Peritoneal Protein Clearance and not Peritoneal Membrane Transport Status Predicts Survival in a Contemporary Cohort of Peritoneal Dialysis Patients

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Background and objectives: Fast peritoneal membrane transport status may be due to inflammation or increased peritoneal membrane surface area. We evaluated the ability of peritoneal protein clearance (Pcl) to distinguish fast peritoneal membrane transport status as a consequence of peritoneal membrane inflammation and assess its impact on patient survival.

Design, setting, participants, & measurements: Patients who initiated peritoneal dialysis at our center since January 1998 and had a baseline peritoneal equilibration test, measurement of dialysis adequacy, and 24-h dialysate Pcl were included. Demography, comorbidities, and biochemical data were prospectively collected. Follow-up was until death or the end of the period studied. Multivariate regression analysis identified factors that were associated with Pcl. A Cox proportional hazards model was used to identify factors that were associated with survival.

Results: A total of 192 patients (56% men, mean age 54.3 ± 15.3; 32% with diabetes) were included. On univariate analysis, Pcl was negatively correlated with serum albumin and positively correlated with age, dialysate/plasma creatinine ratio (D/Pcr), the presence of peripheral vascular disease, and urine volume. On multivariate analysis, serum albumin, D/Pcr, urine volume, and peripheral vascular disease remained significant. Predictors of mortality were age, comorbidity grade, and Pcl but not D/Pcr.

Conclusions: In this cohort, peritoneal transport status no longer predicted survival, whereas Pcl remained a predictor. Increased large-pore protein loss may reflect the severity of underlying cardiovascular disease, portending a poor prognosis for these patients.

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Fast peritoneal membrane transport status (fPTS) is defined by the measurement of the diffusive peritoneal transport rate for small solutes such that the dialysate-to-plasma creatinine ratio (D/Pcr) is ≥0.81 at 4 h (1). It may be present at the initiation of peritoneal dialysis (PD) but may develop with time on treatment (2,3). Studies of continuous ambulatory PD (CAPD) patients have demonstrated baseline fPTS to be an independent predictor of mortality and technique failure (4). Explanations for this association include reduced peritoneal membrane ultrafiltration capacity owing to more rapid dissipation of the glucose osmotic gradient and resultant fluid reabsorption (5). This results in extracellular fluid volume expansion and hypertension (5). Because of an association between fPTS and hypoalbuminemia, it has been postulated that fPTS may be a manifestation of local or systemic inflammation while serving as a surrogate marker for the increased mortality seen with the malnutrition, inflammation, and atherosclerosis syndrome (6). Against this explanation is emerging evidence that fPTS does not seem to be associated with reduced survival and technique failure in contemporary cohorts (7–9).

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To resolve this problem, it has been postulated that fPTS may have two potential etiologies: Increased vascularity of the membrane associated with an increased anatomic membrane area or the result of inflammation and vascular injury. In both instances, fPTS will be due to increased blood flow and increased effective small-pore area in contact with dialysate (10). One way to distinguish these processes, according to the three-pore model of membrane function, is to dissociate the small solute transport rate, proportional to the small-pore area, from peritoneal protein clearance (Pcl), which, depending on the protein size, will be a function of both small pores and large pores (11). Protein leak across large pores, equivalent to large-pore flow, will be determined by their relative number, which will be increased during inflammation or by increased hydrostatic pressure across the capillary (12).

Heaf *et al.* (13) showed that patients whose membranes have increased large-pore flow (JvL) using the personal dialysis capacity (PDC) test have inferior survival; however, the membrane area parameter (A0/δx), a measure essentially equivalent to solute transport, was not included in a multivariate survival model (13). In a subsequent study, Van Biesen *et al.* (14) found that large-poor flow was associated with survival only when corrected for A0/δx such that a higher JvL for a given membrane area decreased survival, yet interpretation of these results is also confounded by the potential for internal mathematical coupling between JvL and A0/δx when using the PDC test,

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because the former is derived from the product of the pressure gradient and the ultrafiltration coefficient, LpS, and this in turn is derived from A0/δx (12). Both of these studies found a high level of correlation between small solute transport rates (either 4-h D/Pcr or A0/δx) and JvL. This might represent true biologic coupling, yet the use of shared parameters in the PDC test makes this unclear (15).

