Dialysate MCP-1 concentration is associated with all-cause mortality in peritoneal dialysis patients: a prospective observational study

Kwang Il Ko

Department of Medicine

The Graduate School, Yonsei University
Dialysate MCP-1 concentration is associated with all-cause mortality in peritoneal dialysis patients: a prospective observational study

Directed by Professor Tae-Hyun Yoo

The Master's Thesis
submitted to the Department of Medicine
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

Kwang Il Ko

June 2014
This certifies that the Master's Thesis of Kwang Il Ko is approved.

Thesis Supervisor: Tae-Hyun Yoo

Thesis Committee Member: Hyeon Joo Jeong

Thesis Committee Member: Shin-Wook Kang

The Graduate School
Yonsei University

June 2014
ACKNOWLEDGEMENTS

First of all, I really appreciate my thesis supervisor, professor Tae-Hyun Yoo, for his great support and encouragement. Without his support, this study would not be possible.

I also would like to appreciate professors Hyeon Joo Jeong and Shin-Wook Kang who gave me experienced advices and warm supports.

I would like to thank my family. My parents have raised me the right way and always give me the greatest love. I am honored to be their son. Always my elderly sister has been gentle with me. Lastly, my wife has given me unchanging love and supports. Thanks to be with me. I give my love and admiration to them from the bottom of my heart.
LIST OF FIGURES

Figure 1. Flow diagram of the study ............................................ 6
Figure 2. Kaplan-Meier plots for the primary outcomes according to dialysate MCP-1 groups ............................................. 14
Figure 3. Multivariate fractional polynomial graphs for the association between dialysate MCP-1 and all-cause or cardiovascular death .............................................................. 17
LIST OF TABLES

Table 1. Baseline characteristics of the subjects based on the median level of dialysate MCP-1 .................................................. 10
Table 2. Correlation between dialysate MCP-1 and various clinical and laboratory parameters ................................................. 12
Table 3. Univariate Cox proportional hazard models of baseline parameters for all-cause mortality ........................................ 15
Table 4. Multivariate Cox proportional hazard models of dialysate MCP-1 group for the primary outcome ...................... 16
ABSTRACT

Dialysate MCP-1 concentration is associated with all-cause mortality in peritoneal dialysis patients: a prospective observational study

Kwang Il Ko

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Tae-Hyun Yoo)

Background:
The aim of this study was to investigate the association of the level of dialysate monocyte chemoattractant protein-1 (dMCP-1) with systemic inflammatory and nutritional markers in peritoneal dialysis (PD) patients. In addition, I examined the prognostic value of dMCP-1 on all-cause or cardiovascular mortality in these patients.

Methods:
I prospectively followed up 169 prevalent PD patients from April 2008 to December 2012. At baseline, dMCP-1 and serum biochemical parameters, including high sensitivity C-reactive protein (hs-CRP) and albumin, were checked. All-cause mortality and the causes of death were determined during the follow-up period. Based on the median level of dMCP-1, patients were classified into two group; low and high dMCP-1 groups.
Results:
Mean age, hs-CRP concentrations, and dialysate-to-plasma creatinine ratio (D/P_{cr}) at 4-hour were significantly higher, while serum albumin levels and %lean body mass (LBM) were significantly lower in the high dMCP-1 group. During the mean follow-up period of 47.7 months, all-cause mortality and cardiovascular mortality rates were significantly higher in the high dMCP-1 group (9.6 and 6.3 per 100 person-years, respectively) compared to the low dMCP-1 group (5.1 and 3.1 per 100 person-years; \(P=0.021\) and 0.038, respectively). In multivariate Cox analysis, high dMCP-1 was a significant independent predictor of all-cause mortality (hazard ratio: 1.83, 95% confidence interval: 1.03-3.24, \(P=0.039\)). Moreover, multivariate fractional polynomial analysis showed that all-cause mortality and cardiovascular death increased steadily with higher dMCP-1 concentrations.

