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Prevalence and risk factors associated with peripheral artery disease in elderly patients undergoing peritoneal dialysis

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Background: Rapid growth of the elderly peritoneal dialysis (PD) population is posing a special challenge for renal teams. Peripheral artery disease (PAD) has been reported to be an independent predictor of cardiovascular and all-cause mortality in hemodialysis patients. However, the prevalence and associated risk factors for PAD in elderly PD patients have not yet been fully investigated.

Methods: A total of 69 elderly PD patients were included in the present study. PAD was defined as either an ankle-brachial index < 0.9 or a history of intermittent claudication, lower-limb amputation, foot ulcers, or gangrene. On enrollment, clinical and biochemical characteristics were collected.

Results: The overall prevalence of PAD was 31.9%. Compared with non-PAD patients, PAD patients were significantly older and more likely to be female and have longer PD duration and lower diastolic blood pressure ($P < 0.001$, $= 0.002$, 0.018, and 0.007, respectively). Serum albumin level ($P < 0.001$) and residual renal Kt/V value ($P < 0.001$) were significantly lower, but the serum C-reactive protein level ($P = 0.005$) was significantly higher, in PAD patients compared with non-PAD patients. Logistic regression analysis showed that serum albumin level (odds ratio = 1.485, $P = 0.040$) and residual renal Kt/V value (odds ratio = 1.725, $P = 0.016$) were independently associated with PAD.

Conclusion: A high prevalence of PAD appeared among elderly PD patients in Macao. Serum albumin level and residual renal Kt/V value were independently related to PAD.

Keywords: ankle-brachial index, atherosclerosis, elderly, peripheral artery disease, peritoneal dialysis

Introduction

Rapid growth of the elderly peritoneal dialysis (PD) population is posing a special challenge for renal teams. According to the US Renal Data System (USRDS) and Hong Kong Renal Registry reports, the mean age for incident PD patients is older than 60 years and has continued to increase gradually during the past decade.[1,2] Moreover, the cumulative 1- and 5-year patient survival rates among PD patients over 65 years old are obviously lower compared with those younger than 65 years old.[2] Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity among patients on chronic dialysis.[3]

Peripheral artery disease (PAD), characterized as a chronic developing atherosclerosis in the peripheral arteries, is common in end-stage renal disease (ESRD) patients.[4] Recently, the USRDS reported an approximately 22% prevalence of PAD among incident PD patients in 2008. Measurement of ankle-brachial index (ABI) has

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been established to be reliable for diagnosing PAD in both the general population and dialysis patients.[5] In addition, PAD or a low ABI (<0.9) has been reported to be a powerful independent predictor of cardiovascular and all-cause mortality in hemodialysis patients.[6,7] Furthermore, a couple of studies have also shown that advanced age, longer duration of dialysis, diabetes, increased pulse pressure, and decreased serum albumin level were independent predictors of PAD in hemodialysis patients.[8,9] However, the prevalence and associated risk factors for PAD in chronic PD patients, especially the elderly population, have not yet been fully investigated. Therefore, this present cross-sectional study aims to evaluate the associated risk factors for PAD among elderly PD patients in Macao.

Methods

Study design and patients

Centro Hospitalar Conde de São Januário, the only government hospital, is responsible for all of the PD patients in Macao. We retrospectively studied all chronic PD patients (n = 115) in our center in this cross-sectional study from June 1, 2010 to June 31, 2010. Finally, 69 chronic PD patients were included. All patients fulfilled the inclusion criteria of PD treatment time > 3 months prior to enrollment and age older than 60 years. Exclusion criteria were: (1) presence of clinically overt congestive heart failure (New York Heart Association class III–IV); (2) peritonitis less than 1 month before the study; and (3) persistent hypotension despite pharmacological therapy (defined as systolic blood pressure [SBP] <90 mmHg or diastolic blood pressure [DBP] <60 mmHg). Patients with atrial fibrillation were excluded due to the technical limitations inherent with ABI measurement. On enrollment, demographic and clinical data were collected, including age, sex, height, weight, blood pressure, presence of diabetes mellitus, smoking history, medication history, and etiology of ESRD. Of the 69 patients, 29 were using low–glucose degradation product (GDP) peritoneal dialysis fluid (PDF). The Charlson comorbidity index (CCI) was scored as described by Beddhu et al.[10] Hyperlipidemia was defined according to Adult Treatment Panel III criteria or use of statins. This study was approved by the ethical committee of Centro Hospitalar Conde de São Januário, and written informed consent was obtained from all patients.

