was used for correlation analysis. P value < 0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

According to the ABI, the patients were divided into two groups, one group who had PAD (n = 19) and the other group without PAD (n = 89). Compared with the non-PAD group, the PAD group was older, more female, lower BMI, longer duration of PD, more diabetic patients (P < .05, Table 1).

Laboratory Indicators

Compared with the non-PAD group, the serum albumin and creatinine levels in the PAD group decreased, CRP and OPG levels increased, and Kt/V (renal) decreased. The difference was statistically significant (P < .05, Table 2).

Multivariate Logistic Regression Analysis

Taking the above statistically significant variables as independent variables and PAD occurrence as the dependent variable, a multivariate logistic regression analysis was performed. The results showed that elder age, diabetes, low serum albumin and Kt/V (renal), high levels of CRP and OPG were independent risk factors for PAD in patients with PD (P < .05, Table 3).

Pearson Correlation Analysis

Pearson correlation analysis showed that OPG

Table 1. Comparison of General Information and Clinical Characteristics Between the Two Groups

	Total (108)	non-PAD Group (89)	PAD Group (19)	t/χ^2	*P*
Age	57.28 ± 12.26	55.84 ± 11.03	63.15 ± 13.66	2.51	< .05
Sex					
Male	45	41	4	4.03	< .05
Female	63	48	15		
BMI	23.62 ± 3.17	24.06 ± 2.12	22.68 ± 2.44	2.51	< .05
SBP, mmHg	140.95 ± 21.59	142.78 ± 22.46	140.16 ± 21.03	0.47	> .05
DBP, mmHg	82.51 ± 10.66	84.93 ± 11.86	81.65 ± 9.97	1.12	> .05
Duration of PD, mo	43.18 ± 21.88	40.36 ± 16.55	49.24 ± 18.71	2.08	< .05
Dialysis Mode					
CAPD	71	61	10	1.76	> .05
APD	37	28	9		
Diabetes	43	31	12	5.24	< .05
Hypertension	65	54	11	0.05	> .05
Smoking	22	19	3	0.05	> .05
ABI	1.02 ± 0.14	1.14 ± 0.16	0.83 ± 0.10	8.10	< .001

Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; APD, automatic peritoneal dialysis.

Table 2. Comparison of Laboratory Test Indexes Between the Two Groups

	Total (n = 108)	non-PAD Group (n = 89)	non-PAD Group (n = 19)	t/χ^2	*P*
Albumin, g/L	38.18 ± 5.32	40.39 ± 5.66	33.26 ± 4.98	5.083	< .001
TC, mmol/L	4.51 ± 1.37	4.54 ± 1.42	4.46 ± 1.23	0.227	> .05
TG, mmol/L	2.01 (0.58, 8.51)	1.95 (0.55, 5.66)	2.07 (1.03, 8.46)	0.862	> .05
LDL-C, mmol/L	2.81 ± 1.37	2.83 ± 1.49	2.78 ± 0.94	0.140	> .05
HDL-C, mmol/L	1.22 ± 0.34	1.24 ± 0.36	1.13 ± 0.27	1.256	> .05
Fasting Glucose, mmol/L	5.38 (3.88, 6.40)	5.34 (3.62, 6.21)	5.54 (3.94,7.02)	0.745	> .05
BUN, mmol/L	21.30 ± 6.04	21.42 ± 6.12	19.91 ± 5.89	0.982	> .05
creatinine, umol/L	952.27 ± 231.64	1012.84 ± 256.98	823.50 ± 210.44	3.001	< .05
calcium, mmol/L	2.33 ± 0.25	2.34 ± 0.26	2.28 ± 0.22	0.936	> .05
Phosphorus, mmol/L	1.52 ± 0.38	1.54 ± 0.39	1.46 ± 0.36	0.822	> .05
PTH, pg/mL	265.20 (23.50, 1541.00)	303.40 (19.20, 1586.00	224.10 (20.00, 1561.00)	1.021	> .05
CRP, mg/L	0.47 (0.10, 14.70)	0.23 (0.10, 5.92)	0.81 (0.10, 15.60)	4.738	< .001
OPG, pg/mL	179.82 ± 67.81	156.26 ± 52.64	250.38 ± 79.63	6.408	< .001
Kt/V (Total)	2.12 ± 0.38	2.17 ± 0.52	1.92 ± 0.41	1.966	> .05
Kt/V (PD)	1.71 ± 0.34	1.70 ± 0.35	1.73 ± 0.32	0.344	> .05
Kt/V (Renal)	0.40 ± 0.24	0.46 ± 0.25	0.19 ± 0.08	4.641	< .001

Table 3. Multivariate Logistic Regression Analysis of PAD

	B	SE	Wald	*P*	OR	95% CI
Age	-0.40	0.21	4.03	< .05	1.26	1.02 to 2.02
Diabetes	-0.54	0.23	5.67	< .05	1.71	1.05 to 2.65
Album	0.25	0.13	3.63	< .05	0.79	0.65 to 0.96
logCRP	-0.42	0.20	3.99	< .05	1.30	1.03 to 2.05
OPG	-0.31	0.19	3.86	< .05	1.13	1.01 to 1.39
Kt/V (Renal)	0.40	0.29	4.35	< .05	0.55	0.37 to 0.81

level was negatively correlated with ABI (r = -0.267, $P < .01$).