Conclusion:
dMCP-1 levels are closely correlated with nutritional and systemic inflammatory markers in PD patients. Furthermore, high dMCP-1 concentration is significantly associated with worse all-cause and cardiovascular outcomes. These findings suggest that local peritoneal inflammation can contribute to poor clinical outcomes in PD patients.

Key words : dialysate MCP-1, hs-CRP, peritoneal dialysis, all-cause mortality
Dialysate MCP-1 concentration is associated with all-cause mortality in peritoneal dialysis patients: a prospective observational study

Kwang Il Ko

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Tae-Hyun Yoo)

I. INTRODUCTION

Non-traditional as well as traditional risk factors such as diabetes, hypertension, smoking, and dyslipidemia contribute to a high prevalence of cardiovascular disease (CVD) in dialysis patients\(^1\). Recently, accumulating evidence indicates that chronic inflammation and malnutrition, which are considered as non-traditional risk factors, are important predictors of morbidity and mortality in end-stage renal disease (ESRD) patients\(^2\). Although it has not been fully elucidated, the causes of chronic inflammation in dialysis patients are multifactorial and several factors including dialysis-related or dialysis non-related factors are regarded to be associated with chronic inflammation\(^3\). Uremia \textit{per se}\(^4\), decreased residual renal function (RRF)\(^5,6\), periodontal disease\(^7\), and infection of microorganisms such as Chlamydia pneumoniae\(^8\) induce the production of pro-inflammatory cytokines such as C-reactive protein (CRP) and interleukin-6 (IL-6). Specifically, in peritoneal dialysis (PD) patients, dialysis catheter implantation, bio-incompatibility of PD solutions, and exposure of endotoxins can induce inflammatory reactions in the peritoneum and may be one of the causes of high inflammatory state in PD patients\(^3,9\).
Peritoneal membrane function assessed by the peritoneal equilibration test is associated with the clinical outcomes in PD patients. Previous reports also showed that high transport status was associated with poor survival in PD patients. Moreover, malnutrition and chronic inflammation are prevalent in high transporters. Acute inflammation can induce transient changes in membrane solute transport to high transporters; thus, indicating a potential relationship between local peritoneal and systemic inflammation in PD patients.

Monocytes and macrophages are the principle cells found at the sites of inflammation. These cells extravasate from the bloodstream through a process mediated by chemokines secreted from resident cells. Monocyte chemoattractant protein-1 (MCP-1) is a potent chemokine synthesized by mononuclear cells and various somatic cells, including human peritoneal mesothelial cells. MCP-1 plays a crucial role in the initiation and progression of inflammation. In addition, high serum MCP-1 levels are demonstrated to be associated with poor cardiovascular outcome in not only the general population but also dialysis patients. Interestingly, a previous cross-sectional study showed that there was a significant correlation between the dialysate MCP-1 (dMCP-1) and systemic MCP-1 concentrations in PD patients. Even though local peritoneal inflammation is one of the potential sources of systemic inflammation and dMCP-1 concentrations are significantly related to systemic MCP-1 levels, the impact of dMCP-1 on patient outcomes including cardiovascular mortality has never been explored in PD patients. Therefore, the aim of this study was to investigate the association of dMCP-1 with systemic inflammatory markers and malnutrition in PD patients. In addition, I examined the prognostic value of dMCP-1 on all-cause or cardiovascular mortality in these patients.
II. MATERIALS AND METHODS

1. Subjects

This study was carried out in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of Yonsei University Health System (YUHS). Informed written consents was obtained from all participants involved in the present study.

I screened 252 prevalent continuous ambulatory PD (CAPD) patients who underwent PD for more than 6 months between April and June 2008. Patients were excluded if they met the following criteria: younger than 20 years or older than 80 years, decompensated liver or lung disease, a history of malignancy, chronic inflammatory disease, or active infection including CAPD peritonitis during the last 3 months before enrollment. A total of 169 prevalent CAPD patients were finally recruited for this study (Figure 1).
Figure 1. Flow diagram of the study.