Biochemical analysis

Laboratory parameters used were the most recent ABI measurement. Fasting blood samples were collected in the morning. Measurements were performed using routing laboratory methods for such serum parameters as creatinine, calcium, phosphate, albumin, lipid profile, hematocrit, and hemoglobin. Serum C-reactive protein (CRP) was measured by a high-sensitivity commercial assay. Serum intact parathyroid hormone (iPTH) was measured by Nichols immunoradiometric assay. Blood, urine, and dialysate samples were collected in order to calculate both total and residual renal weekly Kt/V.

ABI measurement

The ABI was measured using a VP-1000 vascular profiler (Nippon Colin, Komaki, Japan) in PD patients with empty abdomen after drainage of dialysate and at least 15 minutes' supine rest. ABI is used as a PAD marker due to ease of measurement, reproducibility, and validity in previous studies.[11] Briefly, the ABI was automatically calculated as the ratio of ankle SBP to brachial SBP for each side, and the lower value was used for analysis. All the ABI measurements were performed by one experienced operator. PAD was defined as either an ABI < 0.9 or a history of intermittent claudication, lower-limb amputation, foot ulcers, or gangrene.

Statistical analysis

Continuous variables with normal distribution are expressed as means ± standard deviation, while those without normal distribution (including the CCI score, the serum triglycerides level, serum CRP level, and serum iPTH level) are shown as median and interquartile range. Comparisons between the two groups were done by Student's *t*-test or χ^2 test. Nonparametric data were compared using the Mann–Whitney *U* test. A stepwise binary logistic regression analysis was used to assess the independently associated factors for PAD. Because of the skewed distribution, CRP was logarithmically transformed for analysis. A two-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using the SPSS statistical software 17.0 for Windows (IBM, Armonk, NY).

Results

Patient characteristics and comparisons between the PAD and non-PAD groups

A total of 69 elderly PD patients (37 female/32 male) were finally included. The causes of ESRD were diabetes mellitus (n = 28), chronic glomerulonephritis (n = 20), essential hypertension or ischemic nephropathy (n = 20), and obstructive nephropathy (n = 1). The mean ABI value was 0.97 ± 0.20. The overall prevalence of PAD was 31.9% in enrolled

elderly PD patients, including four patients with lower-limb amputation, three patients with intermittent claudication, and two patients with foot ulcers or gangrene. Table 1 shows the demographic and clinical characteristics of enrolled elderly PD patients and the comparisons between PAD and non-PAD patients. Compared with non-PAD patients, PAD patients were significantly older ($P < 0.001$) and more likely to be female and to have a longer PD duration and a lower DBP ($P = 0.002$, 0.018, and 0.007, respectively). Table 2 shows the laboratory parameters of enrolled PD patients and the comparisons between two subgroup patients. Serum albumin level ($P < 0.001$) and residual renal Kt/V value ($P < 0.001$) were significantly lower, but the serum CRP level ($P = 0.005$) was significantly higher, in PAD patients compared with non-PAD patients. However, no significant differences were found in CCI, SBP, pulse pressure, body mass index, smoking history, prevalence of diabetes, previous history of CVD, use of low-GDP PDF or renin–angiotensin system inhibitors, total Kt/V, serum phosphate and iPTH levels between two groups (all $P > 0.05$).

