Dialysate VEGF is an independent determinant of serum albumin levels and predicts future withdrawal from peritoneal dialysis in uremic patients

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ABSTRACT

Aims: Peritoneal protein loss due to high peritoneal permeability may contribute to hypoalbuminemia and early withdrawal from peritoneal dialysis (PD) therapy in end stage renal disease (ESRD) patients. We have found that pigment epithelium-derived factor (PEDF) has anti-vasopermeability properties both in cell culture and animal models by counteracting the biological actions of vascular endothelial growth factor (VEGF). However, it remains unknown which clinical variables, including dialysate VEGF and PEDF, were associated with decreased serum albumin levels and could predict early withdrawal from the PD in ESRD patients. We addressed the issues.

Methods: Twenty-seven ESRD patients undergoing PD were enrolled. Clinical variables were measured at 6 months after commencing PD. We examined the independent correlates of serum albumin in PD patients and then prospectively investigated the predictors of withdrawal from the PD therapy during 4 years.

Results: Dialysate VEGF was associated with peritoneal solute transport rate ($p=0.002$), serum albumin (inversely, $p<0.001$) and dialysate PEDF levels ($p<0.001$). In multiple stepwise regression analysis, age ($p=0.002$) and dialysate VEGF levels ($p<0.001$) were independent determinants of serum albumin levels. High VEGF (>27 pg/ml), low serum albumin (≤3.31 g/dl) and low hemoglobin (≤11.2 g/dl) were correlated with withdrawal

from the PD therapy during the 4 years. The odds ratio of dialysate VEGF for early withdrawal from the PD was 6.310 (p=0.035).

Conclusion: The present study demonstrated that increased dialysate VEGF was associated with decreased serum albumin and early withdrawal from the PD therapy. Inhibition of peritoneal VEGF production may be a therapeutic target in PD patients.

KEY WORDS; hypoalbuminemia, peritoneal dialysis, PEDF, VEGF, withdrawal

INTRODUCTION

Hypoalbuminemia is associated with increased risks of all-cause, cardiovascular and infection-related mortality in end stage renal disease (ESRD) patients undergoing peritoneal dialysis (PD) (1-4). It is generally considered that malnutrition, inflammatory reactions, impaired immune systems, and hypoalbuminemia are interrelated with each other, which could in concert cause ultrafiltration failure of the peritoneum, thereby being involved in early withdrawal from the PD therapy (5-7). Furthermore, prognosis of ESRD patients remaining on PD treatment was reported to be better than those who withdrew from the therapy (8). Therefore, to clarify the biomarkers that could be linked to hypoalbuminemia and may predict early withdrawal from the PD is not only helpful for identifying high-risk ESRD patients on PD, but also may be useful for developing a novel therapeutic strategy that could improve the prognosis in these subjects.

Peritoneal protein loss due to high peritoneal permeability may contribute to hypoalbuminemia in ESRD patients with PD therapy (9). Indeed, in a cross-sectional study of 106 continuous ambulatory PD (CAPD) patients, 4-hour dialysate to plasma creatinine ratio (D/P Cr) was shown to be an independent risk factor for decreased serum albumin levels in these patients (10). Vascular endothelial growth factor (VEGF)

is one of the potent angiogenic mitogens specific for endothelial cells, also known as vascular permeability factor (11). VEGF is produced by human peritoneal tissues, and its expression in the peritoneum was significantly increased in PD patients compared with normal subjects (12). Moreover, increased dialysate VEGF levels were correlated with high peritoneal solute transport rate in ESRD patients (11). On the other hand, we, along with others, have recently found that pigment epithelium-derived factor (PEDF), a glycoprotein that belongs to the superfamily of serine protease inhibitors, has anti-angiogenic and anti-vasopermeability properties both in cell culture and animal models by counteracting the biological actions of VEGF (13). Therefore, a balance between VEGF and PEDF in the peritoneum may regulate the peritoneal permeability and protein loss in PD patients. However, it remains unknown which clinical variables, including dialysate VEGF and PEDF, were associated with decreased serum albumin levels and could predict early withdrawal from the PD in ESRD patients. In this study, we examined the independent correlates of serum albumin levels in PD patients and then prospectively investigated the predictors of withdrawal from the PD therapy during 4 years.

