PRESENCE OF PERIPHERAL ARTERIAL DISEASE PREDICTS LOSS OF RESIDUAL RENAL FUNCTION IN INCIDENT CAPD PATIENTS

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◆ **Background:** Accelerated cardiovascular disease (CVD), including peripheral arterial disease (PAD), is very common in patients with end-stage renal disease. Residual renal function (RRF) is a strong predictor of patient survival that is suggested to be linked to the degree of CVD. However, the relationship between PAD and decline in RRF has not previously been measured.

◆ **Methods:** We studied incident continuous ambulatory peritoneal dialysis patients from Peking University Third Hospital. An ankle brachial index of less than 0.9 was used to diagnose PAD. Residual renal function (RRF) was determined as the mean of 24-hour urea and creatinine clearances (glomerular filtration rate). The Cox proportional hazards model was used to identify factors predicting loss of RRF.

◆ **Results:** The study included 86 patients (age: 61 ± 14 years; men: 51%), 23 of whom had PAD at baseline. Mean follow-up was 19 months (median: 18 months; range: 6–30 months). In univariate analysis, baseline PAD, peritonitis during follow-up, inflammation (C-reactive protein), serum uric acid, Ca $\times$ P, and serum phosphate were all significantly associated with a greater-than-50% decrease in RRF during follow-up. In multivariate analysis, only baseline PAD, Ca $\times$ P, and peritonitis were independently associated with a decline in RRF.

◆ **Conclusions:** Our study suggests that PAD may be a clinically important marker of CVD predicting the loss of RRF. It remains to be determined whether interventions aimed at decreasing PAD may also improve renal vascular status and thus slow the rate of RRF decline.

Loss of residual renal function (RRF) is an important predictor of morbidity and mortality in patients on maintenance dialysis (1,2). A declining RRF is associated with anemia, inflammation, malnutrition, and ectopic calcification (3,4). Meanwhile, preservation of RRF contributes to increased solute clearance and an improved fluid balance (5). Continuous ambulatory peritoneal dialysis (CAPD) is known to be better than hemodialysis (HD) at maintaining RRF (6), but a decline of RRF also occurs in CAPD. This decline is thought to reflect both progression of the primary kidney disease and increased kidney vascular dysfunction related to chronic kidney disease itself (7). Consistent with that hypothesis, cardiac disease and hypotensive events have both been shown to be associated with a decline in RRF (8–11).

Meanwhile, peripheral arterial disease (PAD), a manifestation of atherosclerosis in the lower extremities, is common in dialysis patients (12,13). Given that PAD is the result of an atherosclerotic process similar to that in cardiovascular disease (CVD) and that PAD is associated with a rise of serum creatinine in the community (14), we hypothesized that PAD may also be a marker of vascular bed degeneration and a predictor of RRF decline. We conducted a prospective observational study to investigate the predictive value of PAD for loss of RRF in incident CAPD patients.

METHODS

PATIENTS

Our prospective study included incident CAPD patients in the outpatient clinic of the Division of Nephrology at Peking University Third Hospital who started dialysis between 1 March 2006 and 1 December 2007. Patients were excluded if they had died within 3 months of starting dialysis ($n = 6$); if they had transferred to other centers or to HD or transplantation within 3 months ($n = 11$);

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and if their baseline urine volume was less than 200 mL daily or their glomerular filtration rate (GFR) was below 2 mL/min ($n = 8$).

The 86 patients who qualified for the study were followed until 1 June 2009. On the day that GFR was evaluated, 24-hour urine was collected. A significant decline in RRF was defined as a GFR loss of more than 50% from baseline or a daily urinary volume of less than 100 mL. Patients were censored at death or transfer to HD.

The local ethics committee approved the study, and informed consent was obtained from each patient enrolled.

PAD ASSESSMENT

We defined PAD as an ankle brachial index (ABI) below 0.9. We measured ABI as described by Feigelson *et al.* (15), calculated the value for each leg, and used the lower of the two values for analysis. The ABI measurement was conducted within the first month after the patient started peritoneal dialysis therapy.

Demographic data were collected on the same day that the ABI was measured; the laboratory results used were the most recent before the ABI measurement. Residual renal function was determined as the mean of 24-hour urea and creatinine clearances (GFR). Urine volume was obtained from the first and last evaluations of GFR. Diagnosed coronary artery disease (previous myocardial infarction, angina pectoris, a history of coronary artery bypass grafting or coronary stent implantation), and a history of cerebrovascular events were grouped as CVD. Diabetes status was defined as the use of insulin or oral hypoglycemic agents, or a fasting plasma glucose level higher than 7 mmol/L on at least 2 different days. All patients were followed every 3 months, and dialysis adequacy and incidence of peritonitis were recorded.