Here we determined the association between patient survival and both solute transport and Pcl, measured and calculated independently, in a prospective, single-center cohort that had previously reported worse outcomes in patients with fPTS (16). We explored the relationship among peritoneal protein leak, comorbidity, and BP.

Materials and Methods

Study Design and Patient Population

This was a prospective, single-center cohort study of consecutive new patients who commenced PD from January 1998 until the data were censored in December 2007. Baseline data were collected within 1 mo of treatment and included demographics, cause of renal failure, comorbidity, residual renal urine volume, and solute clearance. Baseline peritoneal solute clearance and membrane function using the peritoneal equilibration test (PET) were determined between 4 and 6 wk of treatment. Patients who had a measure of peritoneal Pcl at that time were considered eligible for the study.

Our PD population was censored in 1998, at which time a survival analysis and description of longitudinal membrane function were published (16). Since 1998, increasing proportions of patients were treated with automated PD (APD), particularly when anuric, as described in the European Automated Peritoneal Dialysis Outcome Study (EAPOS) (9). In patients with solute transport >0.64 (as assessed by D/Pcr at 4 h) on PET testing), icodextrin was used with increased frequency.

Comorbidity and Demographic Data

Comorbidity was documented as described previously and validated by prospective studies (17,18). Seven comorbid domains are considered, including noncutaneous malignancy, ischemic heart disease (IHD), peripheral vascular disease (PVD; including cerebrovascular and renovascular disease), left ventricular dysfunction (LVD; moderate to severe hypokinesia on two-dimensional echocardiogram), diabetes (the current/previous need for oral anti-diabetics or insulin), systemic collagen vascular disease, and any other condition that is known to reduce life expectancy. The comorbidity score for each patient was defined as the number of these domains affected. The comorbidity grade was then derived from the comorbidity score.

Measurement of Solute Clearance, Pcl, Membrane Function, and Blood Biochemistry

The dialysis dosage and residual renal function was calculated as the weekly Kt/V_{urea} from the 24-h urinary and dialysate clearance by direct measurement of urea in urine and each dialysate exchange. The PET was used to measure solute transport. A standard 4-h dwell period was used (first exchange of the day) using a 2.27% glucose concentration 2-L volume exchange. The patient used his or her usual overnight dialysis regimen, and both the overnight and test drainage volumes were measured. The D/Pcr at the completion of the 4-h dwell period was used to estimate low molecular weight solute transport. Plasma and dialysate concentrations of urea, creatinine, and glucose were determined on an automated discrete random access analyzer (DAX72; Bayer Instruments, Basingstoke, UK).

Peritoneal dialysate protein losses were measured from the collection of 24-h peritoneal dialysate effluent by the Biuret method. A validated correction factor was used for the calculation of Pcl (12): 24-h dialysate protein loss/(serum albumin/0.4783). Pcl was expressed as ml of plasma cleared per day.

Statistical Analysis

Continuous data are expressed as means ± SD, and categorical data are expressed as proportions. The relationship between peritoneal Pcl and continuous variables was examined by Pearson correlation coefficient. One-way ANOVA or *t* test was used to examine differences in Pcl among baseline categorical variables. Stepwise multiple linear regression was conducted to identify the determinants of Pcl using variables correlated in the univariate model. The multivariate model was constructed both with and without serum albumin as a covariate, given that albumin was used in the formula to determine Pcl. Significance was considered at $P \leq 0.05$. All statistical analyses were carried out using SAS 9.2 (SAS Institute, Cary, NC).

