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Associations of serum soluble klotho and fibroblast growth factor 23 with carotid artery calcification in patients undergoing continuous ambulatory peritoneal dialysis

A retrospective study

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Abstract

This study aimed to assess the associations of serum soluble klotho and fibroblast growth factor 23 (FGF-23) with the occurrence of carotid artery calcification. Peritoneal dialysis patients treated from June 2018 to June 2019 were retrospectively analyzed. They were divided into the carotid artery calcification and non-carotid artery calcification groups according to color Doppler ultrasound findings. Basic indicators in both groups were compared, and the influencing factors of carotid artery calcification were analyzed by logistic regression. Among the 73 continuous ambulatory peritoneal dialysis (CAPD) patients enrolled, 40 (54.8%) had carotid artery calcification. Significant differences were found in age (68.85 ± 7.45 vs 46.62 ± 5.51 years), dialysis time (8.15 ± 1.42 vs 6.02 ± 1.14 months), klotho amounts (325.56 ± 41.15 vs 436.65 ± 45.58 pg/mL) and FGF-23 levels (114.45 ± 15.56 vs 70.15 ± 12.23 pg/mL) between the carotid artery calcification and non-carotid artery calcification groups (all $P < .001$). The above factors were associated with carotid artery calcification occurrence in univariate analysis. Multivariate analysis showed that elevated age (odds ratio [OR] = 1.55, 95% confidence interval [CI] 1.13–1.74; $P = .025$) and FGF-23 (OR = 2.16, 95% CI 2.01–2.44; $P = .042$), and lower klotho (OR = 0.66, 95% CI 0.47–0.85; $P = .036$) were independent risk factors for carotid artery calcification in CAPD. Serum FGF-23 and age are risk factors for carotid artery calcification in patients with CAPD, whereas klotho is a protective factor.

Abbreviations: Ca = calcium, CAPD = continuous ambulatory peritoneal dialysis, CKD = chronic kidney disease, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, ELISA = evaluated by enzyme-linked immunosorbent assay, FGF-23 = fibroblast growth factor 23, FGFRs = fibroblast growth factor receptors, HDL = high density lipoprotein, hs-CRP = hypersensitive C-reactive protein, iPTH = intact parathyroid hormone, LDL = low density lipoprotein, MBD = mineral and bone disorder, SBP = systolic blood pressure, SD = standard deviation, TC = total cholesterol, TG = triglyceride.

Keywords: carotid artery calcification, continuous ambulatory peritoneal dialysis, FGF-23, klotho, risk factor

1. Introduction

Chronic kidney disease (CKD) refers to kidney damage or an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 lasting for at least 3 months.[1] End-stage renal disease (ESRD) affects >2 million individuals worldwide, and increases mortality by at least 10-fold.[2,3] Continuous ambulatory peritoneal dialysis (CAPD), a stable and convenient dialysis type, is very effective in ESRD patients.[4,5] CAPD assists kidney function, strengthens self-care ability and improves the quality of life of these patients.[6] It is therefore the method of choice for ESRD patients because of the above advantages in addition to its minimal effects on hemodynamics. In ESRD patients, vascular

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calcification is a commonly found complication, associated with mineral and bone disorders (MBD).[7,8] Vascular calcification increases arterial stiffness by medial calcification, resulting in left ventricular hypertrophy and reduced coronary artery perfusion, thus causing myocardial ischemia by intimal calcification.[8,9]

As kidney function and nephron mass decline, phosphaturic hormones such as parathyroid hormone (PTH) and FGF-23 are produced in response to relative calcium-phosphate (Pi) excess.[10] Consequently, CKD-MBD plays an important role in the pathophysiology of uremic cardiomyopathy, showing tight associations with cardiovascular events and mortality.[11] FGF-23 is a phosphaturic hormone mostly found in bone osteocytes; its production is affected by Pi, calcium, vitamin D derivatives, PTH, and other factors.[12] Meanwhile, klotho functions as a co-receptor, which enhances the binding affinity of FGF-23 for fibroblast growth factor receptors (FGFRs), playing an important role in the occurrence and development of vascular calcification.[13–15]

Many reports have assessed the effects of klotho and FGF-23 on vascular calcification in CAPD patients.[16,17] However, the associations of these proteins with carotid artery calcification are not fully understood. Therefore, the present study aimed to assess the status of carotid artery calcification in patients submitted to CAPD, and to determine the associations of serum klotho and FGF-23 with the occurrence of carotid artery calcification. Our findings provide novel insights into the prevention and treatment of uremic vascular calcification.

