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Serum Endocan as a Predictive Marker for Decreased Urine Volume in Peritoneal Dialysis Patients

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Background: Endocan is expressed in vascular endothelial cells, and its expression is enhanced following endothelial injury via inflammatory cytokines. Subsequently, endocan is secreted into the circulation. Thus, serum endocan levels are considered a marker of endothelial injury. However, to the best of our knowledge, no data on the serum endocan levels in peritoneal dialysis (PD) patients are available.

Material/Methods: This study included 21 PD patients who underwent peritoneal equilibration test (PET) more than once between 2011 and 2015. Serum samples were collected from each patient, and the 24-h urine volume was measured at the time of PET. Serum endocan levels were measured using enzyme-linked immunosorbent assay (ELISA) at the time of the first PET, and their relationship with clinical data or the extent of urine volume decline (mL/year) was analyzed retrospectively.

Results: Serum endocan levels were positively correlated with proteinuria level, serum creatinine level, serum tumor necrosis factor (TNF)-α level, β_2-microglobulin level, and PD drainage volume, but not with urine volume at baseline. The extent of decline in urine volume was significantly associated with serum endocan level, proteinuria level, serum creatinine level, and serum TNF-α level at baseline in a simple linear regression analysis. Moreover, multiple linear regression analysis showed that the serum endocan level and proteinuria level at baseline were independent predictors for the extent of decline in urine volume.

Conclusions: The results of this study indicate that serum endocan level and proteinuria level may be useful predictive markers for decreased urine volume in PD patients.

MeSH Keywords: Endocan • Endothelial Injury • Peritoneal Dialysis • Residual Renal Function • Tumor Necrosis Factor-alpha • Urine Volume

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1948 4 — 30

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Background

Peritoneal dialysis (PD), a renal replacement therapy for end-stage renal disease (ESRD), is effective in the preservation of residual renal function (RRF), thereby restoring and maintaining the social and family life of patients [1,2]. However, fluid overload is often a problem in PD patients. A previous report indicated that more than 30% of Japanese PD patients exhibit fluid overload [3]. Fluid overload leads to hypertension and increased risk of cardiovascular events [3,4]. In addition, poor body fluid control has been reported to be the cause for withdrawal from PD in 34.1% of patients in Japan [5]. Because body fluid control is mainly influenced by RRF, the decline of RRF causes poor body fluid control in PD patients. Moreover, many studies have demonstrated that preserving RRF is associated with improved survival in PD patients [6]. Urine volume is a useful indicator of RRF, and a decline in urine volume suggests a decrease in RRF [1,7,8]. Bargman et al. reported a 36% reduction in the risk of death for a 250-mL increment in urine volume in PD patients [9]. Preventing decreased urine volume is important for the continuation of PD and improvement of survival rates. Therefore, a predictive marker of urine volume decline in PD patients would be beneficial.

Endocan (previously called endothelial cell-specific molecule-1) is a 50-kDa soluble proteoglycan that is expressed in vascular endothelial cells in the kidney and various other organs and is secreted into the circulation [10,11]. Serum endocan levels are elevated in many diseases linked to endothelial injury, including sepsis, cancer, hypertension, and chronic kidney disease (CKD), as well as by inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interleukin (IL)-1β [11–18]. In addition, previous studies demonstrated that endocan inhibits the interaction between lymphocyte function-associated antigen-1 and intercellular adhesion molecule-1, which are involved in the adhesion of leukocytes to endothelial cells, and their subsequent migration to inflammatory sites [19,20]. Thus, increased serum endocan level is a marker for both endothelial injury and the anti-inflammatory response of endothelial cells [11,12].

Endothelial injury is associated with a poor prognosis of renal function [21–25]. However, to the best of our knowledge, no data on endocan levels in PD patients and no report on the relationship between serum endocan levels and RRF in PD patients are available. Therefore, in this study, we investigated the relationship between serum endocan levels as a marker of endothelial injury and decreased urine volume as an indicator of RRF in PD patients.