Survival Analysis

Time to death was defined from the date of dialysis initiation until the date of death, censoring for renal transplantation, loss to follow-up, or the end of the study period. Using a Cox proportional hazards model, univariate predictors of survival were identified. A multivariate Cox model was then constructed to obtain covariate adjusted measures of the association (adjusted hazards ratio [HR]) of baseline clinical factors on the risk for death. Cox regression models were performed to test associations of Pcl with model building on the basis of both univariate testing for association with survival and forced entry of variables that previously were shown to have an impact on the survival of PD patients. Covariates included age, comorbidity grade, serum albumin, baseline transport status, and Pcl. Diabetes was not included because of power limitations and its inclusion in the measure of comorbidity grade. Proportionality of hazards over time was verified for each covariate by testing the interaction between the covariate and a linear function of time. Survival was also examined by comparing patients above and below the median value of Pcl with the Kaplan-Meier method and compared using the log-rank test.

Results

Patient Demographics

Between January 1, 1998, and December 30, 2007, a total of 341 patients were initiated on PD at our center. A total of 192 patients had baseline information on Pcl and were included in the study. All patients except for one were treated with lactate-buffered (40 mmol/L), pH 5.2 conventional dialysis solutions. Table 1 displays the main baseline demographic and clinical characteristics of these patients.

Table 2 displays baseline peritoneal membrane transport characteristics and biochemical information of the study patients. Total 24-h protein losses were 6.4 ± 2.3 g/d. Mean Pcl was 86.5 ± 33.6 ml/d (median 78.4 ml/d; range 29 to 276 ml/d). Ten (3.6%) patients were slow/low transporters, 71 (25.7%) patients were slow/low average, 133 (48.2%) patients were fast/high average, and 62 (22.5%) patients were fast/high transporters according to the definition by Twardowski *et al.* (1).

Compared with the 149 patients who were excluded from the study, Patients who were included in the study had higher baseline small solute clearance (D/Pcr 0.73 ± 0.13 *versus* 0.68 ± 0.11; $P < 0.01$) and greater initial use of APD (17 *versus* 6%; $P <$

Table 1. Baseline patient characteristics[a]

Variable	Value (n = 192)
Age (yr; mean ± SD)	54.3 ± 15.3
Male gender (n [%])	108 (56.0)
Cause of ESRD (n [%])	
diabetes	53 (27.6)
glomerulonephritis	41 (21.3)
polycystic kidney disease	17 (8.9)
renovascular disease	22 (11.5)
reflux nephropathy/urinary obstruction	23 (12.0)
other	7 (3.6)
unknown	29 (15.1)
Initial modality APD (n [%])	34 (17.6)
Diabetes (n [%])	61 (32.0)
Previous cardiovascular disease (n [%])	
left ventricular dysfunction	14 (7.0)
ischemic heart disease	42 (22.0)
peripheral vascular disease	33 (17.0)
Comorbidity grade (%)[b]	
low	87 (45.3)
intermediate	85 (44.3)
high	20 (10.4)
MAP (mmHg; mean ± SD)	99.6 ± 16.2
BMI (kg/m^2; mean ± SD)	26.7 ± 5.2

[a]APD, automated peritoneal dialysis; BMI, body mass index; MAP, mean arterial pressure; BMI, body mass index.
[b]Comorbidity Grade- Davies Comorbidity grade as defined previously.

Table 2. Peritoneal transport, dialysis adequacy, and biochemical characteristics[a]

Variable	Mean ± SD
D/Pcr	0.73 ± 0.13
Peritoneal Kt/V	1.46 ± 0.32
Renal Kt/V[b]	0.97 ± 0.71[b]
24-h Pcl (ml)	86.5 ± 33.6
Hemoglobin (g/L)	115 ± 17
24-h dialysate protein losses (g)	6.4 ± 2.3
Serum albumin	36.0 ± 4.6
24-h urine volume (ml; mean ± SD)	1091.5 ± 769.0

[a]D/Pcr, dialysate/plasma creatinine; Pcl, protein clearance.
[b]Data reported on 167 patients.