DISCUSSION

Over the past 20 years, the prevalence of PAD has risen significantly, increasing by 28.7% and 13.1% in low-and middle-income countries,[7] and about 40% in China.[8] ABI was the most commonly used method for the diagnosis of PAD with the advantages of non-invasive, simple, cheap, and

easy to use. The sensitivity of ABI ($\leq$ 0.9) to detect PAD was 95%, and the specificity was about 100%. In the present study, he patients were divided into two groups, one group who had PAD (ABI $\leq$ 0.9) and the other group without PAD (ABI > 0.9). Among them, 19 patients with PAD (accounted for 17.60%), which was lower than previous literature reports. The study by Tian *et al.*[3] showed that the prevalence of PAD in maintenance PD patients was 27.4%, and the study by Lai *et al.*[9] was 21.7%. The reason for this difference may be that the duration of dialysis included in this study was relatively short, and it may also be related to the degree of renal impairment, the proportion of patients with chronic diseases and age differences.

In the present study, multivariate logistic regression analysis found that elder age, diabetes, low serum albumin levels, high CRP and OPG levels, and low Kt/V (renal) were independent risk factors for PAD in patients with PD. The results of previous study[10]showed that patients with a creatine clearance rate < 60 mL/min/ 1.72m^2 had a 2.5-fold higher risk of PAD than those with a creatine clearance rate > 60 mL/min/ 1.72m^2, indicating that renal function may be an independent influencing factor of PAD. The present study showed the same result, the patients with lower Kt/V (renal) had a higher risk of PAD. Furthermore, previous studies have shown that advanced age, smoking, suffering from hypertension, diabetes, dyslipidemia, were independent risk factors for PAD.[2] But smoking and dyslipidemia were not related to the development of PAD in the present study, elder age, diabetes, and low serum albumin levels were in agreement with previous findings. The study by Kuang *et al.*[11] showed that the prevalence of PAD in elderly patients over 60 years old was 31.9%. And the study by Tian *et al.*[3] showed that the prevalence of PAD was up to 45% in elderly patients over 70 years old. Therefore, for elder patients with maintenance PD, special attention should be paid to the development of PAD.

Compared with the non-PAD group, the BMI and serum albumin decreased in the PAD group (P < .05), indicating that the PAD patients had malnutrition. Gu Yue *et al.*[12] discussed the relationship between nutrition and PAD in patients with CAPD and found that albumin (OR = 0.762, 95% CI: 0.611 to 0.948, P < .05) was an independent protective factor for patients with PAD, and it was believed that malnutrition played an important role in the pathophysiology of PAD, but the specific mechanism of action is not yet clear, which may be related to oxidative stress, inflammatory response and endothelial dysfunction. Clinically, patients with hypoalbuminemia should be corrected as soon as possible, given high-protein food or enteral nutrition. Studies have confirmed that diabetes was significantly associated with atherosclerosis, which may be related to glycation end products (AGEs) and nitric oxide disorders.[13] CRP played an important role in the process of diabetes-induced arteriosclerosis. In addition, CRP can induce monocytes to produce tissue factors, and induce endothelial cells to produce adhesion factors, resulting in damage to endothelial cells, and then accelerate atherosclerosis.[14] LEE[15] showed that CRP level was related to the development of PAD in patients with PD.

OPG is a receptor activator of nuclear factor kappa B ligand (RANKL) and TNF-related apoptosis-inducing ligand (TRAIL). The OPG/ RANKL/ RANK system played an important role in pathological angiogenesis, inflammation and cell survival, and also played an important role in cardiovascular diseases.[16-17] The present study found that OPG was an independent risk factor for PAD in maintenance PD patients. The result was agreement with the results of Lin *et al.* [18] Demková[19] showed that compared with non-PAD patients, the level of osteoprotegerin in PAD patients was higher (18.2 ± 1.0 vs. 13.1 ± 2.0 pmol/L, P < .05), and the level of osteoprotegerin in diabetes patients was negatively correlated with the toe arm index (TBI) (r = -0.308, P < .001). The results of present study also showed that OPG levels were negatively correlated with ABI (r = -0.267, P < .01). Studies have shown that OPG ligands and NF-κB receptor activators can be detected in calcified arterial walls, indicating that OPG played a role in the process of arterial calcification,[20] but the specific mechanism of action was not yet clear. In addition, some studies have used atorvastatin or simvastatin to treat diabetes or cardiovascular disease, and found that serum OPG and CRP levels were reduced, and arterial stiffness was reduced, indicating that OPG-induced arteriosclerosis may be related to inflammation.[21] A review included 11 studies showed that OPG levels were related to the occurrence, severity and progression of PAD in 8 studies, and OPG levels

were related to PAD and vascular stiffness in 2 studies, and OPG levels did not increase significantly only in 1 study.[22] Most studies believe that OPG is related to vascular calcification and even PAD, but a large sample of research is still needed to explore its specific pathways for vascular calcification.

CONCLUSION

In summary, elder age, diabetes, low serum albumin levels, high levels of CRP and OPG, low levels of Kt/V (renal) are independent risk factors for PAD in patients with PD; and OPG levels are negatively correlated with ABI.

DISCLOSURE STATEMENT

No potential conflict of interest was reported by the authors.

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Correspondence to:
Lin Zhu
Department of nephropathy, Qingdao Traditional Chinese Medicine Hospital, Qingdao, Shandong 266033, China
Tel: 0086 1519 2510 732
E-mail: zhulin0316@126.com

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