252 patients were screened for the study

178 patients were eligible for the study

74 patients excluded
- Age <20 or >80 yr
- Malignancy
- Decompensated liver or lung disease
- Chronic inflammatory diseases
- Active infection less than 3M

9 denied to participate

169 patients were enrolled in present study
2. Demographic data and sample collection

Demographic data were obtained by a well-trained examiner using a questionnaire. To simulate the actual dialysis conditions, all patients had a full abdomen at the time of sampling. Blood samples for laboratory measurements were drawn from the antecubital vein 2 hours after the first PD exchange with 1.5% dextrose dialysate after overnight fasting. The preceding overnight dwell was regulated with 1.5% dextrose dialysate to standardize the glucose load. Serum was separated from blood within 30 minutes. Samples of peritoneal effluents were collected from overnight bags and were centrifuged immediately at 3,000 g for 15 minutes at 4 °C. Serum and supernatant from peritoneal effluents were stored at -70 °C prior to assay.

3. Laboratory measurements

High sensitivity C-reactive protein (hs-CRP) levels were determined using latex-enhanced immunonephelometric assays on a BN II analyzer (Dade Behring, Newark, DE, USA). dMCP-1 concentrations were measured using commercially available ELISA kits (DuoSet; R&D System, Minneapolis, MN, USA).

4. Peritoneal equilibration test (PET) and assessment of dialysis adequacy

A modified PET using 4.25% glucose dialysate was performed and the value of the dialysate-to-plasma creatinine ratio (D/Pcr) at 4 hours was calculated as previously reported. In addition, urea kinetic studies were performed from a 24-hour collection of dialysate and urine at baseline. Kt/V urea was determined from the total loss of urea nitrogen in spent dialysate using PD Adequest 2.0 for Windows software (Baxter Healthcare, Deerfield, IL, USA). Lean body mass (LBM) was estimated using creatinine kinetics, and percent lean body mass (%LBM) was calculated as LBM normalized to dry weight. Residual renal function (RRF) was estimated by a 24-hour urine collection.
5. Follow-up and study outcomes

Patients were followed up at least every 3 months through December 2012. All deaths and hospitalizations were recorded in the serious adverse event database. All events were retrieved from the database and carefully reviewed to determine the causes of mortality and hospitalization. The primary outcome was all-cause mortality including cardiovascular or infection-related mortality. When a patient died within 60 days after transfer to HD, the death was regarded as a mortality event. Loss to follow-up, renal transplantation, and transfer to HD were censored at the end of PD treatment.

6. Statistical analysis

Data are expressed as means ± standard deviation for continuous variables, and the number and percentage for categorical variables. Normality of distribution for each variable was assessed by the Kolmogorov-Smirnov test. Variables without a normal distribution were either transformed into logarithmic scale for correlation analysis or compared by a nonparametric test. Based on the mean value of dMCP-1, patients were divided into two groups. Continuous variables were compared by the Student’s t-test and Chi square test by categorical variables between the two groups. Correlation analysis between two continuous variables was conducted by Pearson correlation analysis. Cumulative survival curves were generated by the Kaplan-Meier method, and between-group survival was compared by the log-rank test. The independent predictive value of dMCP-1 for all-cause mortality was ascertained by Cox proportional hazards regression models, which included significant variables in univariate Cox analysis. In addition, the prognostic value of dMCP-1 was evaluated in a fractional polynomial model. Statistical analysis was performed using SPSS for Windows version 18.0 (SPSS Inc., Chicago, IL, USA) and STATA version 11.0 (StataCorp, www.stata.com). A P value less than 0.05 was considered statistically significant.
III. RESULTS

