High serum DcR3 levels are associated with the occurrence of peritonitis in patients receiving chronic peritoneal dialysis

En-Pen Chang, Yi-Sheng Lin, Szu-Chun Huang, Der-Cherng Tarng, Tung-Po Huang

Abstract

Background: Peritoneal dialysis (PD)-related peritonitis is a serious complication that typically leads to hospitalization, catheter loss, and even mortality. Previous studies of the risk factors for peritonitis are discordant. To date, no biomarker associated with PD-related peritonitis has been investigated. However, it has been shown that serum decoy receptor 3 (DcR3) is a valuable marker in predicting the outcome of several inflammatory diseases. The aim of this study was to investigate whether serum DcR3 is a predictor of peritonitis in chronic PD patients.

Methods: We conducted a prospective cohort study of PD patients in the PD unit of a tertiary referral center from March 1 to November 30, 2007, and followed up until December 31, 2009. Clinical and laboratory parameters were recorded and serum DcR3 was measured to assess risk factors for developing PD-related peritonitis.

Results: A total of 77 patients (38 men and 39 women; mean age 58 ± 13 years) were enrolled in this study. The average time on PD was 24.5 months and 46 patients (60%) were diabetic. The mean follow-up duration was 499 ± 17 days. The rate of peritonitis incidence was 0.17 episodes per patient-year. Baseline serum DcR3 in 77 patients was 1.94 ± 1.23 ng/mL. Kaplan-Meier survival analysis showed that patients with serum DcR3 > 1.8 ng/mL had a higher risk of peritonitis than those with serum DcR3 < 1.8 ng/mL (p = 0.016). The Cox proportional hazard model further showed that high serum DcR3 (>1.8 ng/mL) was an independent risk factor for subsequent peritonitis (hazard ratio 3.61, 95% CI 1.17–11.08; p = 0.03).

Conclusion: Serum DcR3 was associated with increased risk of PD-related peritonitis.

Keywords: biomarker; decoy receptor 3; peritoneal dialysis; peritonitis

1. Introduction

Peritoneal dialysis (PD) is a well-established treatment modality for patients with end-stage renal disease (ESRD). Despite advances in technology and improvements in dialysis solutions, PD-related peritonitis remains the major complication of PD. Recent observations have shown that it was the main cause of hospitalization, catheter loss, transfer to hemodialysis, and death in PD patients. Therefore, identification of specific risk factors associated with peritonitis in PD patients would be important to help in reducing this major dialysis-related complication. Several predictors have been reported to be associated with PD-related peritonitis, including age, gender, race, diabetes, obesity, low serum albumin, and PD modality. At present, however, studies that examined the risk factors for developing PD-related peritonitis are still limited and conflicting. Moreover, peritonitis rates vary substantially in recently published studies, from a high of 0.70
Decoy receptor 3 (DcR3) is a soluble receptor that lacks a transmembrane domain and neutralizes three members of the tumor necrosis factor (TNF) superfamily, including Fas ligand (FasL), LIGHT (homologous to lymphotixins, exhibits inducible expression, competes with HSV glycoprotein D for herpes simplex virus entry mediator, and expressed by T lymphocytes), and TNF-like molecule 1A (TL1A).12 DcR3 is now regarded as a novel immunosuppressant because of its ability to block the activities of TL1A, LIGHT, and FasL, as well as its non-decoy functions.12 In particular, DcR3 can attenuate the host immune response and modulate the autoimmune response and other inflammatory reactions. DcR3 is not detectable in most normal tissues, but it is upregulated in various cancers and inflammatory conditions. Serum DcR3 levels are elevated in colon cancer,13 renal cell cancer,14 systemic lupus erythematosus,15 silicosis,16 and in patients with chronic kidney disease (CKD).17 CKD PD patients are characterized by a significant inflammatory status.18 However, DcR3 expression in PD patients has not been investigated previously. In a study on acute respiratory distress syndrome (ARDS) patients, high plasma levels of DcR3 correlated with later development of multiple organ failure and can independently predict 28-day mortality.19 Therefore, serum DcR3 is a valuable marker in predicting the outcome of inflammatory diseases. The aim of our study was to investigate whether serum DcR3 is a predictor of peritonitis in chronic PD patients.

2. Methods

2.1. Patients

Patients undergoing peritoneal dialysis treatment at the dialysis center of Taipei Branch, Buddhist Tzu Chi General Hospital were recruited between March 1, 2007 and November 30, 2007, and followed up until December 31, 2009. The inclusion criteria for peritoneal dialysis patients were over 18 years of age, PD treatment for at least 90 days, no chronic inflammation or malignancy, no peritonitis within 30 days, and no active infections such as pneumonia and infective endocarditis. All patients used the twin-bag system with commercially available glucose-based dialysis solutions (Dianeal; Baxter, Singapore). The research protocol was approved by the Institutional Review Board of Taipei Branch, Buddhist Tzu Chi General Hospital. Informed consent was obtained from all patients.

