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CLINICAL STUDY

Inflammation is associated to volume status in peritoneal dialysis patients

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Abstract

Aim: The aim of this study is to investigate whether there is a relationship between inflammation and volume status in patients underwent peritoneal dialysis (PD). *Patients and method*: This cross-sectional study included 159 PD patients. The median duration of PD was 17 (range, 1–151) months. All patients were examined using bioelectrical impedance analysis to estimate the ratio of extracellular water to total body water (ECW/TBW), which was used to assess their volume status. The patients were categorized as having one of the following three volume statuses: hypervolemic (above +2 SD from the mean, which was obtained from healthy controls), normovolemic (between +2 SD and −2 SD), or hypovolemic (below −2 SD from the mean). Five patients with hypovolemia were excluded from the study. Fifty-six patients were hypervolemic whereas 98 patients were euvolemic. High-sensitive C-reactive protein (hs-CRP) levels were measured to evaluate inflammation in all patients. *Results*: hs-CRP value levels were significantly higher in hypervolemic patients compared with euvolemic patients [7.1 (3.1–44.0) mg/L vs. 4.3 (3.1–39.6), *p*: 0.015, respectively]. Left ventricular hypertrophy was more frequent in hypervolemic patients compared with euvolemic patients (53.6% vs. 30.6%, *p*: 0.004, respectively). ECW/TBW ratio positively correlated with hs-CRP (*r*: 0.166, *p*: 0.039). Gender, hs-CRP, and residual Kt/V urea were found to be independent risk factors for hypervolemia in multivariate analysis. *Conclusion*: Inflammation is associated with hypervolemia in PD patients. Residual renal functions play an important role to maintain euvolemia in PD patients.

Keywords

Gender, hypervolemia, inflammation, peritoneal dialysis, residual renal function

History

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Introduction

Cardiovascular diseases (CVD) remain to be the major cause of mortality in patients with end-stage renal disease (ESRD). Traditional risk factors, including diabetes mellitus, hypertension, older age, dyslipidemia, and left ventricular hypertrophy (LVH), and physical inactivity, account for up to 50% of CVD in chronic kidney disease (CKD), whereas non-traditional risk factors, including anemia, albuminuria, abnormal calcium/phosphate metabolism, hypervolemia, oxidative stress, malnutrition, sleep disturbances, homocysteinemia, and inflammation contribute to the total cardiovascular burden in CKD.[1–3]

The frequency of inflammation is high in patients with CKD.[4] However; the cause(s) of inflammation has not been fully elucidated. It may results from the primary renal disease itself. For peritoneal dialysis (PD) patients, the use of bioincompatibility PD solution is another potential source of inflammation.[5]

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In the present study, we aimed to investigate whether there is a relationship between inflammation and hypervolemia in peritoneal dialysis (PD) patients.

Patients and methods

This cross-sectional study included 159 PD patients. The median duration of PD was 17 (range, 1–151) months.

All patients were examined using bioelectrical impedance analysis (RJL Systems Quantum II Bia Analyzer, Clinton Township, MI) to estimate the ratio of extracellular water to total body water (ECW/TBW). To determine the mean ECW/TBW, the control group of our previously study, which consisted of 15 healthy subjects, was used. The patients were categorized as having one of the following three volume statuses: hypervolemic (above +2 SD from the mean), normovolemic (between +2 SD and −2 SD), or hypovolemic (below −2 SD from the mean).[6] Only five patients were hypovolemic. The patients were excluded from the study because data would not be homogeneous and accurate and reliable statistics would not been made. Finally, 56 (36.4%) of 154 patients were hypervolemic whereas 98 (63.6%) patients were euvolemic.

The transport property of peritoneal membrane was determined by the standard peritoneal equilibrium test (PET) as defined by Twardowski.[7] Patients with a history of peritonitis within the previous 2 months, dialysate leak, or dialysis catheter dysfunction were not performed a PET. The PET reported on the time closest to day, in which examinations including bioimpedance measurements, echocardiography, and biochemical analysis were performed, was used. According to 4-h dialysate-to plasma ratio (D/P) for creatinine, patients were categorized as one of the following four peritoneal transport types: high (above +1 SD from the mean), high average (between the mean and +1 SD), low average (between the mean and −1 SD), or low (below −1 SD from the mean).