METHODS

Patients

Twenty-seven ESRD patients (16 male and 11 female; mean age 53.1 ± 17.3 years old; diabetic nephropathy (n=3), chronic glomerulonephritis (n=9), hypertensive nephrosclerosis (n=2), amyloidosis (n=1), Fabry disease (n=1), hypoplastic kidney (n=2) and etiology unknown (n=9)) who were initiated PD therapy from 2005 to 2008 years were enrolled in the present study. The patients with a previous history of peritonitis were excluded. All patients initially received PD therapy with commercially available glucose- and icodextrin-based dialysis solutions. Six months after commencing the PD, clinical variables were measured. Twenty-five patients received inhibitors of renin-angiotensin system (RAS) for the treatment of hypertension and 5 patients received statins for dyslipidemia. We complied the withdrawal criteria from the "Study Group for Withdrawal from PD in Japan" (14).

Data collection

Body mass index (kilograms per meter squared) was calculated as an index of the presence or absence of obesity. Blood was drawn for determinations of hemoglobin (Hb), total protein (TP), serum albumin, lipids (total-cholesterol and triglycerides), blood urea nitrogen (BUN), creatinine and uric acid. Serum high-sensitive C-reactive

protein (hsCRP) was measured with nepherometry (N-Latex, CRPII, Dade Behring Co., Tokyo, Japan) (15). VEGF (R&D systems, Minneapolis, MN, USA) and PEDF levels in the dialysate effluent were measured by an enzyme-linked immunosorbent assay system as described previously (16). Other chemistries were measured at a commercially available laboratory (Wako Pure Chemical Industries, Ltd, Osaka, Japan) (15). The standard peritoneal equilibration test (PET) was evaluated as dialysate to plasma creatinine ratio (D/P Cr). Weekly Kt/V and residual renal function were evaluated by PD adequest 2.0 software (Baxter Healthcare, Deerfield, IL, U.S.A.) (17). Informed consent was obtained from all patients, and studies were approved by ethics committees of the Kurume University School of Medicine, Japan.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Sex, medications for hypertension and dyslipidemia (RAS inhibitors and statin), the presence or absence of diabetes mellitus, and withdrawal or non-withdrawal patients were coded as dummy variables. Clinical data that were not normally distributed such as triglyceride, hsCRP and intact parathyroid hormone (PTH) were log-transformed. To determine the independent correlates of serum albumin levels, univariate and multiple stepwise

regression analyses were performed. To explore the characteristics factors for predicting the withdrawal from PD, univariate liner regression analysis was performed. Further, dialysate VEGF, serum albumin and Hb levels were divided into two groups according to the cut-off point by calculating the sensitivity and specificity in receiver operating characteristic (ROC) analysis. Then cumulative retention rate of PD therapy during the 4 years was tested by the Kaplan-Meier method and interpreted using the log-rank statistical analysis. Cox regression analysis was also performed to estimate the odds ratio for withdrawal of PD. Statistical significance was defined as $p<0.05$. All statistical analyses were performed with SPSS system (Ver. 20, SPSS, Chicago, IL, USA).

RESULTS

Demographic data

Demographic baseline data are shown in Table 1. VEGF and PEDF levels in the effluent dialysate were 34.1 ± 17.5 pg/ml and 1.88 ± 2.18 μg/ml, respectively. Serum albumin (3.35 ± 0.67 g/dl) and Hb (10.6 ± 0.9 g/dl) levels were lower, while hsCRP levels (863 (124-6010) ng/ml) were higher than the normal ranges. Mean D/P Cr in our subjects was 0.61 ± 0.15.

Correlates of serum albumin levels

Univariate analysis showed that age (inversely, $p=0.012$), dialysate VEGF (inversely, $p<0.001$) and PEDF (inversely, $p=0.040$) levels were correlated with serum albumin levels (Table 2). Because these parameters could be closely correlated with each other, to determine the independent determinants of serum albumin, multiple stepwise regression analysis was performed. This analysis showed that age ($\beta=-.427$, $p=0.002$) and dialysate VEGF ($\beta=-.659$, $p<0.001$) were independently correlated with serum albumin levels (Table 2).