1. Demographic characteristics of subjects
   Baseline demographic and laboratory characteristics of the subjects are shown in Table 1. The mean age was 53.22 ± 12.93 years and the mean duration of PD was 62.48 ± 48.55 months. Eighty-seven patients (51.5%) were female and 54 patients (32%) were diabetes. Patients were dichotomized according to the median value of dMCP-1 (201.3 pg/ml). Mean age, serum hs-CRP concentrations, and D/P\textsubscript{cr} ratio at 4 hours were significantly higher, while serum albumin levels and %LBM were significantly lower in the high dMCP-1 group. On the other hand, there were no significant differences in gender, duration of PD, history of past peritonitis, use of icodextrin, total Kt/V, and RRF.
Table 1. Baseline characteristics of the subjects based on the median level of dialysate MCP-1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n = 169)</th>
<th>Low dMCP-1 (n = 85)</th>
<th>High dMCP-1 (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53.22 ± 12.93</td>
<td>50.16 ± 13.59</td>
<td>56.32 ± 11.49†</td>
</tr>
<tr>
<td>Sex, N (% female)</td>
<td>87 (51.5%)</td>
<td>45 (52.9%)</td>
<td>42 (50%)</td>
</tr>
<tr>
<td>Diabetes mellitus, N (%)</td>
<td>54 (32%)</td>
<td>20 (23.5%)</td>
<td>34 (40.5%)‡</td>
</tr>
<tr>
<td>Duration of PD (months)</td>
<td>62.48 ± 48.55</td>
<td>60.65 ± 49.76</td>
<td>64.32 ± 47.53</td>
</tr>
<tr>
<td>Past peritonitis, N (%)</td>
<td>78 (46.2%)</td>
<td>39 (45.9%)</td>
<td>39 (46.4%)</td>
</tr>
<tr>
<td>Icodextrin, N (%)</td>
<td>42 (24.9%)</td>
<td>19 (22.4%)</td>
<td>23 (27.4%)</td>
</tr>
<tr>
<td>%Lean body mass (%)</td>
<td>68.62 ± 10.73</td>
<td>70.54 ± 11.00</td>
<td>66.70 ± 10.18‡</td>
</tr>
<tr>
<td>Serum albumin (mg/dl)</td>
<td>3.68 ± 0.49</td>
<td>3.82 ± 0.49</td>
<td>3.57 ± 0.47†</td>
</tr>
<tr>
<td>Serum hs-CRP (mg/l)</td>
<td>0.82 (0.16-4.43)</td>
<td>0.42 (0.14-1.63)</td>
<td>1.18 (0.24-9.58)‡</td>
</tr>
<tr>
<td>dMCP-1 (pg/ml)</td>
<td>201.3 (133.7-266.8)</td>
<td>133.7 (111.8-149.2)</td>
<td>266.0 (227.0-342.2)*</td>
</tr>
<tr>
<td>D/Pcr at 4-hour</td>
<td>0.67 ± 0.11</td>
<td>0.65 ± 0.10</td>
<td>0.70 ± 0.10†</td>
</tr>
<tr>
<td>Total Kt/V urea (per week)</td>
<td>2.13 ± 0.42</td>
<td>2.16 ± 0.42</td>
<td>2.10 ± 0.43</td>
</tr>
<tr>
<td>RRF (ml/min/1.73 m²)</td>
<td>0 (0-1.07)</td>
<td>0 (0-1.30)</td>
<td>0 (0-0.97)</td>
</tr>
</tbody>
</table>

* < 0.001; † < 0.01; ‡ < 0.05

Data are expressed as mean ± standard deviation, median (interquartile range), number of patients (percent).

PD, peritoneal dialysis; dMCP-1, dialysate Monocyte chemoattractant protein-1; BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; D/Per, dialysate-to-plasma creatinine ratio; PET, peritoneal equilibration test; RRF, residual renal function
2. Correlation between dialysate MCP-1 and other parameters

Table 2 shows the association of dMCP-1 with clinical and laboratory parameters. There were significantly positive correlations between dMCP-1 and age ($r = 0.258, P = 0.001$), duration of PD ($r = 0.187, P = 0.015$), D/P$_{cr}$ ($r = 0.379, P < 0.001$), and log hs-CRP ($r = 0.312, P < 0.001$). Meanwhile, dMCP-1 was inversely correlated with serum albumin levels ($r = -0.293, P < 0.001$) and %LBM ($r = -0.190, P = 0.033$). However, there were no significant associations between dMCP-1 and the other clinical and laboratory parameters.
Table 2. Correlation between dialysate MCP-1 and various clinical and laboratory parameters

dMCP-1, dialysate monocyte chemoattractant protein-1; PD, peritoneal dialysis; D/Pcr, dialysate-to-plasma creatinine ratio; hs-CRP, high-sensitivity C-reactive protein