The echocardiographic studies were performed in three cardiac cycles using a Vivid 7 Dimension (General Electric Healthcare Company, Milwaukee, WI) with a 3 MHz transducer in the left lateral position. Left ventricular end-diastolic and end-systolic diameters (LVEDD and LVESD) and end-diastolic interventricular septum and posterior wall thicknesses (IVSEDD and PWEDD) were measured by the M-mode in the parasternal long-axis view. Ejection fraction (EF) was calculated according to the Teicholz formula.[8] IVSEDD, PWEDD, and internal dimensions were used to calculate LV mass (LVM) using the following equation: $LVM = 1.04 \times 0.8$ [(LV wall thicknesses + internal dimension)-(internal dimension)] + 10.6 g. LVH was defined as the LVM index (LVMI), which was calculated with LVM in grams divided by the body surface area in square meters, higher than 116.0 for men and 104.0 for women.[9] Body surface area was calculated using Mosteller's formula.[10]

Blood samples were taken from all patients for laboratory examinations, including complete blood count, serum glucose, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, total protein, albumin, intact parathyroid hormone (iPTH), and high sensitive C-reactive protein (hs-CRP) levels, and total lipid profile. The iPTH was measured by radioimmunoassay (Immunotect, Marseille, France). Serum hsCRP was measured by CardioPhase hsCRP (Dade Behring, Glasgow, DE) on a Dade Behring.

All examinations including bioimpedance measurements, echocardiography, and biochemical analysis of the patients were performed at the same day.

All patients were evaluated in terms of systemic or local infection and PD-related peritonitis. None of the patients had any signs of systemic infection and peritonitis. The evaluated signs and symptoms of systemic infection were abdominal, nape, back and forehead pain, fever, nausea, vomiting, diarrhea, dysuria, cough, or rash. In addition to these symptoms, pain, fever, pus, redness and swelling at the affected area were evaluated as the symptoms of local infection. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2).

Statistical analysis

Statistical analysis was performed with the software program SPSS for Windows 15.0 (SPSS Inc., Chicago, IL). The Kolmogorov–Smirnov test was used to determine normality of distributions of variables. Continuous variables with normal distribution were presented as mean ± standard deviation. Median value was used in variables without normal distribution. Statistical analysis for the parametric variables was performed using Student's *t*-test between two groups. The Mann–Whitney *U* test was used to compare non-parametric variables between two groups. Qualitative variables were given as percent and the correlation between categorical variables was investigated using the Chi-square test. The correlation analysis was evaluated by Spearman's correlation test. The possible risk factors considered to be related with hypervolemia were analyzed using the multivariate Cox regression model in which we included (in a Backward–Wald manner) all the significant variables from the univariate analysis. A p value <0.05 was considered statistically significant.

Results

Table 1 shows comparison of demographic, clinic, and echocardiographic parameters between hypervolemic patients and euvolemic patients. Female gender, BMI value, ECW/TBW ratio, and frequency of LVH were significantly higher in hypervolemic patients compared with euvolemic patients (p: <0.001, 0.012, <0.001, and 0.004, respectively). The duration of PD was significantly longer in hypervolemic patients compared with euvolemic patients (p: 0.001). Although LVMI was higher in hypervolemic patients than in euvolemic patients, the statistical significance was borderline (p: 0.081). On the other hand, there was no significant difference between two groups with regard to other demographic, clinical, and echocardiographic parameters (p: >0.05).