Correlates of dialysate VEGF

We next examined the independent determinants of dialysate VEGF. As shown in Fig. 1 and 2, dialysate VEGF was correlated with D/P Cr ($p=0.002$, $r=0.569$), serum albumin (inversely, $p<0.001$, $r=0.697$) and dialysate PEDF levels ($p<0.001$, $r=0.647$). These variables were independent determinants of dialysate VEGF in our patients (data not shown).

Correlates of withdrawal from the PD

We then investigated prospectively whether dialysate VEGF was correlated

with withdrawal from the PD during 4 years. During 4 years, 7 patients (26%) received antibiotics therapy due to infectious peritonitis. Eleven patients remained on PD treatment, whereas 16 patients withdrew from the therapy due to the following reasons (peritonitis (n=4), ultrafiltration failure (n=9), death (n=2), and renal transplantation (n=1)).

Univariate analysis revealed that dialysate VEGF (p=0.039), serum albumin (inversely, p=0.039) and Hb (inversely, p=0.034) levels were significantly correlated with withdrawal from the PD therapy (Table 3). When dialysate VEGF, serum albumin and Hb levels were divided into two groups according to the ROC analysis (cut-off points of VEGF, serum albumin and Hb were 27 pg/ml, 3.31g/dl and 11.2 g/dl, respectively), levels of VEGF >27 pg/ml, serum albumin ≤3.31 g/dl and Hb ≤11.2 g/dl were associated with lower cumulative retention rate of the PD therapy during 4 years (Fig. 3). As shown in Table 4, the odds ratio (OR) of dialysate VEGF for early withdrawal from the PD (7.864, 95% CI 1.707-36.220) was statistically significant (p=0.013), while that of serum albumin or Hb not (OR 2.957, 95% CI 0.984-8.885, p=0.053, 4.235, 95% CI 0.950-18.885, p=0.058, respectively). Multivariate analysis revealed that dialysate VEGF was independently correlated with withdrawal from the PD during 4 years (OR 6.310, 95% CI 1.137-35.021, p=0.035).

DISCUSSION

We demonstrated in this study that; [1] dialysate VEGF was an independent determinant of serum albumin levels in PD patients; [2] high VEGF (VEGF >27 pg/ml), low serum albumin (serum albumin ≤3.31 g/dl) and low Hb (Hb ≤11.2 g/dl) levels were correlated with low cumulative retention rate of PD therapy during the 4 years; and [3] dialysate VEGF was independently correlated with early withdrawal from the PD therapy in ESRD patients.

In this study, VEGF levels in the effluent dialysate were positively associated with peritoneal solute transport rate and inversely correlated with serum albumin levels. Given the vasopermeable properties of VEGF, our present results suggest that VEGF may induce peritoneal hyperpermeability and subsequently evoke albumin leakage into the peritoneal cavity, thereby causing hypoalbuminemia in our patients. Peritoneal albumin excretion has been shown to strongly predict future cardiovascular events in PD patients (7). Since VEGF levels in the peritoneum were increased in PD patients (12) and that inhibition of VEGF ameliorated the peritoneal permeability in diabetic rats (18), peritoneal production of VEGF and/or its biological actions may be a novel therapeutic target for hypoalbuminemia and increased cardiovascular events in PD

patients. Further, in our prospective study, dialysate VEGF was a sole independent determinant for early withdrawal from the PD. So, VEGF levels >27 pg/ml in the effluent dialysate may be a marker that could predict early withdrawal from PD therapy and future cardiovascular events in PD patients.

In our study, basal dialysate VEGF levels were not associated with peritonitis-induced withdrawal from the PD ($r=0.046$, $p=0.891$) or future peritonitis ($r=0.086$, $p=0.670$). However, the levels could predict future ultrafiltration failure in these subjects ($r=0.434$, $p=0.024$). These observations suggest that dialysate VEGF could not only affect membrane hyperpermeability, but also impair peritoneal membrane function in PD patients.

In this study, we cannot exactly identify the source of VEGF in the effluent dialysate of our patients. However, dialysate VEGF levels were not correlated with serum levels of VEGF (data not shown). Moreover, total protein levels in the dialysate effluent were not also correlated with dialysate VEGF (data not shown). Therefore, it is unlikely that dialysate VEGF was released passively from the circulating blood.