2. Materials and methods

2.1. Patients

This retrospective study evaluated CAPD patients treated from June 2018 to June 2019 in the Department of Nephrology, Affiliated Hospital of Nantong University. Inclusion criteria were: (1) regular CAPD treatment, and dialysis time above 3 months; (2) complete clinical data. Exclusion criteria were: (1) acute renal injury, severe malnutrition, endocrine disorders or malignant tumor diseases; (2) treatment with hormone, immunosuppressant and antibiotic drugs in the past month; (3) mental illness or poor coordination.

This study was approved by the Ethics Committee of Affiliated Hospital of Nantong University. Informed consent was not required because of the retrospective nature of this study.

2.2. Grouping and treatment

The patients were divided into the carotid artery calcification and non-carotid artery calcification groups according to color Doppler ultrasound findings.[18] All patients were treated with standard CAPD,[19] using the "Baite Y" double bag system. CAPD was performed 4 times a day, with 2.5% peritoneal dialysate solution (2000 mL) containing 1.25% Ca. Routine blood pressure control and anemia correction were performed.

2.3. Carotid ultrasonography

Average carotid intima-media thickness was measured on a Mindray DC-8Pro color Doppler ultrasound system (KFB161405, Hitachi Preirus; Switzerland) in all patients. The vertical distance from the anterior edge of the lumen to the anterior edge of the middle membrane at the end of the diastolic period was considered the intima-media thickness, and a value $\geq$1.2 mm was taken as the diagnostic standard for carotid calcification.[20]

2.4. Data collection

The general data of patients in both groups were assessed, including age, gender, dialysis time, types of combined diseases (diabetes, coronary heart disease, and/or hypertension.

For the assessment of klotho and FGF-23, as well as other biochemical indexes, venous blood was collected after fasting, early in the morning before dialysis initiation. Klotho and FGF-23 levels in serum were evaluated by enzyme-linked immunosorbent assay (ELISA), with specific kits (Millipore Corp., Billerica, MA, USA) according to the manufacturer's instructions. In addition, serum calcium (Ca), phosphorus (P), total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL) were assessed on an automatic biochemical analyzer (Millipore Corp., Billerica, MA, USA). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also measured before and after treatment.

For the assessment of albumin, hypersensitive C-reactive protein (hs-CRP) and serum parathyroid hormone all samples were collected after 8 hours of fasting at night. Plasma was collected and stored at -70°C. Albumin (g/dL) level was measured by colorimetry; hs-CRP concentration was measured by ELISA. Serum parathyroid hormone (PG/mL) concentration was measured by electrochemiluminescence. Morning urine and blood samples were collected to determine residual EGFR. Total kt/V per week was calculated by formula (Total kt/V per week = (daily residual kidney kt/V + daily peritoneal dialysis kt/V) $\times$ Dialysis days per week).

2.5. Statistical methods

The SPSS 20.0 software (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Measurement data are mean $\pm$ standard deviation (SD), and assessed by the t test for normally distributed parameters; the rank sum test was used for non-normally distributed ones. Count data were expressed in percentage, and compared by the chi square test. Logistic regression analysis (univariate and multivariate) was performed for determining the influencing factors of carotid artery calcification. $P < .05$ was considered statistically significant.

3. Results

3.1. Patient baseline characteristics

A total of 89 patients with CAPD were included, and 16 with acute renal injury were excluded. Thus, 73 patients were finally evaluated, including 41 males and 32 females, aged 31 to 84 years (64.2 ± 2.3 years. The disease types were chronic glomerulonephritis (n = 26), diabetic nephropathy (n = 24), hypertensive nephropathy (n = 12), and chronic interstitial nephritis (n = 11). Age (68.85 ± 7.45 vs 46.62 ± 5.51 years) and dialysis time (8.15 ± 1.42 vs 6.02 ± 1.14 months) were significantly elevated in the carotid artery calcification group compared with the non-carotid artery calcification groups (both $P < .001$). However, there were no significant differences in gender, combined diseases and other indicators between the 2 groups ($P > .05$). The general patient characteristics are shown in Table 1.

Table 1

General patient data in the carotid calcification and non-carotid calcification groups.

Characteristic	Carotid artery calcification group (n = 40)	Non-carotid calcification group (n = 33)	P
Age (yr), mean ± SD	68.85 ± 7.45	46.62 ± 5.51	<.001
Gender (male), n (%)	22 (55.0)	19 (57.6)	.825
Dialysis time (mo), mean ± SD	8.15 ± 1.42	6.02 ± 1.14	<.001
Diabetes mellitus, n (%)	27 (67.5)	23 (69.7)	.841
Coronary heart disease, n (%)	25 (62.5)	20 (60.6)	.868
Hypertension, n (%)	25 (62.5)	19 (57.6)	.669

SD = standard deviation.