STATISTICAL ANALYSIS

The statistical analysis was carried out using SPSS (version 13.0: SPSS, Chicago, IL, USA). Continuous variables are presented as mean $\pm$ standard deviation, and categorical variables, as percentages. Serum levels of C-reactive protein (CRP) were logarithmically transformed [$\ln(\text{CRP})$] to approximate linearity. The Student *t*-test and the chi-square test were used, as appropriate, to identify differences between groups. A two-tailed *p* value less than 0.05 was regarded as statistically significant. The RRF survival curve was plotted using the Kaplan–Meier method and a log-rank test between patients that lost more than 50% of RRF during follow-up and those that

did not. A univariate Cox proportional hazards model was used to identify factors predicting the loss of RRF. The variables that achieved statistical significance ($p < 0.05$) were then selected into a multivariate Cox proportional hazards model to test for relative independence.

RESULTS

CROSS-SECTIONAL ANALYSIS

Of the 86 incident CAPD patients enrolled in the study (age: 61 ± 14 years; men: 51%), 26 had PAD at baseline. Table 1 shows the primary kidney diseases in the study group. Table 2 presents baseline clinical characteristics grouped by PAD status. Briefly, patients with PAD were older and more likely to have diabetes, a lower serum albumin level, a higher CPR level, and a higher baseline GFR.

During follow-up [for a mean of 19 months (median: 18 months; range: 6 – 30 months)], 26 patients experienced a more-than-50% loss of RRF (14 in the PAD group, 12 in the non-PAD group). The mean RRF decline in all patients was 2 ± 4 mL/min (1.3 ± 2.3 mL/min in non-PAD patients, 3.7 ± 6.2 mL/min in PAD patients). Urine volume declined to 636 ± 442 mL from 957 ± 378 mL in non-PAD patients, and to 433 ± 232 mL from 978 ± 340 mL in PAD patients.

UNIVARIATE AND MULTIVARIATE ANALYSES

The presence of PAD, peritonitis during follow-up, inflammation [$\ln(\text{CRP})$], serum uric acid, serum phosphate, and $\text{Ca} \times \text{P}$ were all significantly associated with a greater-than-50% loss of RRF during follow-up (Table 3). Table 4 shows the independently associated factors that predicted a greater-than-50% decline in RRF. In the Kaplan–Meier analysis, the presence of PAD predicted loss of RRF (Table 4, Figure 1).

TABLE 1
Primary Causes of Renal Failure in the Study Patients

Primary cause	Patients	
	(<i>n</i>)	(%)
Diabetic mellitus	27	31
Glomerulonephritis	20	23
Hypertension	13	15
Tubulointerstitial nephritis	8	9
Polycystic kidney disease	4	5
Pyelonephritis	4	5
Unknown	10	12

TABLE 2
Characteristics of Patients With and Without Peripheral Arterial Disease

Variable	Peripheral arterial disease		p Value
	No	Yes	
Patients (n)	60	26	
Age (years)	58±14	69±11	<0.001
Sex (% men)	57	42	0.221
GFR (mL/min)	6.4±3.6	9±3.8	0.003
Diabetes mellitus (%)	37	62	0.033
Cardiovascular disease (%)	29	38	0.439
ACEI/ARB (%)	18	23	0.615
Systolic BP (mmHg)	137±20	136±27	0.821
Diastolic BP (mmHg)	82±13	74±10	0.010
Pulse pressure (mmHg)	55±16	61±22	0.178
Height (cm)	162±9	159±10	0.266
Weight (kg)	64±12	60±15	0.205
Body mass index	24±3.5	25±3.6	0.216
Serum creatinine (mmol/L)	910±304	848±301	0.383
fP-Glu (mmol/L)	5.95±1.7	6.68±2.5	0.122
Serum P (mmol/L)	1.51±0.43	1.65±0.48	0.206
Serum Ca (mmol/L)	2.39±0.31	2.3±0.24	0.198
Ca×P	3.58±1	3.7±0.9	0.571
P-Alb (g/L)	40±3.8	38±4.1	0.038
Kt/V (total)	2.06±0.47	2.05±0.43	0.888
Kt/V (renal)	0.89±0.49	0.88±0.52	0.474
CRP (mmol/L)	5.16±11	12.97±20	—
Log-transformed CRP	0.4±1.6	1.6±1.4	0.002
Hemoglobin (g/L)	114±13	115±13	0.665
Uric acid (mmol/L)	394±91	403±83	0.662

GFR = glomerular filtration rate; ACEI = angiotensin converting-enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; fP-Glu = fasting plasma glucose; P-Alb = plasma albumin; CRP = C-reactive protein.