PEDF has been shown to block the VEGF-induced retinal vascular permeability in rats (19) and ameliorate retinal and renal vascular hyperpermeability in animal models of diabetic retinopathy and nephrotic syndrome, by reducing the VEGF

expression, respectively (20, 21). In this study, we demonstrated that PEDF levels in the dialysate effluent were positively associated with VEGF levels, and dialysate PEDF was one of the independent determinants of VEGF in the effluent dialysate. Since the significant inverse correlation between dialysate PEDF and serum albumin levels was lost after the adjustment for dialysate VEGF, dialysate PEDF levels may be increased in response to VEGF for counteracting its biological actions in the peritoneum. Therefore, administration of high-dose of PEDF into the peritoneal cavity and/or pharmacological up-regulation of PEDF production in the peritoneum could be a therapeutic strategy for hypoalbuminemia and early withdrawal from the PD therapy in ESRD patients.

Dialysate VEGF values (34.1 ± 17.5 pg/ml) in our patients were lower than those of previous reports; mean dialysate VEGF levels in low and high permeability groups evaluated by PET were 60.3 (19-159; range) and 96.3 (34.3-540; range) pg/ml, respectively in one report (11), whereas VEGF levels were 58.6 ± 33.7 pg/ml in the other (22). We did not know the exact reasons for the discrepant results between ours and theirs. Although RAS inhibition could alter dialysate VEGF levels, there was no association of the VEGF levels with the use of RAS inhibitors in our subjects ($r=0.217$, $p=0.277$). So, it is unlikely that the presence or absence of RAS inhibitors could affect the present findings. The difference in PD duration, concentration of glucose in the PD

solution and/or number of diabetic patients could account for the discrepancy.

LIMITATIONS

We found that dialysate VEGF levels were an independent risk factor for early withdrawal from PD. However, it might not be clinically practical to measure the dialysate VEGF value in PD patients. Therefore, studies to identify more convenient factors that could determine the dialysate VEGF levels in the clinical setting are needed.

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FIGURE LEGENDS

Fig 1. (A) Correlation between dialysate VEGF and D/P Cr levels in patients with PD.
(B) Correlation between dialysate VEGF and serum albumin levels in patients with PD.
VEGF; vascular endothelial growth factor, D/P Cr; dialysate to plasma creatinine ratio.

Fig 2. Correlation between dialysate VEGF and PEDF levels in patients with PD.
VEGF; vascular endothelial growth factor, PEDF; pigment epithelium-derived factor.

Fig 3. Cumulative retention rate of PD patients.
VEGF; vascular endothelial growth factor, Hb; hemoglobin.

TABLE 1. Clinical characteristics of patients

No of patients	27
Age (years old)	53.1 ± 17.3
Sex (male/female)	16/11
BMI (kg/m^2)	21.0 ± 3.1
Hb (g/dl)	10.6 ± 0.9
TP (g/dl)	6.34 ± 0.81
Serum albumin (g/dl)	3.35 ± 0.67
Total cholesterol (mg/dl)	183 ± 54
Triglyceride* (mg/dl) (range)	132 (53-493)
BUN (mg/dl)	54.3 ± 11.2
Serum creatinine (mg/dl)	9.60 ± 2.88
Uric acid (mg/dl)	6.91 ± 1.36
HsCRP* (ng/ml) (range)	863 (124-6010)
Intact PTH* (mg/dl) (range)	172 (23-500)
D/P Cr	0.61 ± 0.15
Dialysate VEGF (pg/ml)	34.1 ± 17.5
Dialysate PEDF (μg/ml)	1.88 ± 2.18
Dialysate TP (mg/dl)	18.2 ± 12.8
Residual renal function ($l/week/1.73m^2$)	0.60 ± 0.42
KT/V	1.85 ± 0.49
Diabetes mellitus (-/+) (%)	24/3 (11)
Medication	
RAS inhibitors (-/+) (%)	2/25 (93)
Statins (-/+) (%)	22/5 (19)

Values are shown as mean ± SD or median (range). *Log-transformed values were used. No= number; BMI=body mass index; Hb=hemoglobin; TP=total protein; BUN=blood urea nitrogen; HsCRP=high-sensitive C-reactive protein; PTH=parathyroid hormone; D/P Cr=dialysate to plasma creatinine ratio, VEGF=vascular endothelial growth factor; PEDF=pigment epithelium-derived factor; RAS=renin angiotensin system.