<table>
<thead>
<tr>
<th></th>
<th>Log dMCP-1</th>
<th>Age</th>
<th>Duration of PD</th>
<th>D/Pcr at 4-hour</th>
<th>Serum albumin</th>
<th>%LBM</th>
<th>Log hs-CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log dMCP-1</td>
<td>$r$</td>
<td>1</td>
<td>0.258</td>
<td>0.187</td>
<td>-0.293</td>
<td>-0.190</td>
<td>0.312</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>0.001</td>
<td>0.015</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.033</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age</td>
<td>$r$</td>
<td>1</td>
<td>0.083</td>
<td>0.181</td>
<td>-0.277</td>
<td>-0.391</td>
<td>0.299</td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>0.284</td>
<td>0.444</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of PD</td>
<td>$r$</td>
<td>1</td>
<td>0.081</td>
<td>-0.087</td>
<td>0.064</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>0.343</td>
<td>0.259</td>
<td>0.480</td>
<td>0.820</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D/Pcr at 4hours</td>
<td>$r$</td>
<td>1</td>
<td>-0.215</td>
<td>-0.052</td>
<td>0.031</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>0.011</td>
<td>0.581</td>
<td>0.714</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumin</td>
<td>$r$</td>
<td>1</td>
<td>0.194</td>
<td>-0.091</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td>0.030</td>
<td>0.242</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%LBM</td>
<td>$r$</td>
<td>1</td>
<td>-0.248</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td></td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log hs-CRP</td>
<td>$r$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$P$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
3. Clinical outcomes of patients

During a mean follow-up duration of 47.7 ± 15.3 months, 50 patients (29.6%) died. The most common cause of death was cardiovascular disease (32, 64.0%) followed by infection (13, 26.0%). All-cause mortality and cardiovascular mortality rates were significantly higher in the high dMCP-1 group (9.6 and 6.3 per 100 person-years, respectively) compared to the low dMCP-1 group (5.1 and 3.1 per 100 person-years; P=0.021 and 0.038, respectively), but infection-associated mortality rates were comparable between the high and low dMCP-1 groups (2.7 and 1.1 per 100 person-years, respectively; P = 0.161). Kaplan-Meier plots also showed that event-free survival rates for all-cause or cardiovascular death were significantly lower in the high dMCP-1 group than the low dMCP-1 group (log-rank test; P = 0.014 or 0.029, respectively) (Figure 2). Univariate Cox proportional hazard analysis indicated that older age, diabetes, lower %LBM and serum albumin concentrations, higher hs-CRP levels, lower RRF, and high dMCP1 were significant risk factors of patient death (Table 3). In multivariate Cox analysis, high dMCP-1 (>201.3 pg/mL) was a significant independent predictor for all-cause mortality (hazard ratio: 1.83, 95% confidence interval: 1.03-3.24, P = 0.039) after adjustment for age, sex, PD duration, diabetes, serum albumin, %LBM, and residual GFR. Meanwhile, when hs-CRP levels were included in the analysis, the significance of dMCP-1 as an independent risk for all-cause mortality disappeared (hazard ratio: 1.68, 95% confidence interval: 0.93-3.02, P = 0.083; Table 4). Furthermore, when dMCP-1 was evaluated by fractional polynomial analysis, the risk of all-cause mortality or cardiovascular death increased steadily with higher dMCP-1 values (Figure 3).
Figure 2. Kaplan-Meier plots for the primary outcomes according to dMCP-1 groups. The high dMCP-1 group had significantly higher risks of all-cause (A) and cardiovascular death (B) than the low dMCP-1 group (log-rank test, $P = 0.014$ and 0.029, respectively). There was no significant difference of infection related mortality between two groups (C).