DISCUSSION

In this study of incident patients starting CAPD, we conclude that the presence of PAD is an independent predictor of a subsequent greater-than-50% loss of RRF. We suggest that these results reflect the fact that PAD is a systemic atherosclerotic process involving the whole vascular bed, and thus also reflects vascular health and disease in the kidney. It is possible that the association between PAD and loss of RRF reflects a shared risk factor profile between end-stage renal disease and atherosclerosis, but the association could not be explained away by controlling for many of the known risk factors for RRF decline.

Renal ischemia, a likely consequence of dysfunction in the renal vasculature, is known to predict loss of renal function (14,16), an observation supported by the fact that volume depletion also independently predicts decline in RRF (17,18).

Atherosclerosis often co-exists in different vascular beds (19). Missouris *et al.* reported a prevalence of 45% for renal artery stenosis in patients with PAD (20). Given that finding, our study suggests that PAD is a manifestation of atherosclerotic vascular disease in the lower limb vascular bed, likely reflecting a systemic disease also involving the kidneys (14,20–22). Atherosclerosis is also a process of inflammation, which has been found to predict the loss of RRF (1,23). In the present study, ln(CRP) was associated in univariate analysis with a decline in RRF (Table 3). Its loss of significance in the multivariate analysis (Table 4) may reflect the inflammatory process of PAD.

Previous data indicate that the presence of coronary artery disease, another systemic atherosclerotic manifestation, is associated with loss of RRF (9,11,18),

TABLE 3
Factors Significantly Associated with a More-Than-50% Loss of Residual Renal Function in the Study Patients

Variable	Adjusted risk ratio	95% CL		p Value
		Lower	Upper	
PAD at baseline (yes/no)	2.675	1.350	5.298	0.005
Peritonitis during follow-up	2.252	1.104	4.596	0.026
Log-transformed CRP (per unit)	1.277	1.047	1.556	0.016
Ca×P (per unit)	1.500	1.109	2.030	0.009
P (per mmol/L)	2.414	1.140	5.111	0.021
Age (per year)	1.010	0.979	1.042	0.519
Diabetes mellitus (yes/no)	1.268	0.587	2.740	0.545
Cardiovascular disease (yes/no)	0.762	0.300	1.935	0.567

CL = confidence limits; PAD = peripheral arterial disease; CRP = C-reactive protein.

TABLE 4
Factors Independently Predicting a More-Than-50% Loss of Glomerular Filtration Rate During Follow-Up^a in the Study Patients

Variable	Adjusted risk ratio	95% CL		<i>p</i> Value
		Lower	Upper	
PAD at baseline (yes/no)	2.237	1.099	4.555	0.026
Peritonitis during follow-up	2.208	1.030	4.735	0.042
Ca×P (per unit)	1.613	1.161	2.241	0.004

CL = confidence limits; PAD = peripheral arterial disease.

^a Median: 18 months; range: 6 – 30 months.

Figure 1 — Kaplan-Meier estimate of preservation of residual renal function (RRF) in patients with and without peripheral arterial disease (PAD).

supporting our hypothesis. Interestingly, in our study, PAD predicted loss of RRF more powerfully than CVD did, CVD having been excluded from the multivariate model. It should be noted, however, that previous studies (9,18) included congestive heart failure as a manifestation of CVD, something that was not done in the present study. Moreover, in the present study, only 9 patients with CVD had concurrent PAD, suggesting that our CVD definition may be somewhat arbitrary.

In agreement with previous findings (24,25), our data also suggest that peritonitis is an independent risk factor for RRF loss, likely related to the septic vascular damage associated with bacteremia and also potentially to the associated use of nephrotoxic antibiotics (26). Another possible mechanism could be temporary ultrafiltration failure and extracellular fluid volume expansion during peritonitis, leading to elevation of systemic blood pressure, which could have a deleterious effect on remnant nephrons (5).

There is a discrepancy concerning the role of disordered mineral metabolism on RRF. We found that serum phosphorus and Ca×P predict loss of RRF, consistent with previous findings (18,27). However, a recent publication by Noordzij and colleagues (Netherlands Cooperative Study on the Adequacy of Dialysis) failed to demonstrate an effect of disordered mineral metabolism on decline of RRF (28), concluding that the association exists only in pre-dialysis uremic patients in light of the many reports of the accelerative role of mineral disorders on renal function in chronic kidney disease patients (29–32). More studies are needed to clarify this issue.

CONCLUSIONS

Subclinical PAD is a common complication often ignored by nephrologists. The predictive role of PAD for RRF loss, as illustrated in the present study, strongly supports its role as an important marker of generalized CVD risk, providing new impetus for aggressive treatment aimed at minimizing the progression of atherosclerosis.

DISCLOSURES

All of the authors declare that no financial conflicts of interest exist.

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