3.2. Serum klotho and FGF-23 levels

Klotho amounts (325.56 ± 41.15 vs 436.65 ± 45.58 pg/mL) were significantly lower while FGF-23 (114.45 ± 15.56 vs 70.15 ± 12.23 pg/mL) levels were markedly higher in the carotid artery calcification group compared with the non-calcification group ($P < .001$), as shown in Table 2.

3.3. Biochemical and clinical indexes

Weekly total kt/V (1.17 ± 0.22 vs 1.73 ± 0.25) and hs-CRP (11.32 ± 1.18 vs 5.23 ± 1.05 mg/L) were found significant differences between the calcification and non-calcification groups (both $P < .05$), there were no significant differences in other clinical biochemical indexes and blood pressure ($P > .05$; Table 3).

3.4. Influencing factors of carotid artery calcification in CAPD cases

Age (odds ratio [OR] = 1.01, 95% confidence interval [CI] 1.00–1.02; $P = .000$), dialysis time (OR = 2.50, 95% CI 1.46–5.23; $P = .000$), klotho amounts (OR = 1.53, 95% CI 0.89–2.64; $P = .000$) and FGF-23 levels (OR = 0.22, 95% CI 0.05–1.06; $P = .000$) were associated with carotid artery calcification occurrence in univariate analysis (Table 4). Multivariate analysis showed that elevated age (OR = 1.55, 95% CI 1.13–1.74; $P = .025$) and FGF-23 (OR = 2.16, 95% CI 2.01–2.44; $P = .042$), and lower klotho (OR = 0.66, 95% CI 0.47–0.85; $P = .036$) were independent risk factors for carotid artery calcification in CAPD. These findings indicated that age and FGF-23 levels were risk factors for carotid artery calcification, while klotho had a protective function. These data are detailed in Table 4.

Table 2

Klotho and FGF-23 amounts in the carotid calcification and non-carotid calcification groups.

Characteristic, mean ± SD	Carotid calcification group (n = 40)	Non-carotid calcification group (n = 33)	P
Klotho (pg/mL)	325.56 ± 41.15	436.65 ± 45.58	<.001
FGF-23 (pg/mL)	114.45 ± 15.56	70.15 ± 12.23	<.001

GF = fibroblast growth factor, SD = standard deviation.

Table 3

Other biochemical indexes in the carotid calcification and non-carotid calcification groups.

Index, mean ± SD	Carotid artery calcification group (n = 40)	Non-carotid calcification group (n = 33)	P
Ca (mmol/L)	2.14 ± 0.26	2.17 ± 0.24	.613
P (mmol/L)	1.84 ± 0.18	1.91 ± 0.15	.079
Weekly total kt/V	1.17 ± 0.22	1.73 ± 0.25	<.05
iPTH (pg/mL)	220.13 ± 19.37	209.21 ± 18.29	.058
eGFR (mL/min)	7.15 ± 5.42	7.04 ± 1.34	.231
Albumin (g/L)	28.21 ± 7.59	32.17 ± 9.80	.024
hs-CRP (mg/L)	11.32 ± 1.18	5.23 ± 1.05	<.05
TC (mmol/L)	1.42 ± 0.36	1.51 ± 0.34	.279
TG (mmol/L)	2.02 ± 0.41	2.04 ± 0.39	.833
LDL (mmol/L)	2.74 ± 0.56	2.71 ± 0.54	.818
HDL (mmol/L)	1.02 ± 0.21	1.05 ± 0.23	.563
SBP (mmHg)	138.85 ± 14.45	140.15 ± 14.05	.700
DBP (mmHg)	87.75 ± 8.56	88.12 ± 8.42	.854

Ca = calcium, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, hs-CRP = hypersensitive C-reactive protein, iPTH = intact parathyroid hormone, LDL = low-density lipoprotein, P = phosphorus, SBP = systolic blood pressure, SD = standard deviation, TC = total cholesterol, TG = triglyceride.

4. Discussion

The present study showed that serum FGF-23 and age are risk factors for carotid artery calcification in patients with CAPD, whereas klotho is a protective factor in CAPD patients.