Multivariate logistic regression analysis of independently associated factors for PAD

In order to identify the independently associated factors for PAD, age, sex, PD duration, DBP, serum albumin level, lnCRP, DM status, hyperlipidemia, and residual renal Kt/V value were selected for binary logistic regression analysis. As listed in Table 3, serum albumin level (odds ratio [OR] = 1.485; $P = 0.040$; 95% confidence interval, 1.003–2.710) and residual renal Kt/V value (OR = 1.725; $P = 0.016$; 95% confidence interval, 1.108–2.686) were found to be independently associated with PAD. Additionally, age was found to be a protective factor against PAD (OR = 0.794; $P = 0.046$; 95% confidence interval, 0.634–0.996).

Discussion

The present study investigated the prevalence of PAD and its associated risk factors among elderly PD patients in Macau. We found that prevalence was 31.9% in this specified aging PD patient population. However, it was much higher than the prevalence reported by previous studies in community-based populations (10.5%) and general PD patients (27.4%).[12,13] Meanwhile, our findings also indicated that serum albumin level and residual renal Kt/V value were independently associated with PAD in elderly PD patients.

Although PD has been recognized as a successful method of choice for elderly ESRD patients, especially those with impaired cardiac function and difficult vascular access, numerous available studies have shown that advanced age is associated with shorter survival on PD.[2,14] Nevertheless, survival data from these studies need to be interpreted with caution, due to different dialysis policies and sociodemographic and clinical characteristics between centers and between countries.[15] Nutritional status, late referral, and functional dependency were suggested as independent predictors of death in the elderly PD patients.[16] Furthermore, CVD is the leading cause of hospitalization and mortality in elderly PD patients.[14]

Table 1 Demographic and clinical characteristics of study population and comparisons between subgroups

Variables	Total (n = 69)	PAD group (n = 22)	Non-PAD group (n = 47)	*P*-value
Age (years)	71.84 ± 8.47	78.41 ± 5.70	68.77 ± 7.81	<0.001
Female sex	53.6%	77.3%	42.6%	0.007
CCI (score)	5.0 (3.0, 9.0)	6.0 (4.0, 8.0)	5.0 (3.0, 9.0)	0.227
PD duration (months)	42.00 ± 27.30	59.23 ± 32.56	33.94 ± 20.23	0.002
SBP (mmHg)	133.96 ± 20.53	127.77 ± 20.15	136.85 ± 20.27	0.087
DBP (mmHg)	73.65 ± 14.64	66.86 ± 16.72	76.83 ± 12.53	0.018
PP (mmHg)	60.30 ± 16.07	60.91 ± 18.82	60.02 ± 14.83	0.832
BMI (kg/m^2)	24.28 ± 3.62	24.87 ± 4.24	24.01 ± 3.31	0.362
Dose of erythropoietin (U/kg/week)	122.47 ± 94.49	122.17 ± 97.71	122.61 ± 94.02	0.986
RAS-inhibitor use	56.5%	40.9%	63.8%	0.073
Hyperlipidemia	43.5%	40.9%	44.7%	0.768
Low-GDP PDF use	42.0%	45.5%	40.4%	0.693
Previous CVD history	36.3%	39.5%	34.6%	0.218
Diabetes mellitus	39.1%	36.4%	40.4%	0.747
Ever-smokers	18.8%	18.2%	19.1	0.924
ABI	0.97 ± 0.20	0.73 ± 0.14	1.08 ± 0.10	<0.001

Abbreviations: PAD, peripheral artery disease; CCI, Charlson comorbidity index; PD, peritoneal dialysis; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; BMI, body mass index; RAS, renin–angiotensin system; GDP, glucose degradation product; PDF, peritoneal dialysis fluid; CVD, cardiovascular disease; ABI, ankle-brachial index.

