An elevated level of C-reactive protein (CRP), which is a marker of inflammation, is a risk factor for morbidity and mortality in the general population and in dialysis patients. Recently, the relationship between inflammation and nutrition status has received much attention. Serum prealbumin is a highly sensitive marker of nutrition and survival in dialysis patients. The objective of the present study was to evaluate the prognostic value and clinical correlates of CRP in peritoneal dialysis (PD) patients.

Using retrospective chart review, we collected demographic, clinical, and laboratory data on 66 PD patients for the period June 2001 to January 2005. High-sensitivity CRP (hs-CRP) levels were measured in a subgroup of 32 patients starting in May 2003. Over the study period, prealbumin and CRP were assayed serially by the immunoturbidimetric method. Mean age (± standard deviation) of the patients was 55 ± 15 years, and 73% were African American. Mean and median enrollment CRP were 15.2 ± 24 mg/L (range: 4.2 – 149.5 mg/L) and 6.45 mg/L respectively. Mean and median enrollment hs-CRP were 15.3 ± 23.5 mg/L (range: 0.2 – 96 mg/L) and 6.55 mg/L respectively. Enrollment CRP was elevated (>15 mg/L) in 29% of the patients, and hs-CRP was elevated (>5 mg/L) in 63% of the patients. Enrollment CRP was strongly correlated with hs-CRP (r = 0.7, p < 0.0001). The presence of diabetes (22 mg/L vs. 7.8 mg/L, p = 0.02), infection and inflammatory conditions (44.9 mg/L vs. 11.6 mg/L, p = 0.001), and lower levels of markers of nutrition such as prealbumin (r = –0.47, p < 0.0001) and creatinine (r = –0.35, p = 0.006) were associated with a higher level of CRP. Enrollment hs-CRP was a significant predictor of mortality in PD patients (relative risk = 1.044, p = 0.023). The observed cumulative survival (Kaplan–Meier) of patients with hs-CRP < 15 mg/L was significantly better (p = 0.007) than was the survival of patients with a hs-CRP ≥ 15 mg/L. In a multivariate regression analysis, serum prealbumin was the best and only significant predictor of CRP level (β = –0.37, p = 0.005). Elevated CRP was associated with infection and inflammation. Therefore, routine testing of hs-CRP in PD patients should be considered.

Key words

C-reactive protein, CRP, hs-CRP, prealbumin, inflammation, survival

Introduction

Inflammation is highly prevalent in hemodialysis (HD) and peritoneal dialysis (PD) patients (1). The acute-phase protein C-reactive protein (CRP) is a well-known indicator of inflammation (2). Inflammation has been linked to cardiovascular risk and mortality in HD patients (3), and an increased level of CRP has been reported to be a strong predictor of all-cause and of cardiovascular mortality in HD and PD patients (4–6).

Protein–energy malnutrition is highly prevalent among dialysis patients and is associated with the high mortality in those patients (7). Over the past decade, various parameters of nutrition have emerged as powerful predictors of mortality in dialysis patients. We and others have reported that, in addition to advanced age and diabetes, serum measures of markers of nutrition such as albumin, cholesterol, creatinine, and prealbumin are important predictors of survival in HD and PD patients (8,9). Among the various indices of nutrition, serum prealbumin has been reported to be a highly sensitive marker with powerful prognostic value in dialysis patients (7,10).

Recently, the relationship between malnutrition and inflammation in dialysis patients has received much attention. Malnutrition has long been recog-
nized to have deleterious effects on immune function. There appears to be a strong association between protein–energy malnutrition (PEM) and inflammation in dialysis patients (11). Moreover, both PEM and inflammation are associated with increased morbidity and mortality, including risk of cardiovascular death. Although an association appears to exist between markers of nutrition and inflammatory markers such as CRP, that association has not been studied critically in PD patients. The predictive power of markers of nutrition may be influenced by inflammatory state as well as by nutritional state.

The objective of the present study was to evaluate the prognostic value and clinical correlates of CRP in PD patients.