dMCP-1, dialysate monocyte chemoattractant protein-1
Table 3. Univariate Cox proportional hazard models of baseline parameters for the all-cause mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>1.08 (1.04-1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male (vs. female)</td>
<td>1.23 (0.57-1.74)</td>
<td>0.23</td>
</tr>
<tr>
<td>DM (vs. non-DM)</td>
<td>2.46 (1.41-4.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>PD duration (month)</td>
<td>1.01 (0.99-1.01)</td>
<td>0.31</td>
</tr>
<tr>
<td>%LBM (%)</td>
<td>0.95 (0.92-0.98)</td>
<td>0.01</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>0.85 (0.70-1.03)</td>
<td>0.11</td>
</tr>
<tr>
<td>Ca (mg/dL)</td>
<td>0.77 (0.54-1.09)</td>
<td>0.13</td>
</tr>
<tr>
<td>P (mg/dL)</td>
<td>0.84 (0.67-1.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>0.33 (0.19-0.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Log hs-CRP (mg/L)</td>
<td>3.17 (2.27-4.42)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>D/Pcr</td>
<td>3.86 (0.46-9.21)</td>
<td>0.19</td>
</tr>
<tr>
<td>RRF (mL/min/1.73m²)</td>
<td>0.52 (0.32-0.85)</td>
<td>0.01</td>
</tr>
<tr>
<td>High dMCP-1 group (vs. low dMCP-1 group)</td>
<td>2.14 (1.23-3.72)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

DM, diabetes mellitus; PD, peritoneal dialysis; LBM, lean body mass; Ca, calcium; P, phosphorus; hs-CRP, high-sensitivity C-reactive protein; D/Pcr, dialysate-to-plasma creatinine ratio; RRF, residual renal function; dMCP-1, dialysate monocyte chemoattractant protein-1; HR, hazard ratio; CI, confidence interval
Table 4. Multivariate Cox proportional hazard models of dMCP-1 group for the primary outcome

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crude</td>
<td>2.14 (1.23-3.72)</td>
<td>0.007</td>
</tr>
<tr>
<td>Model 1</td>
<td>2.02 (1.19-3.61)</td>
<td>0.009</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.83 (1.03-3.24)</td>
<td>0.039</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.68 (0.93-3.02)</td>
<td>0.083</td>
</tr>
</tbody>
</table>

*aModel 1: adjusted for age, sex
*bModel 2: Model 1 + DM, PD duration, albumin, %LBM, and RRF
*cModel 3: Model 2 + log hs-CRP

dMCP-1, dialysate monocyte chemoattractant protein-1; HR, hazard ratio; CI, confidence interval; PD, peritoneal dialysis; DM, diabetes mellitus; LBM, lean body mass; RRF, residual renal function; hs-CRP, high-sensitivity C-reactive protein
Figure 3. Multivariate fractional polynomial graphs for the association between dMCP-1 and all-cause (A) or cardiovascular death (B). Hazard ratios were calculated after adjustment for age, sex, PD duration, diabetes, %LBM, albumin, and RRF. Shaded areas indicate the 95% confidence interval.

dMCP-1, dialysate monocyte chemoattractant protein-1; PD, peritoneal dialysis; LBM, lean body mass; RRF, residual renal function
IV. DISCUSSION

CVD is the most common cause of death in ESRD patients\textsuperscript{24}, and chronic inflammation is known to be implicated in high cardiovascular risk. Since the use of the peritoneal membrane is one potential source of systemic inflammation in PD patients, investigating the association between local peritoneal inflammation and the clinical outcomes is of clinical importance in these patients. In the present study, dMCP-1 was closely related with systemic inflammatory markers as well as nutritional parameters. Furthermore, I demonstrated that high dMCP-1 was significantly associated with worse all-cause and cardiovascular outcomes in ESRD patients undergoing PD.