0.01). No other differences existed between the two groups on the basis of the clinical and biochemical data listed in Tables 1 and 2 (all $P > 0.05$).

During the course of PD treatment, APD was used in 106 (55%) patients and icodextrin in 131 (68%) patients. APD was introduced at a median duration of PD of 6 mo (range 1 to 80 mo) and icodextrin at a median duration of PD of 7 mo (range 1 to 39 mo). Thirty-nine (20%) patients were treated without the use of APD or icodextrin.

Association of Peritoneal Pcl with Clinical and Biochemical Variables

Univariate correlations between Pcl and clinical and biochemical variables of interest are presented in Table 3. Higher Pcl was seen with increasing age (r = 0.18, P = 0.01) and male gender (91.5 ± 3.0 *versus* 80.4 ± 4.6 ml/d; P = 0.02). No association was seen with Pcl and increasing comorbidity grade (P = 0.08), but the presence of PVD was associated with higher Pcl (98.9 ± 46 *versus* 84.1 ± 30 ml/d; P = 0.02),). A trend of higher mean Pcl was seen in the presence of diabetes (91.7 ± 42.0 *versus* 84.3 ± 29.0 ml/d), IHD (93.2 ± 27.0 *versus* 84.8 ± 35.0 ml/d), and LVD (97.8 ± 32.0 *versus* 85.8 ± 34.0 ml/d), but these did not reach statistical significance (all $P > 0.05$)

A negative correlation was seen between Pcl and serum albumin ($r = -0.38$) as well as a positive correlation with small solute transport status (D/Pcr; r = 0.29) and small solute transport category (all $P < 0.01$; Figure 1). There was also a positive correlation with Pcl and 24-h urine volume (r = 0.24) and pulse pressure (PP) (r = 0.23), but no association between Pcl and peritoneal ultrafiltration was seen (Figure 2).

On stepwise multivariate linear regression analysis, serum albumin, D/Pcr, and 24-h urine volume were independently associated with Pcl (all $P \leq 0.05$; Table 4). In model 2, with albumin excluded, D/Pcr and 24-h urine volume remained in the model ($P < 0.05$) with the additional inclusion of PVD (P = 0.04).

Peritoneal Pcl and Survival

The median duration of observation was 38.8 mo (range 0.6 to 136.9 mo). Forty-eight patients died during the period of observation. Patients above the median value of Pcl (78.4 ml/d) had worse survival than those below the median (log-rank P = 0.008; Figure 3). Results of the Cox proportional hazard model are summarized in Table 5.

Table 3. Univariate associations between peritoneal Pcl and patient characteristics[a]

Parameter	Bivariate Correlation	
	R	P
Age at PD start	0.18	0.01
Gender	−0.16	0.02
Comorbidity grade	–	0.08[b]
PVD	0.16	0.02
IHD	0.10	0.15
LVD	0.09	0.19
Diabetes	0.10	0.15
Serum albumin	−0.38	<0.0001
D/Pcr	0.29	0.0001
24-h urine volume	0.24	0.0009
24-h peritoneal UF	−0.03	0.7
PP	0.23	0.006

[a]IHD, ischemic heart disease; LVD, left ventricular dysfunction; PD, peritoneal dialysis; PP, pulse pressure; PVD, peripheral vascular disease; UF, ultrafiltration.
[b]P value by ANOVA.