This study found an incidence of carotid artery calcification in CAPD patients of 54.8%, in line with the previous findings reported by Carrie et al.[20] The incidence of vascular calcification in CKD3 patients is about 40%, and could be as high as 80% to 90% in CKD5D patients.[21] The factors affecting vascular calcification in CKD patients are complex. In addition to traditional high-risk factors such as age, hypertension, diabetes, lipid metabolism disorder, smoking and other parameters, genetic susceptibility, mineral metabolism disorder and non-mineral metabolism related factors play important roles.[22] This study found that age, elevated FGF-23 and reduced klotho were high risk factors for carotid calcification in CAPD patients. Conversely, dialysis time and iPTH were not associated with carotid calcification, which might be explained by the short dialysis time (<1 year) and the low calcium dialysate used.

In addition to being an anti-aging protein, klotho also regulates calcium and phosphorus metabolism and PTH secretion, counters oxidative stress, inhibits inflammation and apoptosis, promotes autophagy and inhibits fibrosis.[23] Klotho is reduced in CKD patients for various reasons, leading to the occurrence of vascular calcification.[24] FGF-23, a cytokine produced by osteoblasts, regulates the metabolism of bone and minerals. It requires klotho to inhibit 1,25-(OH)2-vitamin D3 synthesis and phosphorus absorption by activating FGF receptor, thus promoting phosphorus secretion. It is well-accepted that the FGF-23-klotho axis plays an important role in the occurrence and development of CKD-MBD.[13] These findings were confirmed here in CAPD patients. The notion that FGF-23 and klotho are potential therapeutic targets attracts increasing attention, with the klotho/ FGF-23 axis representing a new target for renal clinics.[25,26] Therefore, specific interventions modulating klotho and/or FGF-23 could provide novel treatment options for vascular calcification in CAPD cases.

Table 4

Univariate and multivariate logistic regression analysis of carotid calcification in peritoneal dialysis.

	Univariate analysis			Multivariate analysis		
Characteristic	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
Age	1.01	1.00–1.02	.000	1.55	1.13–1.74	.025
Gender (male/female)	1.04	0.83–1.46	.825			
Dialysis age	2.50	1.46–5.23	.000	1.02	0.92–1.14	.059
Diabetes mellitus	0.98	0.85–1.19	.841			
Coronary heart disease	1.01	0.75–1.52	.868			
Hypertension	0.96	0.79–1.21	.669			
Klotho	1.53	0.89–2.64	.000	0.66	0.47–0.85	.036
FGF-23	0.22	0.05–1.06	.000	2.16	2.01–2.44	.042

CI = confidence interval, FGF = fibroblast growth factor, OR = odds ratio.

In this study, the level of serum inflammatory factor hsCRP in carotid artery calcification group of ESRD patients was higher than that in non-carotid calcification group. At the same time, the risk of vascular calcification was higher in patients with inadequate dialysis. It is speculated that uremic toxin and micro inflammatory state *in vivo* may aggravate vascular calcification in maintenance peritoneal dialysis patients. Therefore, in the treatment of maintenance peritoneal dialysis patients, it is possible to reduce the risk of vascular calcification and improve the prognosis of ESRD patients by strengthening peritoneal dialysis, regulating the abnormalities of FGF-23 and klotho, and improving the micro inflammatory state.

In CAPD patients with higher FGF-23 level and lower serum klotho level, there was no significant difference in other risk factors such as serum calcium level, phosphorus level, iPTH level, LDL level and so on. It was considered possible that patients with ESRD may preferentially initiate changes in the FGF-23/klotho axis early in the process of vascular calcification, which is followed by abnormalities in serum calcium level, phosphorus level and other conventional laboratory indicators and disturbances in calcium and phosphorus metabolism, leading to an increased incidence of coronary heart disease.[27]

The present study had limitations. First, it was a retrospective trial, with inherent shortcomings. In addition, it was performed in a single center with a small sample size. Furthermore, dialysis time was relatively short. Therefore, large multi-center, prospective studies with long-term follow-up are warranted to confirm the current findings.

5. Conclusions

In conclusion, serum FGF-23 and age are risk factors for carotid artery calcification in patients with CAPD, while klotho is a protective factor. Attention should be paid to these factors in patients undergoing renal replacement therapy. Using low calcium dialysate in high-risk patients could help reduce the occurrence of vascular calcification. Finally, specific interventions modulating klotho and/or FGF-23 would provide novel therapeutic options for vascular calcification in CAPD cases.

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Author contributions

GNF contributed to the conception of the study; CX contributed significantly to analysis and manuscript preparation; CYJ performed the data analyses and wrote the manuscript; LGY helped perform the analysis with constructive discussions. All authors reviewed and edited the manuscript and approved the final version of the manuscript

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