To further assess the effect of the volume status on blood pressure, 97 patients taking an antihypertensive agent including angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta blocker, and calcium canal blocker, were excluded. Some of these 97 patients were taking a single antihypertensive agent, whereas the rest were taking more than one antihypertensive agent. When only 57 patients, who do not use an antihypertensive agent, were analyzed, it was found that mean systolic blood pressure was significantly higher in 23 hypervolemic patients than in 34 euvolemic patients (141 ± 26 mmHg vs. 125 ± 22 mmHg, respectively, p: 0.013). Similarly, although there is no statistically significant difference between two groups, mean diastolic blood pressure was slightly higher in 23 hypervolemic patients than in 34 euvolemic patients (84 ± 16 mmHg vs. 82 ± 15 mmHg, respectively, p: 0.534).

A comparison of laboratory parameters between hypervolemic patients and euvolemic patients is shown in Table 2. Hemoglobin concentration, iPTH level, residual Kt/V urea, total creatinine clearance, and residual creatinine clearance were significantly lower in hypervolemic patients compared with euvolemic patients (p: 0.003, 0.011, 0.046, 0.001, and 0.033, respectively). hs-CRP levels, percent of patient with high hs-CRP, and peritoneal Kt/V urea were significantly higher in hypervolemic patients compared with euvolemic patients (p: 0.015, 0.019, and 0.021, respectively). On the other hand, there was no significant difference between two groups with regard to other laboratory parameters ($p > 0.05$).

Table 1. Comparison of demographic, clinic, and echocardiographic parameters between hypervolemic patients and euvolemic patients.

	Hypervolemic group (*n*: 56)	Euvolemic group (*n*: 98)	*p* Value
Age (year)	47.7 ± 14.1	46.9 ± 13.2	0.711
Female (%)/male (%)	41 (73.2)/15 (26.8)	27 (27.6)/71 (72.4)	<0.001
Peritoneal dialysis duration (mo)	30 (1–151)	11 (1–123)	0.001
Body mass index (kg/m^2)	27.5 ± 6.1	25.1 ± 4.5	0.012
Presence of diabetes mellitus (%)	15 (26.8)	34 (34.7)	0.203
Peritoneal transport status			0.592
Low (%)	3 (5.4)	5 (5.1)	
Low-average (%)	20 (35.7)	25 (25.5)	
High-average (%)	22 (39.3)	44 (44.9)	
High (%)	11 (19.6)	24 (24.5)	
Systolic blood pressure (mmHg)	140 (100–220)	140 (80–230)	0.344
Diastolic blood pressure (mmHg)	90 (60–130)	90 (60–140)	0.362
Heart rate (beat/min)	85 (61–118)	82 (59–109)	0.469
ECW/TBW ratio	0.47 ± 0.03	0.36 ± 0.05	<0.001
Use of ACEI or ARB (%)	22 (39.3)	33 (33.7)	0.299
Use of beta blocker (%)	14 (25.0)	22 (22.4)	0.432
Left ventricular mass (g)	186 (83–392)	173 (76–657)	0.498
Left ventricular mass index (g/m^2)	112 (49–248)	98 (49–327)	0.081
Presence of left ventricular hypertrophy (%)	30 (53.6)	30 (30.6)	0.004
Ejection fraction (%)	65.9 ± 10.2	66.3 ± 9.9	0.809

Note: ECW, extracellular volume; TBW, total body water; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Table 2. Comparison of laboratory parameters between hypervolemic patients and euvolemic patients.