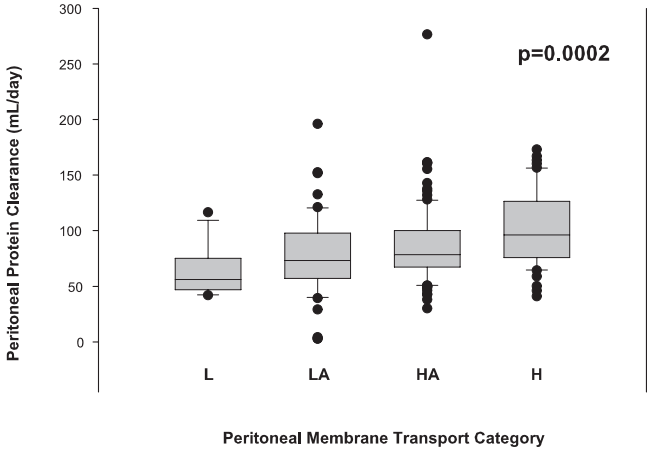

Figure 1. Association between peritoneal protein clearance (Pcl) and peritoneal membrane transport status. *P value by ANOVA. L, low; LA, low average; HA, high average; H, high.

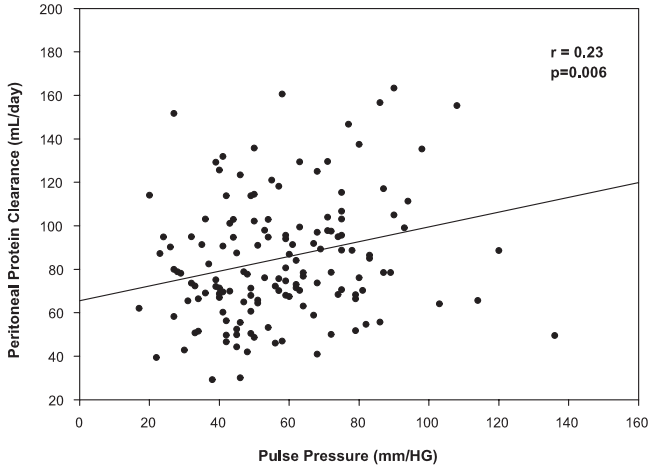

Figure 2. Association between peritoneal Pcl and pulse pressure.

Table 4. Multivariate association between peritoneal Pcl and patient characteristics[a]

Parameter	Model 1		Model 2	
	β	P	β	P
Serum albumin	−0.26	<0.0001	–	–
D/Pcr	4.4	0.03	6.3	0.004
PVD	1.17	0.06	1.4	0.04
24-h urine volume	0.001	0.05	0.0008	0.03
PP	–	–	0.02	0.10

[a]Model 1 includes albumin; model 2 excludes serum albumin.

On multivariate analysis, age, comorbidity grade, and Pcl remained independent predictors of survival. For each 10-ml increase in Pcl, the adjusted HR of death was 1.09 (95% confidence interval [CI] 1.01 to 1.18). In contrast, peritoneal small solute clearance as measured by D/Pcr was not associated with increased mortality (adjusted HR 0.42; 95% CI 0.04 to 5.07).

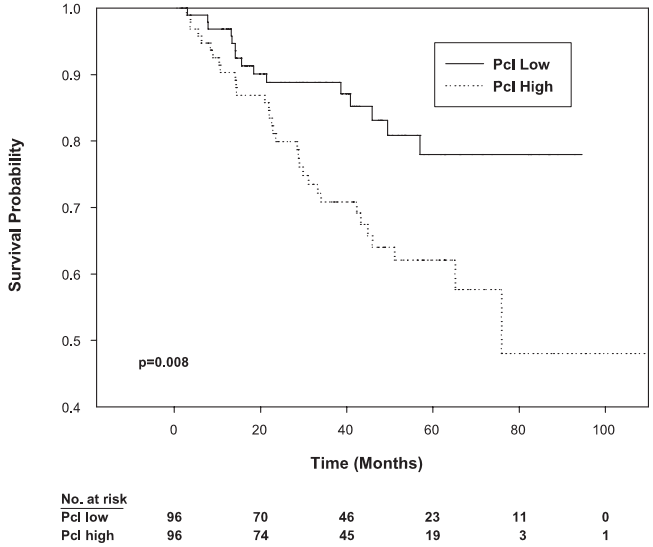

Figure 3. Survival of patients above and below the median value of daily peritoneal Pcl. Peritoneal Pcl was divided into high and low by separation of patients above and below the median value of 78.4 ml/d.

