Peritoneal Kinetics and Anatomy

PART ONE
Inflammation, dialysis adequacy, and peritoneal transport rate (PTR) influence clinical outcomes in peritoneal dialysis (PD) patients. The present study examined the relationship of C-reactive protein (CRP), a marker of inflammation, to PTR and residual renal function (RRF) in PD patients. We recorded the baseline dialysate-to-plasma creatinine (D/P Cr) of 210 PD patients starting in 1986. In a subgroup of 42 patients, we serially measured high-sensitivity CRP levels and dialysis adequacy, including weekly Kt/V urea and creatinine clearance (CCr), starting in May 2003. The patients were followed to January 2006. Mean age was 53 ± 16 (standard deviation) years, and 70% of the patients were African American. Enrollment mean and median CRP levels were 13.53 ± 20.8 (range: 0.2 – 95.8) and 7.15 mg/L respectively. Mean weekly residual CCr and Kt/V during follow-up were 7.11 ± 15.47 L/1.73 m² and 0.14 ± 0.30 respectively. The mean enrollment D/P Cr was 0.649 ± 0.12 (range: 0.429 – 0.954). Patients with CRP > 10 mg/L had significantly lower weekly residual CCr (0.59 L/1.73 m² vs. 10.1 L/1.73 m², p = 0.01), residual Kt/V (0.01 vs. 0.20, p = 0.01), total CCr (56 L/1.73 m² vs. 62 L/1.73 m², p = 0.047), and total Kt/V (2.09 vs. 2.49, p = 0.001) than did those with CRP ≤ 10 mg/L. Levels of CRP correlated negatively with weekly residual CCr (r = −0.42, p = 0.006), residual Kt/V (r = −0.43, p = 0.006), and total Kt/V (r = −0.44, p = 0.004). Enrollment D/P Cr was inversely correlated with serum albumin (r = −0.24, p = 0.001) and directly correlated with peritoneal protein loss (r = 0.34, p = 0.028). Higher enrollment D/P Cr was associated with lower observed cumulative survival (Kaplan–Meier) in PD patients.

However, D/P Cr was not an independent predictor of long-term survival in PD patients. Using multivariate Cox regression analysis, and including D/P Cr and residual Kt/V in the model, enrollment CRP was an independent predictor of mortality (relative risk = 1.036, p = 0.018). We conclude that elevated CRP is associated with lower RRF. As a predictor of mortality, CRP may be better than RRF and D/P Cr.

Key words
Survival, peritoneal transport rate, residual renal function, C-reactive protein (CRP)

Introduction
Adequacy of dialysis and residual renal function (RRF) influence survival in peritoneal dialysis (PD) patients (1,2). We have shown that RRF affects dialysis adequacy, nutritional status and morbidity in PD patients. In PD patients, RRF is an independent predictor of mortality, especially over the first two years (3). It contributes to total solute clearance—that is, measures of adequacy such as Kt/V urea and creatinine clearance (CCr).

C-Reactive protein (CRP) is an acute-phase protein produced by the liver in response to cytokine [interleukin-6 (IL-6), interleukin-1, tumor necrosis factor] production during tissue injury, inflammation, or infection. Inflammation is a common feature in dialysis patients. We and others have shown that CRP is elevated in PD patients. Higher CRP levels are associated with increased morbidity and all-cause mortality in PD patients (4,5). In pre-dialysis chronic renal failure patients, an inverse relationship with renal function has been reported for proinflammatory mediators and CRP (6). In PD patients, the relationship between RRF and inflammation needs to be studied in detail (7).
Peritoneal transport rates (PTRs) have an important role in the clinical management of PD patients. A PD patient’s PTR is an important factor in determining optimal dialysis prescription and dialysis dose. A higher PTR has been shown to be associated with decreased patient survival (8). It has been suggested that several factors may contribute to higher PTR in PD patients. We investigated the relationship of CRP, an inflammatory marker, with PTR and RRF in PD patients.