	Hypervolemic group (*n*: 56)	Euvolemic group (*n*: 98)	*p* Value
White blood cell count (mm^3)	7522 ± 2343	7277 ± 1989	0.492
Hemoglobin (g/dL)	10.8 ± 1.6	11.6 ± 1.9	0.003
Glucose (mg/dL)	106 (77–299)	100 (66–458)	0.356
Total cholesterol (mg/dL)	198 ± 48	199 ± 63	0.891
Triglyceride (mg/dL)	144 (37–471)	148 (46–537)	0.823
High-density lipoprotein cholesterol (mg/dL)	36 ± 12	38 ± 15	0.554
Low-density lipoprotein cholesterol (mg/dL)	127 ± 38	126 ± 52	0.904
Blood urea nitrogen (mg/dL)	55 ± 17	54 ± 15	0.535
Serum creatinine (mg/dL)	8.6 ± 3.2	8.6 ± 3.8	0.930
Calcium (mg/dL)	8.6 ± 0.8	8.7 ± 0.9	0.270
Phosphorus (mg/dL)	4.5 ± 1.3	4.4 ± 1.4	0.798
Calcium x phosphorus (mg^2/dL^2)	41 ± 11	41 ± 14	0.846
Serum total protein (g/dL)	6.6 ± 0.7	6.5 ± 0.6	0.334
Serum albumin (g/dL)	3.2 ± 0.5	3.3 ± 0.4	0.370
hs-CRP (mg/L)	7.1 (3.1–44.0)	4.3 (3.1–39.6)	0.015
hs-CRP category			0.019
Normal (0–6 mg/L) (%)	25 (44.6)	62 (63.3)	
High (higher than 6 mg/L) (%)	31 (55.4)	36 (36.7)	
Intact parathormon (pg/mL)	138 (17–786)	198 (17–1923)	0.011
Weekly total Kt/V urea	2.4 (1.7–5.5)	2.4 (1.6–5.8)	0.447
Weekly peritoneal Kt/V urea	2.0 (1.2–3.7)	1.8 (1.0–2.7)	0.021
Weekly residual Kt/V urea	0.2 (0–1.6)	0.4 (0–3.7)	0.046
Weekly total creatinine clearance (mL/min)	69 (49–231)	87 (43–244)	0.001
Weekly peritoneal creatinine clearance (mL/min)	51 (39–76)	52 (31–226)	0.772
Weekly residual creatinine clearance (mL/min)	8 (0–73)	19 (0–198)	0.033

ECW/TBW ratio correlated positively with hs-CRP (*r*: 0.166, *p*: 0.039), diastolic blood pressure (*r*: 0.162, *p*: 0.044), and BMI (*r*: 0.200, *p*: 0.013). It inversely correlated with hemoglobin concentration (*r*: −0.213, *p*: 0.008), serum albumin (*r*: −0.174, *p*: 0.031), weekly total creatinine clearance (*r*: −0.188, *p*: 025), and iPTH level (*r*: −0.204, *p*: 0.011). However, it did not correlate with age, ejection fraction, LVMI, heart rate, systolic blood pressure, WBC count, serum glucose and lipid levels, BUN, serum creatinine, calcium, phosphorus, calcium x phosphorus value, total protein, and weekly total Kt/V urea (*p*: >0.05).

Univariate and multivariate analyses were performed to identify the risk factors considered to be related with hypervolemia. Table 3 shows the results regarding 14 variables examined in univariate analysis as potential risk factors for hypervolemia. Seven of the 14 factors (gender, PD

Table 3. Univariate and multiple (by Backward–Wald model) logistic regression analysis for risk factors considered to be related with hypervolemia.

Risk factor	Univariate analysis OR (95% CI)	*p* Value	Multiple analysis OR (95% CI)	*p* Value
Age	1.01 (0.98–1.03)	0.709	–	–
Gender (male or female)	7.19 (3.43–15.05)	<0.001	9.95 (3.46–28.56)	<0.001
Peritoneal dialysis duration	1.01 (1.00–1.02)	0.012	–	–
Diabetes mellitus (yes or no)	1.42 (0.71–2.99)	0.312	–	–
Peritoneal transport status (low or high)	1.58 (0.80–3.13)	0.190	–	–
Body mass index	1.09 (1.02–1.17)	0.008	–	–
Use of ACEI or ARB (no or yes)	1.28 (0.65–2.51)	0.485	–	–
Hemoglobin	0.75 (0.62–0.92)	0.005	–	–
Low-density lipoprotein	1.00 (0.99–1.01)	0.903	–	–
Calcium x phosphorus	1.00 (0.97–1.02)	0.845	–	–
Serum albumin	0.73 (0.36–1.46)	0.368	–	–
hs-CRP	1.05 (1.01–1.08)	0.010	1.06 (1.01–1.11)	0.010
Peritoneal Kt/V urea	3.14 (1.24–7.94)	0.016	–	–
Residual Kt/V urea	0.40 (0.19–0.88)	0.022	0.26 (0.09–0.74)	0.012

Note: OR: odds ratio, CI: confidence interval, BMI: body mass index, ACEI: angiotensin converting enzyme inhibitor, ARB: angiotensin receptor blocker, hs-CRP: high-sensitive C-reactive protein

Table 4. Comparison of risk factors considered to be related with hypervolemia between male and female patients.