2.2. Clinical data collection and blood sampling

For our study subjects, diagnosis of PD-related peritonitis was according to International Society for Peritoneal Dialysis (ISPD) criteria when two of the following three findings were presented: abdominal pain, cloudy effluent, and effluent white blood cell count exceeding 100/μL with at least 50% neutrophils.20 Analyses of cultures collected from all cases with peritonitis were carried out at the Microbiology Laboratory of Taipei Branch, Buddhist Tzu Chi General Hospital.

In the prospective cohort study, baseline clinical data were recorded by patient chart review, including age, gender, type of PD regimen, and time on dialysis. Associated comorbidities, including diabetes mellitus, were also recorded. Body weight and blood pressure were collected from patient diaries and clinic visits. All laboratory data, including serum albumin, hemoglobin, high-sensitivity C-reactive protein (hs-CRP) and serum DcR3, were checked at the beginning of the study. Serum DcR3 was measured using a commercially available ELISA kit (BioVendor, Brno, Czech Republic) according to the manufacturer’s instructions.17

2.3. Statistical analysis

Descriptive statistics include mean ± SD values for continuous data and percentages for categorical data. For between-group comparisons, the Student t test was used for normally distributed data and the Mann—Whitney rank sum test for data with a non-normal distribution. Categorical variables were compared using the Pearson χ² test. Receiver operating characteristics (ROC) analysis was used to find the optimal DcR3 cutoff value. A peritonitis-free survival curve was generated by the Kaplan—Meier method and we analyzed hazard ratios using the Cox proportional hazards method. The level of significance was set at p < 0.05 for all tests. Statistical analysis was performed using the computer software Statistical Package for the Social Sciences (SPSS 17.0; SPSS Inc., Chicago, IL, USA).

3. Results

Seventy-seven PD patients were enrolled in the study. Their mean age was 58 ± 13 years and the average time on dialysis was 24.5 ± 10.5 months. Thirty-eight (49%) patients were male and 46 (60%) patients were diabetic. The mean follow-up duration was 499 ± 17 days. Overall, 15 episodes of peritonitis were identified. Coagulase-negative Staphylococcus (26.7%) was the most common causative organism (Table 1). The incidence rate for peritonitis was 0.17 episodes per patient-year.

Accordingly, patients were stratified into two groups: a peritonitis-free group (n = 62) and a peritonitis group (n = 15). Table 2 presents the differences between these groups. Patients who had peritonitis had significantly higher levels of serum DcR3 (2.63 ± 1.67 vs. 1.78 ± 1.05 ng/mL; p = 0.01). There were no significant differences between the groups in terms of age, gender, presence of diabetes and hypertension, dialysis modality (automated PD, APD; or continuous ambulatory PD, CAPD), PD solution (standard glucose-based solution or icodextrin), baseline serum albumin,
Table 1
Micro-organisms in PD patients with peritonitis.

<table>
<thead>
<tr>
<th>Organisms</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram-positive organisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative <em>Staphylococcus</em></td>
<td>4</td>
<td>26.7</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td>Enterococcus</td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Gram-negative organisms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td><em>Serratia</em></td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td>Culture negative</td>
<td>1</td>
<td>6.7</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 2
Comparison of clinical and laboratory data between the peritonitis and peritonitis-free groups.

Table 3
Crude and adjusted hazard ratios for serum DcR3 for PD-related peritonitis.

Table 4
ROC curve analysis revealed that serum DcR3 of 1.8 ng/mL was the best cutoff value in predicting PD-related peritonitis, with sensitivity of 76.7% and specificity of 69.7%. Kaplan–Meier analysis showed that time to the first PD peritonitis episode was significantly longer in patients with serum DcR3 > 1.8 ng/mL than in those with serum DcR3 < 1.8 ng/mL ($p = 0.016$; Fig. 1). In univariate Cox proportional hazards analysis, serum DcR3 was significantly associated with a higher likelihood of peritonitis (Table 3). Otherwise, age, gender, diabetes mellitus, time on PD, albumin, and hs-CRP were not related to peritonitis. After adjustment for age, gender, and other potential confounders, DcR3 was still significantly associated with PD-related peritonitis, with a hazard ratio of 3.61 (95% CI, 1.17–11.08, $p = 0.03$).

The most compelling finding in our study is that elevated serum DcR3 was associated with increased risk of PD-related peritonitis. To the best of our knowledge, our study is the first to focus on serum DcR3 as a biomarker for PD-related peritonitis.

PD-related peritonitis is a serious complication of PD. Although less than 4% of peritonitis cases directly result in death, PD-related peritonitis is a contributing factor to 16% of the deaths in PD patients. Therefore, identification of high-risk patients for PD-related peritonitis is very important to doctors, who can devote more efforts and resources to reduce the risk of infection in PD programs.