Patients and methods
In this single-center retrospective observational study, we collected data by chart review. We enrolled 210 PD patients treated at the Avram Center for Kidney Diseases, Long Island College Hospital’s outpatient facility, from 1986 to 2005. Enrollment demographic, clinical, and biochemical data were obtained. Peritoneal equilibration tests had been performed after the start of dialysis therapy, and PTR values [dialysate-to-plasma creatinine (D/P Cr)] were recorded. In 30 patients, follow-up PTR values were available for analysis. In a subgroup of 42 patients, high-sensitivity CRP was assayed serially over the study period by the immunoturbidimetric method. All patients were followed to January 2006. Dialysis adequacy, including Kt/V urea and CCr, were measured serially at the time of CRP assays by a computer-based kinetic modeling program (PD Adequest: Baxter Healthcare Corporation, McGaw Park, IL, U.S.A.). Weekly CCr and total (residual renal and peritoneal) Kt/V urea, normalized to 1.73 m² of body surface area, were calculated. In a given patient, the mean follow-up value is the arithmetic mean of all serial measurements of a given variable.

| TABLE I | Correlations of C-reactive protein with dialysis adequacy (Kt/V) and peritoneal transport rate in peritoneal dialysis patients |
|-----------------|-----------------|-----------------|-----------------|
| Correlation coefficient | p Value |
| Weekly mean total CCr (L/1.73 m²) | –0.19 | 0.23 |
| Weekly mean total Kt/V | –0.44 | 0.004 |
| Weekly mean residual CCr (L/1.73 m²) | –0.42 | 0.006 |
| Weekly mean residual Kt/V | –0.43 | 0.006 |
| Enrollment D/P Cr | 0.004 | 0.98 |

CCr = creatinine clearance; D/P Cr = dialysate-to-plasma ratio of creatinine.

Statistical analysis
Continuous variables are reported as mean ± standard deviation. For selected comparisons between group means, either parametric (t-test) or nonparametric (Mann–Whitney test) methods were used, as applicable. Observed survival of patients was computed by the Kaplan–Meier method. Multivariate Cox regression analysis was used to determine independent predictors of survival. Correlations are reported using the Spearman rank correlation coefficient. Calculations were performed using SPSS for Windows 12.0.1 (SPSS, Chicago, IL, U.S.A.).

Results
Demographics and patient characteristics
Mean age of the patients was 53 ± 16 years, 70% were African American, 59% were women, and 39% had diabetes. Mean duration on dialysis at enrollment was 10.33 ± 25 months. Of 42 patients, 20 (48%) were anuric at enrollment.

Mean and median CRP levels at enrollment were 13.5 ± 20.8 mg/L and 7.15 mg/L respectively (range: 0.2 – 95.8 mg/L). Mean follow-up CRP was 11.63 ± 14.15 mg/L (range: 0.55 – 75.8 mg/L). Mean D/P Cr at enrollment was 0.649 ± 0.12 mg/L (range: 0.429–0.954 mg/L). No significant difference was observed between enrollment D/P Cr and D/P Cr at 1 year after enrollment (0.653 vs. 0.676, p = 0.32). Mean weekly residual CCr and Kt/V during follow-up were 7.11 ± 15.47 L/1.73 m² and 0.14 ± 0.30 respectively.

The patients were divided into two groups by mean follow-up CRP level (<10 mg/L and ≥10 mg/L). Patients with CRP > 10 mg/L had significantly lower mean residual CCr (0.59 L/1.73 m² vs. 10.1 L/1.73 m², p = 0.01), residual Kt/V (0.01 vs 0.20, p = 0.01), total CCr (56 L/1.73 m² vs. 62 L/1.73 m², p = 0.047), and total Kt/V (2.09 vs. 2.49, p = 0.001) than did those with a CRP level ≤10 mg/L. Mean follow-up levels of CRP correlated negatively with mean total Kt/V (r = –0.44, p = 0.004), mean residual CCr (r = –0.42, p = 0.006), and mean residual Kt/V (r = –0.43, p = 0.006; Table I). No significant correlation was observed between enrollment levels of CRP and enrollment levels of residual renal clearance (r = –136, p = 0.397) and residual Kt/V (r = –173, p = 0.28).

As compared with patients who were not anuric, patients who were anuric had significantly higher mean follow-up CRP levels (16.66 mg/L vs. 6.92 mg/L,
Enrollment D/P Cr was inversely correlated with serum albumin ($r = -0.24$, $p = 0.001$; Figure 1). Total peritoneal protein loss was positively correlated with D/P Cr ($r = 0.34$, $p = 0.028$).