Material and Methods

Patient selection

This longitudinal, observational cohort study included 21 PD patients who underwent peritoneal equilibration test (PET) more than once (performed annually at the Nagasaki University Hospital in Japan) between January 2011 and December 2015. We excluded patients who were treated with a combination of PD and hemodialysis, had anuria (urine volume <200 mL/day) at baseline, or underwent PET only once. All patients were followed up until death, loss to follow-up, transfer to hemodialysis, or the end of the study.

This study was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects. The Ethics Review Board of Nagasaki University Hospital approved the study protocol (approval number: 16020822).

Clinical data and sample collection

The baseline data of the patients were collected at the time of the first PET during the study period. The results of PET were analyzed using PD ADEQUEST 2.0 software (Baxter International Inc., Deerfield, IL). Urine volume was used as an indicator of RRF. We collected serum samples from each patient and measured the 24-h urine volume at the time of PET. The extent of decline in urine volume (mL/year) was calculated using the following formula: (24-h urine volume at the first PET – volume at the most recent PET)/number of follow-up years. The glomerular filtration rate (GFR) was calculated by averaging the renal urea and creatinine (Cr) clearances. We retrospectively investigated the relationship between serum endocan levels and the clinical data or decline of urine volume.

Measurements of endocan (human endothelial cell-specific molecule-1) and TNF-α levels

The concentration of serum and 4-h PD fluid endocan, as well as serum TNF-α at the first PET, was measured using commercial ELISA kits (the Human Endothelial Cell-specific Molecule-1 ELISA Kit from Aviscera Bioscience, Santa Clara, CA and the Human TNF-α Quantikine HS ELISA Kit from R&D Systems, Minneapolis, MN) according to the manufacturers' protocols. Measurements were carried out with an ELISA plate reader (Thermo Scientific Multiskan FC; Thermo Fisher Scientific Inc., Waltham, MA). All the samples were measured in duplicate.

Statistical analysis

Data are shown as mean ± standard deviation. For all analyses that involve comparison of 2 groups, Pearson's chi-squared

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Table 1. Patient characteristics at baseline (n=21).

Age (years)	56.5±12.6	PD duration (months)	15.1±11.4
Gender (Male: Female)	13: 8	PD drainage volume (mL/day)	281±294
Primary disease of ESRD (%)		D/P Cr 4-h	0.63±0.09
Nephrosclerosis	47.6	Total weekly Kt/V	1.93±0.41
Chronic glomerulonephritis	47.6	Dialysate weekly Kt/V	0.98±0.34
Diabetic nephropathy	4.8	Residual weekly Kt/V	0.95±0.46
Cardiovascular disease (%)	23.8	Serum endocan (ng/mL)	4.84±3.81
ARB/ACE-i (%)	71.4	Serum TNF-α (pg/mL)	6.87±1.51
CCB (%)	76.2	Hb (g/dL)	10.8±1.4
Statin (%)	19.0	Alb (g/dL)	3.35±0.31
BMI (kg/m^2)	24.2±4.2	CRP (mg/dL)	0.31±0.65
SBP (mmHg)	124.6±17.8	BUN (mg/dL)	54.4±13.9
DBP (mmHg)	74.4±13.8	Cr (mg/dL)	8.89±3.28
Urine volume (mL/day)	1529±470	GFR (mL/min/1.73 m^2)	3.93±1.97
Proteinuria (mg/day)	706±486	b2-MG (mg/mL)	15.6±4.3

Data are shown as n (%) or mean ± standard deviation. ESRD – end-stage renal disease; ARB – angiotensin II receptor blocker; ACE-i – angiotensin-converting enzyme inhibitor; CCB – calcium channel blocker; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; PD – peritoneal dialysis; D/P Cr – dialysate-to-plasma creatinine ratio; Kt/V – urea clearance index; TNF-α – tumor necrosis factor-α; Hb – hemoglobin; Alb – albumin; CRP – C-reactive protein; BUN – blood urea nitrogen; Cr – creatinine; GFR – glomerular filtration rate; β_2-MG – β_2-microglobulin.