There has been increasing interest in the role of peritoneal small solute transport rate (PSTR) as a predictor of mortality in PD patients\textsuperscript{11,14,25}. Several studies have shown that PSTR is influenced by several factors including hypoalbuminemia, diabetes, and inadequate ultrafiltration, all of which are established mortality risks in PD patients\textsuperscript{13,26}. ANZDATA registry report has also confirmed that peritoneal transport type is a significant risk factor for mortality in PD patients\textsuperscript{10}. In addition, high PSTR has been associated with peritoneal protein loss as well as chronic inflammation. Moreover, prolonged use of the peritoneal membrane is associated with high transport status and PSTR is influenced by local peritoneal inflammation\textsuperscript{12,27}. My data also showed that dMCP-1 was associated with PSTR and hypoalbuminemia, which might be significant risk factors for mortality in PD patients. Based on the respects of previous studies and the present findings, local peritoneal inflammation assessed by dMCP-1 seems to be related to chronic inflammation in PD patients.

A previous morphologic study showed that peritoneal macrophage infiltration is related to elevated levels of IL-6 in the peritoneum, and IL-6 is associated with CRP as a systemic inflammatory marker as well as serum albumin as a nutritional marker\textsuperscript{28}. Malnutrition and inflammation are commonly found together and are
closely linked to accelerated atherosclerotic CVD in ESRD patients\textsuperscript{29}. Chronic infection, dialysis membrane, and uremia per se predispose ESRD patients to pro-inflammatory status. Pro-inflammatory cytokines in turn cause malnutrition by increasing protein hydrolysis, directly affecting the gastrointestinal system, or indirectly decreasing appetite\textsuperscript{2}. MCP-1 is a potent C-C chemokine and induces the migration of various inflammatory cells. The close interplay between MCP-1 and inflammation has been validated in various diseases, and MCP-1 has been shown to have an important role in the pathogenesis of various inflammatory diseases\textsuperscript{30,31}. Numerous reports have shown that high MCP-1 levels are closely related to inflammation and atherosclerosis\textsuperscript{32-34}. In PD patients, MCP-1 has been suggested as an important monocyte chemoattractant in steady-state and CAPD peritonitis\textsuperscript{35}. Furthermore, dMCP-1 has been found to be associated with serum MCP-1 and past history of peritonitis\textsuperscript{21}. I also observed significantly higher serum hs-CRP concentrations and lower serum albumin concentrations in PD patients with elevated dMCP-1 levels. In addition, the significance of dMCP-1 in predicting all-cause mortality disappeared after adjusting for hs-CRP. These findings indicate that high dMCP-1 concentrations and systemic inflammation are interrelated and do not impose separate risks for patient death.

In contrast to the present study, a recent report demonstrated that dialysate inflammatory markers including IL-6 and TNF-\(\alpha\) did not predict patient outcome, even though intra-peritoneal inflammation assessed by effluent markers is closely associated with PSTR\textsuperscript{36}. Although it cannot be fully explained, there are several differences in the study population between the study by Lambie et al.\textsuperscript{36} and my study. In the previous study by Lambie et al.\textsuperscript{36}, subjects were a mix of incidental and prevalent PD patients, who underwent a relatively shorter duration of PD (approximately 1 year). The subjects had relatively preserved RRF with a urine volume of more than 600 mL/day. However, the duration of PD in the present study was relatively long and most of the patients were anuric. In ESRD patients including PD patients, reduced RRF is significantly associated with inflammation...
and patient mortality\textsuperscript{37,38}, whereas, preserved RRF is protective from accelerated cardiovascular risk\textsuperscript{5,39}. According to the study of Lambie et al., dialysate IL-6 in the prevalent PD group was significantly inversely associated with urine volume contrary to incidental PD patients. In the current study, dMCP-1 levels also tended to be higher in anuric subjects rather than those with preserved urine volume (241.2 vs. 185.1 pg/mL, data not shown). Taking account into the findings of previous studies as well as the present data, I suggest that local peritoneal inflammation may directly affect systemic inflammation when RRF is negligible. Therefore, conflicting results between the prior study and this study could be partly attributed to the effect of dialysis duration and RRF; however, further studies are needed to clarify this issue.