TABLE 2. Univariate and multiple stepwise regression analysis for the correlates of serum albumin levels

	Univariate analysis			Multiple stepwise analysis		
Variables	β	SE	*P*-value	β	SE	*P*-value
Age	**-.485**	**.007**	**0.012**	**-.427**	**.005**	**0.002**
Sex	-.053	.272	0.797			
BMI	-.118	.049	0.582			
Hb	-.283	.146	0.161			
BUN	-.026	.012	0.901			
Serum creatinine	.029	.048	0.886			
Uric acid	-.119	.101	0.563			
Total cholesterol	.240	.003	0.249			
Triglyceride*	.149	.237	0.498			
HsCRP*	-.148	.116	0.471			
Intact PTH*	.114	.157	0.587			
D/PCr	-.360	.919	0.077			
Dialysate VEGF	**-.697**	**.006**	**<0.001**	**-.659**	**.005**	**<0.001**
Dialysate PEDF	**-.406**	**.057**	**0.040**			
Dialysate TP	.121	.010	0.631			
Residual renal function	.010	.470	0.968			
KT/V	.478	.411	0.052			
Diabetes mellitus	-.739	-.358	0.073			
Use of RAS inhibitors	.145	.058	0.777			
Use of statins	.523	.313	0.120			

*Log-transformed values are used. β, standardized regression coefficients. SE, standard error. R^2=0.666, BMI=body mass index; Hb=hemoglobin; BUN=blood urea nitrogen; HsCRP=high-sensitive C-reactive protein; PTH=parathyroid hormone; D/P Cr=dialysate to plasma creatinine ratio, VEGF=vascular endothelial growth factor; PEDF=pigment epithelium-derived factor; RAS=renin angiotensin system.

TABLE 3. Univariate regression analysis for the correlates of withdrawal of PD

Variables	β	SE	*P*-value	
Age		-.171	.006	0.404
Sex		-.123	.206	0.549
BMI		-.268	.034	0.260
Hb		**-.416**	**.105**	**0.034**
Serum albumin		**-.416**	**.141**	**0.039**
BUN		.262	.009	0.197
Creatinine		-.019	.035	0.928
Uric acid		.250	.076	0.228
Total cholesterol		-.153	.002	0.474
Triglyceride*		-.190	.171	0.386
HsCRP*		.304	.083	0.130
D/PCr		.161	.708	0.422
Dialysate VEGF		**.407**	**.005**	**0.039**
Dialysate PEDF		.289	.046	0.152
Dialysate TP		.313	.315	0.750
Residual renal function		.115	.274	0.660
Weekly KT/V		-.143	.240	0.585
Diabetes mellitus		.066	.378	0.750
Use of RAS inhibitors		.045	.378	0.827
Use of statins		-.175	.252	0.393

*Log-transformed values are used. β, standardized regression coefficients. SE, standard error. PD=peritoneal dialysis; BMI=body mass index; Hb=hemoglobin; BUN=blood urea nitrogen; HsCRP=high-sensitive C-reactive protein; D/P Cr=dialysate to plasma creatinine ratio, VEGF=vascular endothelial growth factor; PEDF=pigment epithelium-derived factor; TP=total protein; RAS=renin angiotensin system.