test or Fisher's exact test was conducted to compare nominal variables. Continuous variables were compared using the Wilcoxon rank sum test. Comparisons of multiple groups were evaluated by one-way analysis of variance (ANOVA). Pearson's product moment correlation analysis and Spearman's rank correlation analysis were performed to evaluate the correlation between variables. A simple linear regression analysis was used to identify variables associated with the decline in urine volume. A multiple linear regression analysis that included the variables associated with the decline in urine volume (*P* value <0.05) was used to determine independent predictors of urine volume decline. Moreover, we used Akaike's information criterion (AIC) to determine the best model in a multiple linear regression analysis and selected the model whose AIC score was the lowest. All statistical analyses were carried out using JMP version 11 software (SAS Institute Inc., Cary, NC). A *P* value of <0.05 was considered statistically significant.

Results

Patient characteristics

The clinical characteristics of the patients are listed in Table 1. The serum endocan level was 4.84±3.81 ng/mL (mean ± standard deviation; minimum: 1.65 ng/mL, maximum: 16.33 ng/mL). However, endocan was not detected in the 4-h PD fluid. The classifications of the primary disease of ESRD were nephrosclerosis (47.6%), chronic glomerulonephritis (47.6%), and diabetic nephropathy (4.8%). Subsequently, we investigated comorbidities, such as malignancies, chronic inflammatory diseases, and sepsis, that could increase serum endocan levels, but none of these diseases were found at baseline.

Table 2. Correlation between serum endocan levels and clinical data at baseline.

Variables	*r*	*P* value
Proteinuria (mg/day)	0.460	0.036
Cr (mg/dL)	0.639	0.002
Serum TNF-α (pg/mL)	0.589	0.005
β_2-MG (mg/mL)	0.479	0.033
PD drainage volume (mL/day)	0.500	0.021
Urine volume (mL/day)	–0.368	0.101

Cr – creatinine; TNF-α – tumor necrosis factor-α; β_2-MG – β_2-microglobulin; PD – peritoneal dialysis.

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Relationship between serum endocan levels and clinical data in PD patients

The relationship between serum endocan levels and clinical data in PD patients is shown in Table 2. The serum endocan levels were positively correlated with proteinuria level (r=0.460, P=0.036), serum Cr level (r=0.639, P=0.0018), serum TNF-α level (r=0.589, P=0.0050), β_2-microglobulin level (β_2-MG; r=0.479, P=0.033), and PD drainage volume (r=0.500, P=0.021), but were not correlated with urine volume at the time of endocan measurement (r=–0.368, P=0.10).

Clinical factors associated with decreased urine volume in PD patients

The patients were followed up for a mean duration of 26.7±15.9 months. To investigate the clinical factors associated with decreased urine volume in PD patients, we divided the PD patients into 2 groups: the rapid-decrease group (≥200 mL/year, n=12, defined as rapid-decrease) and the slow-decrease group (<200 mL/year, n=9, defined as slow-decrease). As shown in Table 3, the rapid-decrease group exhibited significantly higher serum endocan levels (rapid-decrease group: 6.28±4.47 *vs.* slow-decrease group: 2.92±1.25 ng/mL, P=0.036) and proteinuria level (rapid-decrease group: 979±458 *vs.* slow-decrease group: 344±208 mg/day, P=0.0010) than the slow-decrease group. No significant differences were found in the other clinical parameters, including urine volume, GFR, serum Cr level, dialysate/plasma (D/P) Cr level, total weekly Kt/V, and serum TNF-α level. A simple linear regression analysis was then performed to evaluate the relationship between the extent of decrease in urine volume and clinical data, including serum endocan level and proteinuria level. As shown in Table 4, the extent of decrease in urine volume was significantly associated with serum endocan level, proteinuria level, and serum Cr level, and serum TNF-α level at baseline, but not with urine volume. Finally, a multiple linear regression analysis, whose AIC score was the minimum, showed that the serum endocan level and proteinuria level at baseline were independent predictors of the extent of decrease in urine volume in PD patients (adjusted R^2 of the model=0.657, P<0.0001; Table 4).