**Patient survival**

For PD patients enrolled since 1986, mean, maximum, minimum, and median survival were 3.323 years, 12.19 years, 0.12 years, and 2.727 years respectively. The cumulative observed survival of PD patients with D/P Cr $\leq 0.67$ was significantly higher ($p = 0.034$) than that of patients with D/P Cr $> 0.67$. But D/P Cr as a continuous variable was not a significant predictor of mortality in univariate [relative risk (RR) = 2.58, $p = 0.24$] or multivariate Cox regression analysis. The independent predictors of patient survival were determined using multivariate Cox regression analysis (Table II). In the Cox model, adjusting for age, race, sex, diabetes, and D/P Cr, CRP remained a significant independent predictor of mortality (RR = 1.036, $p = 0.018$). For every 1 mg/L increase in serum CRP at enrollment, mortality rate increased by 3.6%.

**Discussion**

This study has provided important evidence that circulating levels of CRP, an important marker of inflammation, is associated with low RRF in PD patients, in agreement with previously published reports. Negative correlation between RRF and CRP may be explained by the association of decreased renal function with an inflammatory state. Inflammatory state may cause a more rapid loss of RRF, or CRP may somehow damage the kidney. It is also possible that CRP may normally be cleared by the kidney and that it accumulates with reduced renal function. Wang et al. reported that inflammation, RRF, and left ventricular hypertrophy are interrelated and combine adversely to increase mortality and cardiovascular death in PD (7). Chung et al. reported that, in patients starting PD, low initial RRF is associated with inflammation (9).

Although mean follow-up CRP levels were significantly different between anuric and non anuric patients, we observed no significant differences in the enrollment CRP values between anuric and non anuric patients. That finding may be attributable to the fact that, in 10% of our PD patients, CRP levels were measured only within 1 month of starting PD. It has been reported that a low glomerular filtration rate per se is associated with an inflammatory state in chronic renal failure patients (10). Recently Memoli et al. demonstrated that in uremic non dialyzed patients, as compared with healthy subjects, urinary excretion of soluble IL-6 was significantly lower (11). Concentrations of CRP and IL-6 are related to renal function in pre-dialysis patients (12). In this regard, our finding of a negative correlation between RRF and CRP may indicate that a reduction in renal function may aggravate the inflammatory state because of reduced renal function.

**TABLE II Multivariate Cox regression analysis: independent predictors of mortality in peritoneal dialysis patients**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative risk</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>1.059</td>
<td>0.12</td>
</tr>
<tr>
<td>Diabetes (yes vs. no)</td>
<td>3.046</td>
<td>0.13</td>
</tr>
<tr>
<td>Sex (female vs. male)</td>
<td>0.177</td>
<td>0.058</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American vs.</td>
<td>2.09</td>
<td>0.56</td>
</tr>
<tr>
<td>Hispanic vs. white</td>
<td>0.38</td>
<td>0.62</td>
</tr>
<tr>
<td>D/P Cr</td>
<td>0.035</td>
<td>0.28</td>
</tr>
<tr>
<td>Weekly residual Kt/V</td>
<td>1.743</td>
<td>0.62</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>1.036</td>
<td>0.018</td>
</tr>
</tbody>
</table>

D/P Cr = dialysate-to-plasma ratio of creatinine; Kt/V = adequacy of dialysis; CRP = C-reactive protein.

![Figure 1](image1.png)  
Figure 1: Correlation between enrollment dialysate-to-plasma ratio (D/P) of creatinine and serum albumin in peritoneal dialysis patients.
clearance of CRP at the start of PD. Clearance of CRP in PD patients should be further investigated.

Our observation that D/P Cr is not correlated with CRP agrees with a previously published report by Wang et al. (13), who could not find an association between PTR and cytokine levels in PD patients. Recently it was reported that the IL-6 inflammation system is associated with peritoneal solute transport rate (PSTR) in PD patients, particularly in the early phase of treatment, and that this association could be one reason for the high mortality in patients with high PSTR (6). Chung et al. reported that PTR during first year on PD may be linked with inflammation and a decline in RRF (14).

A limitation of our study is that CRP values were not measured in all patients within 1 year of PD start. Our observation that enrollment D/P Cr is inversely correlated with enrollment serum albumin may indicate a possible relationship of D/P Cr with malnutrition and inflammation in our PD patients. It has been reported that hypoalbuminemia is a marker of inflammation and malnutrition (15,16).

Conclusions
Elevated CRP is associated with lower RRF in PD patients. Inverse correlation of D/P Cr with serum albumin may indicate a possible relationship of D/P Cr with malnutrition and inflammation in PD patients. As a predictor of mortality, CRP may be better than RRF and D/P Cr. Higher baseline D/P Cr may be associated with decreased survival in PD patients. However, D/P Cr was not an independent predictor of long-term survival in PD patients.

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References
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