Table 2 Laboratory parameters of study population and comparisons between subgroups

Variables	Total (n = 69)	PAD group (n = 22)	Non-PAD group (n = 47)	*P*-value
Serum albumin (g/L)	38.28 ± 5.19	33.50 ± 5.06	40.51 ± 3.48	<0.001
Cholesterol (mmol/L)	4.90 ± 1.22	4.73 ± 0.85	4.97 ± 1.36	0.449
Triglycerides (mmol/L)	2.00 (0.59, 8.70)	2.08 (1.01, 8.70)	1.94 (0.59, 5.56)	0.479
LDL cholesterol (mmol/L)	2.76 ± 1.17	2.69 ± 0.92	2.79 ± 1.28	0.737
HDL cholesterol (mmol/L)	1.20 ± 0.35	1.11 ± 0.33	1.24 ± 0.35	0.141
Hemoglobin (g/dL)	11.24 ± 1.40	10.95 ± 1.33	11.38 ± 1.42	0.233
Hematocrit (%)	32.94 ± 4.08	32.15 ± 3.81	33.31 ± 4.19	0.271
C-reactive protein (mg/L)	0.49 (0.10, 15.70)	0.80 (0.10, 15.70)	0.24 (0.10, 5.94)	0.005
Calcium (mmol/L)	2.41 ± 0.25	2.46 ± 0.35	2.39 ± 0.19	0.403
Phosphate (mmol/L)	1.48 ± 0.41	1.35 ± 0.40	1.53 ± 0.40	0.074
Calcium-phosphate product ([mmol/L]^2)	3.55 ± 1.00	3.29 ± 1.00	3.67 ± 0.98	0.143
Intact PTH (pg/mL)	299.00 (17.20, 1761.00)	245.10 (32.20, 1761.00)	313.40 (17.20, 1486.00)	0.898
Kt/V (total)	2.13 ± 0.42	1.98 ± 0.34	2.19 ± 0.45	0.052
Kt/V (PD)	1.73 ± 0.40	1.84 ± 0.30	1.68 ± 0.43	0.107
Kt/V (renal)	0.49 ± 0.40	0.18 ± 0.09	0.54 ± 0.53	<0.001

Abbreviations: PAD, peripheral artery disease; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PTH, parathyroid hormone; PD, peritoneal dialysis.

Atherosclerosis has taken on great importance in the pathophysiology of CVD. As a systemic disease, atherosclerosis in the peripheral arteries is a chronic, slowly developing condition causing narrowing of the arteries. In the present study, it is not surprising that PD duration was found to be longer in PAD patients. Measurement of ABI using the Doppler technique is a simple, noninvasive, and reliable method for detecting PAD. An ABI of <0.9 has 95% sensitivity and almost 100% specificity in confirming angiogram-positive PAD in apparently healthy populations.[17] Consistent with a previous report,[13] our study also indicated that ABI measurement may contribute to the identification of many cases with clinical, unrecognized PAD.

Interestingly, we found PAD was more likely in elderly female patients. The exact mechanism for this sex difference remains unclear. Since all the women in our study were postmenopausal, it seemed sex-hormone levels might not have contributed to the sex difference in elderly PD patients. In addition, we also found that DBP was significantly lower in PAD patients. It is worth noting that the mean DBP was only 66.86 mmHg, which was a little lower according to the general target level, in our studied patient group. The presence of a negative correlation between DBP and the presence and extent of atherosclerosis in the general population has been previously reported.[18] Moreover, lower DBP has also been identified as an independent factor of cardiovascular morbidity and mortality in ESRD patients.[19] However, the exact pathophysiologic mechanisms for low DBP to precipitate the occurrence of atherosclerotic events are still poorly understood. Moreover, a reversed epidemiology on relationship between BP and survival rate has also been found in dialysis patients.[20]

Available evidence has demonstrated that malnutrition is more frequent in elderly than in younger PD patients.[14,21] Several factors may contribute to anorexia and malnutrition in elderly PD patients, including abdominal fullness, inadequate energy intake, social and psychological factors, comorbidity, dialytic losses of protein or amino acids, and infection.[22]