Discussion

The serum endocan levels in this study were higher in all the PD patients than in the healthy population, where the normal range is ≤1 ng/mL [12,14,16]. Our study showed that the serum endocan levels at baseline were positively correlated with proteinuria level, serum Cr level, serum TNF-α level, β_2-MG level, and PD drainage volume, but not with urine volume at baseline. Moreover, the serum endocan level and proteinuria level at baseline were independent predictors of the extent of decrease in urine volume in PD patients. Although nephrotoxic medication is reported to cause a decrease in urine volume [8], none of the patients in the present study used nephrotoxic medications, such as non-steroidal anti-inflammatory drugs, nephrotoxic antibacterial drugs like aminoglycoside and vancomycin, and contrast agents, during the follow-up period.

Although the physiological function of endocan is not clearly elucidated, serum endocan levels increase in response to endothelial injury via inflammation. Thus, serum endocan level is considered a marker of endothelial injury [11,12]. In CKD patients, the levels of circulating uremic toxins are elevated, and the toxins cause endothelial injury by increasing the production of inflammatory cytokines, such as TNF-α and IL-1β [26–28]. Here, we demonstrated that serum endocan levels are positively correlated with serum TNF-α levels and significantly associated with the extent of decrease in urine volume in PD patients. Endothelial injury causes glomerulosclerosis and interstitial fibrosis [29], which ultimately leads to the deterioration of kidney function. Therefore, we believe that serum endocan level could be a useful predictor for decreased RRF in PD patients.

This study has several limitations. First, we could not take into account the serial change in serum endocan levels in response to changes in endothelial function, because a single serum endocan level was determined at baseline. Second, serum samples were collected from patients while they still had PD fluid in their abdomen. The possibility of changes in serum endocan levels before and after PD exchanges was not examined. However, we could not detect endocan in the 4-h PD fluid. Therefore, we assumed that the possibility of changes in serum endocan levels before and after PD exchanges was extremely low. Third, serum endocan levels may be affected by medications because they are significantly decreased following antihypertensive therapy using agents such as valsartan and amlodipine [30]. However, no significant difference was found in serum endocan levels between patients with and without angiotensin II receptor blocker (ARB)/angiotensin-converting enzyme inhibitor (ACE-i), calcium channel blocker (CCB), or statin in this study (data not shown). Moreover, evaluation and comparison of the strength of each drug are difficult because many types of ARB/ACE-i, CCB, or statin were used. Thus, we could not investigate the correlations between serum endocan levels and the doses of these drugs. The slow-decrease group showed a tendency to take renoprotective medicines, such as ARB, ACE-i, CCB, and statins. However, significant difference was not found in medications between the slow-decrease and rapid-decrease groups. Finally, this was a retrospective observational study with a small number of patients. We cannot preclude the existence of an unrecognized factor that confounds the observed associations. In addition, we could not examine the association between endocan and

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Table 3. Comparison of clinical characteristics between the slow-decrease (<200 mL/year) and rapid-decrease (≥200 mL/year) groups.