There are several limitations of my study. First, the study subjects were all Korean prevalent PD patients from a single center, and the duration of PD in the present study subjects was relatively long. Thus, there is a possibility of selection bias and the results may not be generalized to other populations. Second, effluent inflammatory markers could not fully reflect intraperitoneal milieu. Therefore, further morphologic analysis of the peritoneal mesothelium is needed to clarify the association between effluent markers and local peritoneal inflammation. Finally, a single measurement of dMCP-1 levels at baseline was conducted; therefore, the effect of changes in dMCP-1 levels during follow-up was not evaluated.
V. CONCLUSION

In conclusion, the current study demonstrates that dMCP-1 levels are closely correlated with nutritional and systemic inflammatory markers in PD patients. In addition, high dMCP-1 concentration is significantly associated with worse all-cause and cardiovascular outcomes. These findings suggest that local peritoneal inflammation can contribute to poor clinical outcomes in PD patients.
REFERENCES


ABSTRACT (IN KOREAN)

복막투석 환자에서 복강 내 MCP-1 농도와 총 사망률 사이의 연관성에 관한 전향적 관찰연구

<지도교수 유태현>

연세대학교 대학원 의학과

고광일

배경:
본 연구에서는 복막투석 환자에서 복강 내 MCP-1과 전신염증 및 영양 상태 지표 사이의 연관성을 조사하고자 하였다. 또한 복막투석 환자에서 총 사망률 또는 심혈관계 사망률에 대한 복강 내 MCP-1의 예후적 가치를 알아보고자 하였다.

방법:
2008년 4월부터 2012년 12월까지 총 169명의 복막투석 환자를 대상으로 전향적 관찰연구를 시행하였다. 복강 내 MCP-1 농도와 혈청 내 hs-CRP 농도 및 혈청 내 알부민 농도를 포함한 생화학 검사 지표를 측정하였으며, 연구 기간 동안 총 사망률과 사망 원인을 조사하였다. 복강 내 MCP-1 농도의 중앙값을 기준으로 복강 내 MCP-1 농도가 낮은 군과 높은 군으로 나누어 분석을 시행하였다.
결과:

복강 내 MCP-1 농도가 낮은 군에 비하여 MCP-1 농도가 높은 군에서 연령, 혈청 내 hs-CRP 농도, 복막투석 용액 내 혈장 크레아티닌 농도가 통계적으로 유의하게 높았다. 반면에 혈청 내 앞부분 농도와 체지방 층은 복강 내 MCP-1 농도가 낮은 군에 비하여 MCP-1 농도가 높은 군에서 의미 있게 늘었다. 추적관찰 기간 (47.7 개월) 동안 복강 내 MCP-1 농도가 낮은 군에 비하여 복강 내 MCP-1 농도가 높은 군에서 총 사망률과 심혈관계 사망률이 통계적으로 의미 있게 높았다. Cox 다변량 분석 결과, 복강 내 MCP-1 농도는 총 사망률에 대한 독립적 예측 인자로 나타났다. 또한, 부분적 다항 분석상으로도 복강 내 MCP-1 농도가 증가함에 따라 총 사망률 또는 심혈관계 사망률이 점진적으로 증가함을 알 수 있었다.

결론:

복막투석 환자에서 복강 내 MCP-1 농도는 전신염증 및 영양상태 지표와 긴밀한 상관관계가 있었다. 그리고, 복강 내 MCP-1 농도의 증가는 총 사망률 및 심혈관계 사망률의 증가와 유의한 연관성이 있었다. 이상의 결과를 고려해 볼 때, 국소적인 복강 내 염증은 복막투석 환자의 불량한 임상적 경과에 관여할 것으로 생각된다.

핵심되는 말 : 복강 내 MCP-1, 염증, 사망률, 복막투석