As previously mentioned, D/Pcr values were higher for patients who were included in the study (n = 192) when compared with the 149 patients who were excluded on the basis of missing information regarding Pcl. To limit the potential bias that this may have introduced in the survival analysis, we constructed a Cox proportional hazards model to examine the impact of transport status on the survival of all 341 incident patients; however, after inclusion of all 341 patients, transport status (D/Pcr) did not remain a predictor of survival on unadjusted analysis (HR 1.50; 95% CI 0.26 to 8.70) and after adjustment for age, comorbidity grade, and serum albumin (adjusted HR 0.83; 95% CI 0.13 to 5.20; P = 0.8).

Discussion

Here we report that increased Pcl at the start of PD therapy is a predictor of death, independent of baseline small solute transport status when measured separately, as well as serum albumin, age and detailed comorbidity. It supports and extends the observations of Heaf and Van Biesen (13,14). An independent association between Pcl and PVD was demonstrated. Pcl correlated with increasing age and PP, and a trend was seen with higher Pcl values in the presence of IHD, LVD, and diabetes.

In this cohort of PD patients, baseline small solute transport was no longer a predictor of survival. We reported a relationship between increased small solute transport and reduced survival in CAPD patients who initiated PD at our center before 1995 (16). It is tempting to speculate that, after 1998, increased use of APD and icodextrin at our center resulted in improved outcomes for patients with fPTS at the start of therapy. Both of these treatment strategies benefit the impaired salt and water removal that is associated with fPTS. The disappearance of

Table 5. Univariate and multivariate Cox regression model on patient survival[a]

Variable	Unadjusted RR for Death			Adjusted RR for Death		
	RR	95% CI	*P*	RR	95% CI	*P*
Age at PD initiation (per year)	1.07	1.04 to 1.09	<0.0001	1.06	1.03 to 1.09	<0.0001
Gender (female reference)	0.59	0.32 to 1.08	0.09	–	–	–
Comorbidity grade (per increase in 1)	2.35	1.52 to 3.63	0.0001	1.74	1.06 to 2.85	0.02
Diabetes	1.56	0.85 to 2.76	0.15	–	–	–
Albumin baseline (for each 1-g/L increase)	0.93	0.87 to 0.98	0.01	0.987	0.92 to 1.06	0.72
Pcl (for each 10-ml/d increase)	1.11	1.05 to 1.12	0.0009	1.09	1.01 to 1.18	0.02
D/Pcr	1.11	0.098 to 12.460	0.93	0.42	0.04 to 5.07	0.5
BMI (kg/m^2)	0.99	0.93 to 1.05	0.69	–	–	–
24-h urine volume (for each 100-ml increase)	1.00	0.99 to 1.00	0.16	–	–	–
Peritoneal Kt/V	1.04	0.39 to 2.81	0.93	–	–	–
PP	1.01	0.998 to 1.03	0.09	–	–	–

[a]CI, confidence interval; RR, relative risk; PD, peritoneal dialysis; BMI, body mass index; PP, pulse pressure.

increased mortality risk of fPTS in other reported patient cohorts using APD and icodextrin would strongly suggest that fPTS is an intrinsic characteristic of membrane function that can be managed successfully (7–9). This argues against fPTS as solely a manifestation of systemic inflammation, which would be less responsive to the discussed treatment strategies.