In this study, several conventional risk factors such as hypalbuminemia, diabetes mellitus, female gender, age, and PD modality (APD or CAPD) were not associated with an increased risk of peritonitis. ISPD recommendations (revised in 2010) suggest that the rate of peritonitis for a center should...
In our study, the type of dialysis technique did not influence patient survival. In either case, nonrandomized treatment assignment makes it difficult to interpret its role in increased risk. Furthermore, other factors such as age, gender, and time on dialysis are still controversial as risk factors for PD-related peritonitis.23,24 However, the mean serum albumin in our study (3.6 g/dL) was higher than that in some other studies (3.1 g/dL).25 Other investigators could not show serum albumin (average 3.3—3.6 g/dL) as a risk factor for PD-related peritonitis in recent studies,26,27 which is consistent with our findings.

Diabetes mellitus is the major cause of ESRD in patients undergoing renal replacement therapy in Taiwan28 and worldwide.29 Reports on whether diabetes is a risk factor for PD-related peritonitis are still conflicting. Some studies have shown that diabetes mellitus is associated with compromised immune response of the peritoneum in PD patients.24,26,30 On the contrary, diabetes mellitus was not identified as a risk factor in some studies,6,27 including the present study. Part of the reason for this is better control of blood glucose in these patients to ameliorate vulnerability to peritonitis.

A previous study found a lower rate of peritonitis in patients treated with APD compared to patients treated with CAPD.31 In our study, the type of dialysis technique did not influence patient survival. In either case, nonrandomized treatment assignment makes it difficult to interpret its role in increased risk. Furthermore, other factors such as age, gender, and time on dialysis are still controversial as risk factors for PD-related peritonitis in previous studies.6,9,11,26,27,30

In the present study, serum DcR3 was associated with the risk of PD-related peritonitis. High serum DcR3 might imply that PD patients were experiencing sustained low-grade inflammation. DcR3 has been recognized as a novel immunosuppressant with a biological function involving modulation of the immune response and inflammatory reactions. DcR3 can suppress the Th1 response and attenuate cell-mediated immunity in vitro.32 When DcR3 transgenic mice were infected with bacteria, interferon-gamma expression was attenuated and susceptibility to infection increased.32 In in vitro studies, phagocytic activity towards immune complexes and apoptotic bodies and the production of free radicals and proinflammatory cytokines in response to lipopolysaccharide were impaired in DcR3-treated macrophages.33 DcR3 also inhibited major histocompatibility complex II expression via epigenetic regulation.33 In humans, DcR3 in serum or tissue correlated with poor prognosis and/or resistance to treatment in cancer patients, including colorectal cancer,13 renal cell carcinoma,14 and ovarian cancer.34 Moreover, DcR3 levels are elevated in infection and inflammatory diseases, such as bacterial infection,35 acute appendicitis,36 systemic lupus erythematosus,15 and silicosis.16 Therefore, DcR3 can be a biomarker for disease severity or a predictor for disease outcomes. In patients with systemic sclerosis, serum DcR3 was associated with later development of pulmonary arterial hypertension.37 In another study involving ARDS patients, higher DcR3 (>3 ng/mL) was correlated with subsequent development of multiple organ failure and independently predicted the 28-day mortality rate. Sustained low-grade systemic inflammation is highly prevalent in CKD and is even more severe in PD patients.38,39 It is an important prognostic factor for morbidity and mortality in PD patients. Chronic inflammation is closely related to malnutrition, characterized by elevated CRP and a decrease in albumin level, the so-called malnutrition—inflammation—atherosclerosis syndrome.40 The mechanism underlying inflammation—malnutrition correlation is multifactorial and is yet to be elucidated. In our study, serum DcR3 was inversely related to albumin and positively related to hs-CRP, which suggests that DcR3 might serve as a marker for malnutrition—inflammation status. Taken together, results suggest that DcR3 may involve pathologic processes that deregulate the immune system.

Unlike other retrospective or database-derived studies, the strength of our present study is that it is a prospective observational study. However, there are some limitations to the study. All the PD patients were classified as having either high or low serum DcR3 based on a single blood test, without follow-up levels being recorded. In addition, the small population size and the short follow-up period suggest that caution is required in deriving conclusions and statistical significance. We also did not collect and analyze information on the impact of patient education level, cognitive function, and nasal carriage Staphylococcus aureus status. These factors have been implicated in previous studies.41,42 Larger series and longer follow-up studies are required to better understand the association between serum DcR3 and PD-related peritonitis. At this point, the benefits of routine screening for serum DcR3 in a PD unit have not been fully examined and require additional research. Furthermore, it will also be important to clarify the pathomechanism involved between DcR3 and PD peritonitis.

In conclusion, our study suggests that serum DcR3 might be suitable as a biomarker for PD-related peritonitis. Further large cohort studies are needed to elucidate this possibility and further investigation is merited to examine the pathogenesis of DcR3 in PD-related peritonitis.

Acknowledgments

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