At baseline	Slow-decrease group (n=9)	Rapid-decrease group (n=12)	*P* value
Age (years)	57.6±12.2	55.7±13.4	0.80
Sex (Male: Female)	5: 4	8: 4	0.60
Primary disease of ESRD (%)			0.053
Nephrosclerosis	77.8	25.0	
Chronic glomerulonephritis	22.2	66.7	
Diabetic nephropathy	0	8.3	
Cardiovascular disease (%)	33.3	16.7	0.61
ARB/ACE-i (%)	88.9	58.3	0.18
CCB (%)	88.9	66.7	0.34
Statin (%)	33.3	8.3	0.27
BMI (kg/m^2)	23.0±2.4	25.0±5.0	0.36
SBP (mmHg)	118.3±12.1	129.3±20.4	0.30
DBP (mmHg)	68.0±11.2	79.3±14.0	0.11
Urine volume (mL/day)	1535±392	1525±537	0.94
Proteinuria (mg/day)	344±208	979±458	<0.001
PD duration (months)	17.9±9.2	13.0±12.8	0.24
PD drainage volume (mL/day)	315±243	256±336	0.55
D/P Cr 4-hour	0.62±0.08	0.64±0.09	0.52
Total weekly Kt/V	1.96±0.40	1.91±0.43	0.55
Dialysate weekly Kt/V	0.96±0.30	1.00±0.38	0.80
Residual weekly Kt/V	1.00±0.38	0.91±0.53	0.64
Serum endocan (ng/mL)	2.92±1.25	6.28±4.47	0.036
Serum TNF-α (pg/mL)	6.17±0.98	7.40±1.65	0.065
Hb (g/dL)	11.1±1.7	10.5±1.1	0.70
Alb (g/dL)	3.41±0.25	3.31±0.36	0.45
CRP (mg/dL)	0.09±0.11	0.46±0.83	0.39
BUN (mg/dL)	58.4±17.5	51.4±10.2	0.37
Cr (mg/dL)	7.74±2.55	9.74±3.60	0.27
GFR (mL/min/1.73 m^2)	4.43±2.03	3.56±1.93	0.30
β_2-MG (mg/mL)	14.5±2.9	16.4±5.2	0.59
At the end of follow-up time			
Follow-up duration (months)	28.9±14.7	25.1±17.3	0.45
Peritonitis rate (episodes/person-year)	0.05	0.2	0.44
Extent of changes in urine volume decrease (mL/year)	18±134	505±265	<0.001

Data are shown as n (%) or mean ± standard deviation. ESRD – end-stage renal disease; ARB – angiotensin II receptor blocker; ACE-i – angiotensin-converting enzyme inhibitor; CCB – calcium channel blocker; BMI – body mass index; SBP – systolic blood pressure; DBP – diastolic blood pressure; PD – peritoneal dialysis; D/P Cr – dialysate-to-plasma creatinine ratio; Kt/V – urea clearance index; TNF-α – tumor necrosis factor-α; Hb – hemoglobin; Alb – albumin; CRP – C-reactive protein; BUN – blood urea nitrogen; Cr – creatinine; GFR – glomerular filtration rate; β_2-MG – β_2-microglobulin.

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Table 4. Clinical factors associated with the extent of decrease in urine volume in PD patients at baseline.

Variables	Simple linear regression		Multiple linear regression	
	β (95% CI)	*P* value	β (95% CI)	*P* value
Serum endocan (ng/mL)	69.0 (41.8, 96.3)	<0.001	54.8 (27.1, 82.5)	<0.001
Proteinuria (mg/day)	0.44 (0.18, 0.70)	0.002	0.24 (0.03, 0.46)	0.031
Cr (mg/dL)	57.5 (16.1, 99.0)	0.009	–	–
Serum TNF-α (pg/mL)	116.5 (23.6, 209.3)	0.017	–	–
Urine volume (mL/day)	–0.13 (–0.47, 0.21)	0.429	–	–

Cr – creatinine; TNF-α – tumor necrosis factor-α; β – regression coefficient; CI – confidence interval.

atherosclerosis parameters or development of cardiovascular events, although Yilmaz et al. reported that serum endocan level is a marker of mortality (all causes) and cardiovascular events in CKD patients [15]. A prospective study is necessary to validate the results of this study in the future.

Conclusions

Serum endocan levels were increased in PD patients. This study is the first to demonstrate that serum endocan level and proteinuria level are independent predictors for the extent of decrease in urine volume in PD patients.

Conflicts of interest

The authors have declared that no conflicts of interest exist.

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