The three-pore model of the peritoneal membrane provides a mechanistic framework to understand why Pcl might be uncoupled from small solute transport as a predictor of mortality (11). The difficulty in applying this model to our data is that albumin, the predominant plasma and dialysate protein, may pass through both small pores (predominantly by convection) as well as large pores, where the driving force is hydrostatic pressure (19). Ideally, to dissect out precisely the contribution of the relative pores to this process, it is necessary to measure a series of proteins at different molecular weights, a procedure that is beyond the feasibility of large prospective long-term epidemiologic studies (in this case 10 yr). In the aforementioned studies, using the PDC test, JvL is determined using either dialysate albumin (13) or total protein, although this is not always clear (14). Using these different approaches, these studies have found correlations between their measures of small- and large-pore pathways: We found that approximately 8% of the variance in Pcl could be explained by solute transport, whereas 16 to 25% of the variance in JvL could be explained by $A0/\delta x$ in the PDC studies (13,14). These higher values may well represent the greater potential for mathematical coupling when using the PDC as discussed already. Taken together, these findings suggest that there is at least a degree of true coupling between these measures.

The majority of Pcl is uncoupled from small pores, and Pcl is an independent predictor of survival. One possible explanation for this association is the known link between cardiovascular disease and endothelial dysfunction as evidenced by microalbuminuria (20). Van Biesen *et al.* (14) found a weak but significant association with inflammation and JvL. Heaf *et al.* (13) observed greater values for JvL in older patients and those with cardiovascular comorbidity. This is in keeping with the observation in a small single-center cohort of PD patients in which a single measure of dialysate albumin >300 mg/L was associated with increased cardiovascular events and a tendency to more atheromatous disease on carotid Doppler (21). Sanchez-Villanueva *et al.* (22) also found an independent association between baseline peritoneal protein losses and peripheral arterial disease. Here, we found associations with age, the presence of PVD, and the PP, which although explaining only a small amount of variance was highly statistically significant. Early in treatment, Pcl may serve as a marker for the severity of systemic vascular disease and injury. Future studies are needed to establish the role of local inflammation within the peritoneal cavity, which may be driving membrane injury and increases in Pcl.

Similar to other studies, a positive association between Pcl and urine volume was noted (13,14). It is possible that patients with increasing comorbid conditions and, in turn, greater Pcl may have been selected to initiate PD with greater residual renal function. In our cohort, 24-h urine volume was inversely correlated with comorbidity grade ($P < 0.05$), arguing against this hypothesis. Alternatively, it is possible that urine volume may be a surrogate for urinary protein losses, which may positively correlate with peritoneal protein losses *via* a common pathway of endothelial dysfunction. Lack of measurement of urinary protein excretion limits the testing of this hypothesis in this study. Further experimental verification and testing are required to explain this relationship.

The findings of this study must be interpreted in the context of the study design. The strengths of the study include the large number of patients studied, long duration of follow-up, and adjustment for multiple confounding covariates. Limitations include the single-center nature of the study and the potential bias introduced by measurements of Pcl available only for a subset of patients. Efforts were made to limit this bias by inclusion of the entire cohort in a survival analysis with available covariates.

All of these studies, including this one, used plasma albumin and applied a formula when required to estimate either total

protein concentration to calculate clearances or plasma and dialysate oncotic pressures to determine JvL. It is possible that under extreme systemic inflammation, serum protein may be underestimated and Pcl overestimated by an uncoupling between serum albumin, which is a negative acute-phase protein, and other proteins that are positive acute-phase proteins. Pcl (or JvL in the PDC studies) may have been amplified under extreme conditions of systemic inflammation. Even when we considered absolute protein losses corrected to body surface area, an association with reduced survival persisted after the adjustment for serum albumin. We did not have an independent measure of inflammation such as C-reactive protein. Future studies will be required to determine the association between Pcl and a panel of systemic and peritoneal markers of inflammation.

Conclusions

The measurement of Pcl provides valuable prognostic and therapeutic implications for patients who commence PD. Whether Pcl at the start of therapy represents a marker of systemic inflammation and comorbid conditions or is affected by treatment-related factors remains to be borne out in clinical trials. Studies that focus on the description of changes in Pcl with time on treatment and the associated prognostic significance are needed.

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Disclosures

None.

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