Patients and methods
We retrospectively reviewed the medical records of 66 PD patients treated at the Avram Center for Kidney Diseases (the outpatient facility at Long Island College Hospital) from June 2001 until September 2004. Demographic, clinical, and biochemical data were collected. Also collected were data on hospitalizations, infection, and inflammatory conditions. Defined inflammatory states were collagen vascular disease, cancer, and recent infection. Prealbumin and CRP were assayed serially over the study period by the immunoturbidimetric method (Spectra East Laboratories, Rockleigh, NJ, U.S.A.). Because high-sensitivity CRP (hs-CRP) is more sensitive than routine CRP, and because routine CRP cannot be measured below 4 mg/L, we switched from the routine CRP assay to hs-CRP assay in a subgroup of 32 patients starting in May 2003.

Statistical analysis
Continuous variables are reported as mean ± standard deviation. For selected comparisons between two group means, parametric (t-test) or nonparametric (Mann–Whitney) methods were used. Correlations were reported as either Pearson correlation coefficients or Spearman rank correlation coefficients. Simple linear regression was used to identify the predictors of CRP level. Multiple linear regression was used to produce a predictive model for CRP level. Observed survival of patients was computed by the Kaplan–Meier method. Survival was also evaluated using the univariate and multivariate Cox proportional hazards models. Logistic regression analysis was performed to assess for significant associations with mortality. A two-tailed p value less than 0.05 was considered to be statistically significant. Calculations were performed using SPSS for Windows, version 9.0.1 (SPSS Inc., Chicago, IL, U.S.A.).

Results
Demographics and patient characteristics
Mean age of the patients was 55 ± 15 years. In the patient group, 73% were African American, 62% were female, and 38% had diabetes. The causes of ESRD were diabetes (36%), hypertension (31%), glomerulonephritis (7%), polycystic kidney disease (3%), obstruction (2%), human immunodeficiency virus (7%), and other or unknown causes (14%). The mean time on PD at enrollment was 49 ± 43 months.

At enrollment, mean and median CRP were 15.2 ± 24 mg/L (range: 4.2 – 149.5 mg/L) and 6.45 mg/L respectively. Mean and median hs-CRP were 15.3 ± 23.5 mg/L (range: 0.2 – 96 mg/L) and 6.55 mg/L respectively. In addition, the mean serum prealbumin level was 40 ± 12 mg/dL, the mean albumin level was 3.61 ± 0.51 g/dL, the mean serum creatinine level was 10.8 ± 3.6 mg/dL, and the mean serum urea nitrogen level was 43 ± 15 mg/dL.

Enrollment CRP (≥15 mg/L) and hs-CRP (≥5 mg/L) were elevated in 29% and 63% of the patients respectively. In 9 patients (13.6%), all serial CRP values stayed consistently within the normal range (<15 mg/L); in 5 patients (7.6%), all serial CRP values measured above the normal range (≥15 mg/L). In 4 patients (12.5%), all serial hs-CRP values stayed consistently within the normal range (<5 mg/L); in 3 patients (9.4%), all serial hs-CRP values measured above normal range (≥5 mg/L).

Enrollment CRP (≥15 mg/L) and hs-CRP were highly correlated (r = 0.7, p < 0.0001). Diabetic patients had a significantly higher enrollment CRP (22 mg/L vs. 7.8 mg/L, p = 0.02) and enrollment hs-CRP (27 mg/L vs. 9.92 mg/L, p = 0.05) than did nondiabetic patients. The mean of all serial hs-CRP measurements was also significantly higher in diabetic patients than in nondiabetic patients (20.63 mg/L vs. 8.1 mg/L, p = 0.03). As expected, patients having infectious and inflammatory conditions had significantly higher CRP levels than did patients who did not have such conditions (44.9 mg/L vs. 11.6 mg/L, p = 0.001).
Survival
At 1.7 years of observation, cumulative survival of patients with hs-CRP < 15 mg/L was significantly better than that of patients with hs-CRP ≥ 15 mg/L (Figure 1). At 3.45 years of observation, cumulative survival of patients with CRP < 15 mg/L was better than those with CRP ≥ 15 mg/L, but those results did not reach statistical significance.