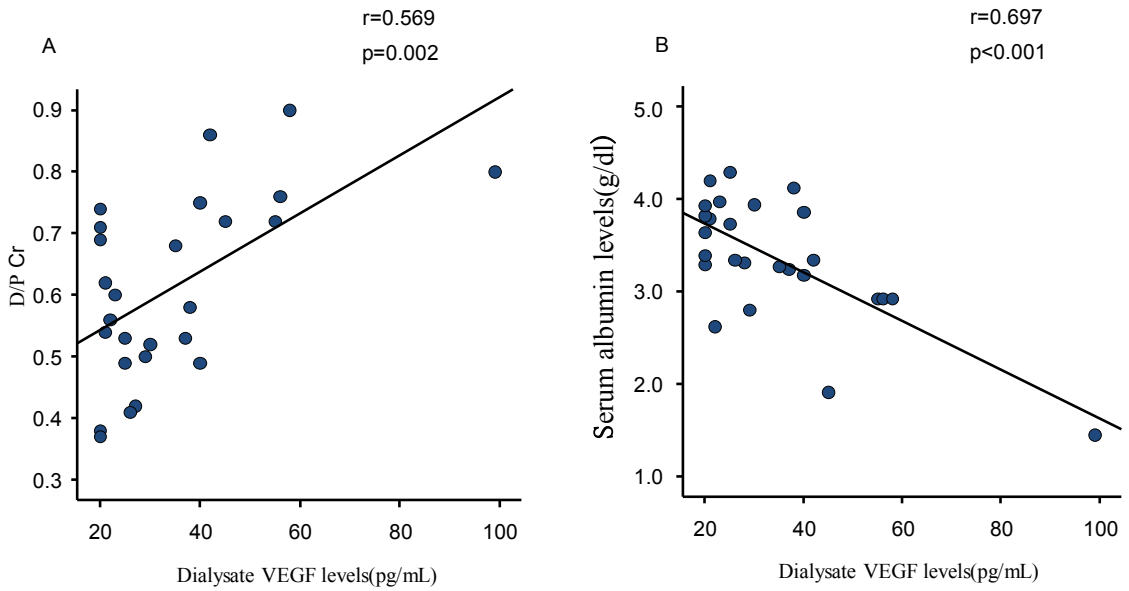
TABLE 4. OR for the withdrawal of PD during the 4 years

	Crude model		Bivariate model[1]		Multivariate model[2]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
VEGF*	7.864(1.707-36.220)	0.013	7.439(1.332-41.383)	0.022	6.310(1.137-35.021)	0.035
Albumin*	2.957(0.984-8.885)	0.053	1.092(0.317-3.754)	0.889		
Hb*	4.235(0.950-18.885)	0.058				

*****Values were categorized into two groups according to the cut-off value. [1]Bivariate model includes VEGF and albumin simultaneously. [2]Multiple model includes VEGF, albumin and hemoglobin. OR=odds ratio; PD=peritoneal dialysis; VEGF=vascular endothelial growth factor; Hb=hemoglobin.

FIG. 1.

(A) Correlation betweendialysate VEGF and D/P Cr levels in patients undergoing peritoneal dialysis (PD). (B) Correlation between dialysate VEGF and serum albumin levels in patients with PD. VEGF, vascular endothelial growth factor; D/P Cr, dialysate to plasma



creatinine ratio.

FIG. 2.

Correlation between dialysate VEGF and PEDF levels in patients undergoing peritoneal dialysis (PD). VEGF, vascular endothelial growth factor; PEDF, pigment epithelium-derived factor.

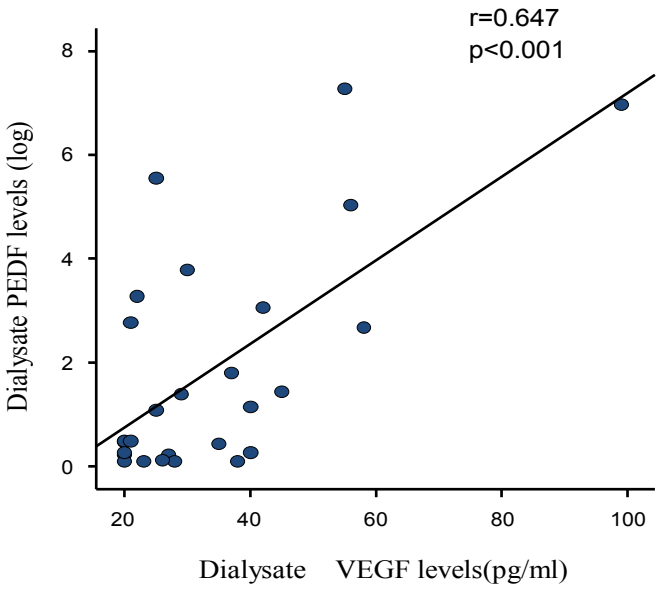


FIG. 3.

Cumulative retention rate of peritoneal dialysis (PD) patients. VEGF, vascular endothelial growth factor; Hb, hemoglobin.