	Female patients (*n*: 68)	Male patients (*n*: 86)	*p* Value
Peritoneal dialysis duration (month)	23 (1–151)	12 (3–123)	0.023
Body mass index (kg/m^2)	27.2 ± 6.1	25.1 ± 4.3	0.014
Hemoglobin (g/dL)	10.6 ± 1.4	11.8 ± 2.0	<0.001
hs-CRP (mg/L)	4.6 (3.1–44.0)	5.6 (3.1–42.3)	0.221
Peritoneal Kt/V urea	2.1 (1.3–3.7)	1.7 (1.0–2.9)	0.001
Residual Kt/V urea	0.1 (0–3.6)	0.4 (0–3.7)	0.120

duration, BMI, hemoglobin, hs-CRP, peritoneal Kt/V, and residual Kt/V) were significantly and independently associated with the presence of hypervolemia in univariate analysis. All these significant variables in the univariate analysis were included in the multivariate Cox regression to analyze the risk factors considered to be related with hypervolemia. In multivariate analysis, gender, hs-CRP, and residual Kt/V were significantly and independently associated with hypervolemia.

Table 4 shows a comparison of risk factors considered to be related with hypervolemia between male and female patients. PD duration was significantly longer in female patients compared to male patients (*p*: 0.023). BMI and peritoneal Kt/V urea values were significantly higher in female patients compared with male patients (*p*: 0.014 and 0.001, respectively). The hemoglobin concentration was significantly lower in female patients compared with male patients (*p*: <0.001). On the other hand, there was no significant difference between female and male patients in terms of hs-CRP and residual Kt/V urea values (*p*: >0.05).

We also evaluated whether there is association between inflammation and residual renal functions and found that median weekly residual Kt/V value was significantly lower in patients with high hs-CRP levels than in those with normal hs-CRP levels [0.12 (0–1.68) vs. 0.39 (0–3.67), *p*: 0.025, respectively]. Similarly, median weekly residual creatinine clearance values were significantly lower in patients with high hs-CRP levels than in those with normal hs-CRP levels [7.4 mL/min (0–81.3) vs. 19.5 mL/min (0–198.3), *p*: 0.039, respectively].

Discussion

In the present study, there were three main findings. First, the frequency of hypervolemia, which was evaluated by bioelectrical impedance analysis, was high. Second, female gender and inflammation, which was evaluated by hs-CRP values, were factors increasing the risk of development of hypervolemia. Finally, residual renal function was a factor reducing the risk of development of hypervolemia.

Inflammation is a very frequent condition in patients with pre-dialysis and dialysis-dependent CKD.[11,12] In uremic patients, there are several underlying causes of inflammation, including intercurrent clinical events such as infections, surgery, malignancy, and vascular diseases; comorbidities such as atherosclerosis, diabetes mellitus, and obesity; dialysis-related factors such as bioincompatible membranes and PD solutions; and other factors such as depression and genetics. Uremia *per se* and cultural habits (such as food intake) may be associated with an inflammatory response in dialysis patients.[5,13]