By univariate Cox regression analysis, hs-CRP as a continuous variable was a significant predictor of mortality in PD patients [relative risk (RR) = 1.027, \( p = 0.005 \)]. Thus, for each 1 mg/L increase in hs-CRP level at enrollment, the relative risk of death increased by 2.7%. The independent predictors of patient survival were determined using a multivariate Cox proportional hazard analysis, which adjusts for other variables known to influence survival (Table I). In the Cox model, adjusting for age, sex, and race, serum hs-CRP remained a significant independent predictor of mortality (RR = 1.049, \( p = 0.023 \)). For every 1 mg/L increase in serum hs-CRP at enrollment, mortality risk increased by 4.9%. However, the predictive significance of hs-CRP for mortality diminished when an additional adjustment was made for diabetic status.

Table II shows the results of the univariate logistic regression analysis of factors associated with mortality in PD patients. Age [odds ratio (OR) = 1.053, \( p = 0.012 \)], diabetes (OR = 1.89, \( p = 0.001 \)), and hs-CRP (OR = 1.074, \( p = 0.036 \)) were the factors significantly associated with mortality in PD patients.

Predictors of CRP level
By univariate analysis, the presence of diabetes (\( \beta = 0.31, p = 0.02 \)), lower serum prealbumin (\( \beta = -0.36, p = 0.005 \)), and lower creatinine (\( \beta = -0.26, p = 0.04 \)) were associated with higher CRP levels. Stepwise multivariate regression analysis confirmed that, in PD patients, among the markers of nutrition studied, serum prealbumin is the best and only significant predictor of CRP level.

Discussion
The results of the present study show that a significant proportion of our PD patients, 29% by routine CRP test (≥15 mg/L) and 63% by hs-CRP test (≥5 mg/L) have elevated levels of CRP. The prevalence of inflammation (hs-CRP ≥ 5 mg/L) was much lower (36%) in Chinese PD patients than had been reported earlier (6). In another study with white dialysis patients, the prevalence was 50% – 60% (12). Only 12% of Asian PD patients had a CRP level greater than 8 mg/L (13). Most of our PD patients (73%) are African American, and CRP level may vary by inflammatory response, race, and ethnicity (14). Interestingly, few patients in our study had persistently elevated CRP levels without an accompany-
ing apparent reason. That finding requires further study.

One of the most important findings in the present study is the association of elevated levels of hs-CRP with increased risk of all-cause mortality in PD patients. That finding agrees with previously published reports on the predictive power of CRP in non ESRD patients, the general population, and HD patients (5,15). But the data in the literature concerning elevated CRP levels and death in PD patients are conflicting. Herzig et al. could not demonstrate CRP as independent predictor of death in a multivariate model (16). Two previously published papers have reported that, after adjustment for confounding variables, CRP is a strong independent predictor of cardiovascular and all-cause mortality in PD patients (6,17).

Our finding of higher levels of routine CRP and hs-CRP in diabetic patients as compared with non-diabetic patients agrees with similar results found in a non ESRD population (18) and in our previously published paper on PD patients (19). In contrast, recent reports showed no significant difference in CRP levels between diabetic and nondiabetic HD patients (20).

The inverse association of CRP with markers of nutrition such as prealbumin and creatinine may suggest a link between nutrition and inflammation. This possible link needs to be further investigated in large-scale randomized clinical trials.

Conclusions
Enrollment hs-CRP significantly predicts survival in PD patients. Because prealbumin acts both as a marker of nutrition and a negative acute-phase reactant protein, the inflammatory state of the patient should be considered when evaluating nutrition status.

Acknowledgments
This work was supported in part by grants from the Kidney Urology Foundation of America and the Nephrology Foundation of Brooklyn.

References


Corresponding author:
Morrell M Avram, MD, Avram Division of Nephrology, Long Island College Hospital, 339 Hicks Street, Brooklyn, New York 11201 U.S.A.

E-mail:
mavram@chpnet.org