Table 3 Multiple logistic regression analysis of factors associated with PAD

Variables	B	SE	Wald	*P*	OR	95% CI for OR
Constant	–3.766	11.805	0.102	0.750	0.023	
Age (per year)	0.230	0.115	3.970	0.046	0.794	0.634–0.996
Kt/V_{renal} (per 0.1 unit)	–0.545	0.226	5.835	0.016	1.725	1.108–2.686
Serum albumin (per 1 g/L)	–0.395	0.200	3.892	0.040	1.485	1.003–2.710
Female (yes vs no)	0.234	1.405	0.028	0.868	0.791	0.050–12.432
PD duration (per month)	0.002	0.028	0.004	0.951	1.002	0.949–1.058
DM (yes vs no)	2.739	1.734	2.494	0.114	0.065	0.002–1.935
Hyperlipidemia (yes vs no)	1.765	1.409	1.569	0.210	0.171	0.011–2.710
lnCRP (per unit)	1.487	0.823	3.268	0.071	0.226	0.045–1.134
DBP (per 1 mmHg)	0.082	0.054	2.312	0.128	1.086	0.976–1.208

Abbreviations: PAD, peripheral artery disease; PD, peritoneal dialysis; DM, diabetes mellitus; lnCRP, log C-reactive protein; DBP, diastolic blood pressure; CI, confidence interval; OR, odds ratio; B, regression coefficient Beta; SE, standard error; Wald, Wald value; *P*, p value.

Although the precise mechanisms remain unknown, hypoalbuminemia is found to be an independent predictor of increased CVD and mortality in dialysis patients.[23] In the present study, we showed that serum albumin level was independently associated with PAD in elderly PD patients. It has been suggested that increased oxidative stress, micro- or clinical systemic inflammation, and endothelial dysfunction may play an important role in accelerating the atherosclerosis process in PD patients.[24,25] Additionally, it is well known that malnutrition–inflammation–atherosclerosis syndrome is common in chronic PD patients. Local inflammatory mediators such as proatherogenic adhesion molecules, chemokines, and growth factors may induce the synthesis of acute-phase proteins (for example, CRP) and inhibit the hepatic generation of albumin.[23] We found that the CRP level was significantly higher in elderly patients with PAD than those without PAD, but a difference of 0.56 is more likely to reflect statistical rather than clinical significance. Consistent with a previous study,[26] we had no direct evidence to link hypoalbuminemia and the inflammatory process in our patients. Anyway, we believe that inflammation might play a key role in the prevalence of PAD in elderly PD patients.

Residual renal function (RRF) has been clearly demonstrated to be related to all-cause mortality and risk of cardiovascular death in PD patients.[27] Recently, a reanalysis of data from the CANUSA study clearly showed that the predictive power for mortality is attributable to RRF and not to PD dose.[28] In the present study, residual renal Kt/V, but not peritoneal Kt/V, was found to be independently associated with PAD in elderly PD patients. Indeed, a recent study reported that a low ABI was an independent predictor for decline of RRF over time in PD patients.[29] Apart from better solute clearance and volume removal, better RRF may also contribute to improvement of vascular endothelial dysfunction and atherosclerosis, partly by decreased levels of circulating inflammatory markers and free radicals, reduced blood pressure, increased phosphorus removal, malnutrition, and reduced left ventricular hypertrophy.[30,31] The exact mechanisms behind lower renal Kt/V being related to higher prevalence of PAD remain unclear. However, a recent study indicated that PAD may be rather an important marker of CVD predicting the loss of residual renal function.[32] Consequently, more effective therapeutic strategies are warranted to preserve RRF in these elderly PD patients.

There are several limitations to the present study. Firstly, although our findings have reflected the current PAD status among elderly PD patients in Macao, it is a single-center study that is limited in power by sample size. Secondly, many potential confounding factors have been assessed in the present study; nonetheless, the existence of other unrecognized variables should not be neglected. Finally, because of the technical limitations inherent with ABI measurement, patients with atrial fibrillation were excluded. However, these PD patients are generally at high risk for arterial stiffness.

In conclusion, the presented data clearly show that a high prevalence of PAD appeared among elderly PD patients in Macao. Serum albumin level and residual renal Kt/V value were independently associated with PAD in elderly PD patients. Whether strategies to correct the possible causes of malnutrition and declining residual renal function might reduce the incidence of PAD and improve the CVD outcome in elderly PD patients needs further investigation.

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Disclosure

The authors declare that they have no conflicts of interest.

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