One of the main results in the present study was that inflammation was associated with hypervolemia in PD patients. This relationship between inflammation and hypervolemia appears to be bidirectional in the patient group. Hypervolemia may be a contributing factor for the inflammatory process. In the cross-sectional study of 22 prevalent PD patients, Gangi et al. have found that serum and peritoneal effluent interleukin-6, which is an inflammatory marker, correlated with bioimpedance-derived measures of hypervolemia.[14] Salt may be a potential uremic toxin.[15] Increase in

dietary salt intake can induce inflammation.[16] Recently, Telini et al. have reported that dietary sodium restriction is associated with the attenuation of the inflammatory process, without changes in blood pressure and ECW, suggesting inhibition of a salt-induced inflammatory process.[17] Similarly, the same group has observed that dialysate sodium reduction give rise to similar results.[18] Furthermore, it has been shown that a relationship between LV filling pressure and inflammation in pre-dialysis patients.[4] One of the possible mechanisms underlying the link between hypervolemia and inflammation is that the use of more hypertonic PD solutions is required to re-establish normovolemia in PD patients with hypervolemia. The inflammatory process per se may cause hypervolemia indirectly.[19] Inflammation is associated with increased peritoneal permeability,[20] which can result in loss of the osmotic gradient and ultrafiltration that may trigger ECW expansion. In this study, the median duration of PD was higher in hypervolemic patients compared with euvolemic patients, thus clearly the hypervolemic patients had a greater exposure to bioincompatible PD solutions and had a higher inflammatory load.

Residual renal function is an important predictor for clinical outcomes in PD patients and plays an important role maintaining volume balance in PD patients compared with hemodialysis patients.[21] Similarly, in the present study, residual Kt/V urea was significantly and independently associated with hypervolemia. We have found that 1 unit/week of residual Kt/V urea value reduces by 76% the risk of developing hypervolemia. Residual renal function not only provides small solute clearance but also plays an important role in phosphorus control, and removal of middle molecular uremic toxins, and shows strong inverse relationships with valvular calcification and cardiac hypertrophy in dialysis patients.[21] In addition, there is increasing evidence that residual renal and peritoneal dialysis clearance cannot be assumed to be equivalent qualitatively.[21–23] Indeed, the present study, residual Kt/V urea but not peritoneal Kt/V urea was a powerful predictor of hypervolemia in multivariate analysis.

It has been shown that there is a relationship loss of RRF and increase in systemic inflammatory burden in predialysis[24] and dialysis patients.[25] A low GFR *per se* is associated with an inflammation, suggesting an increase in the generation of proinflammatory cytokines in uremia, impaired renal clearance of the cytokines, or an adverse effect of inflammation on renal function.[24,26] An impaired renal clearance of inflammatory cytokines has been shown in animal models where bilateral nephrectomy results in both an increase of the levels of soluble tumor necrosis factor (TNF) receptors and an increase in circulating TNF.[27] Animal models have demonstrated that uremic toxins such as *p*-cresyl sulfate (PCS) and indoxyl sulfate (IS) induce proinflammatory cytokine production.[28,29] In addition, recently, Rossi et al.[30] have demonstrated that IS and PCS levels were associated with elevated levels of selected inflammatory markers and an antioxidant in 149 predialysis patients with a mean eGFR of 40 ± 9 mL/min/1.73 m^2. Similarly, we found that there was an association between inflammation and residual renal functions. Residual renal function was significantly lower in patients with high hs-CRP levels than in those with normal hs-CRP levels.

In the present study, multivariate analysis found that female gender was the most important risk factor for hypervolemia. Risk of hypervolemia was approximately 10-fold higher in female patients compared with male patients. The reason for this appears to be a combination of several factors. As shown in Table 4, female patients had higher BMI values, longer PD durations, and lower hemoglobin concentrations, all of which were risk factors for the development of hypervolemia in univariate analysis, than male patients. In addition, although a statistically significant difference between females and males was observed, male patients had higher residual Kt/V urea value, which was a factor reducing the risk of development of hypervolemia. On the other hand, peritoneal clearance was higher in women. This can be explained by the longer duration of PD; this could have impacted the ultrafiltration and led to hypervolemia.

Knowledge of normal volume status is essential in the management of dialysis. Determination of euvolemic state is generally difficult due to the absence of accurate diagnostic methods.[31] Bioimpedance analysis is a diagnostic method that may enable the assessment of body composition and hydration status.[32] The technique calculates ECW, ICW, and TBW by measuring resistance and reactance of the arms, trunk, and legs using multi-frequencies from 1 kHz to 1000 kHz from an eight-polar tactile electrode impedance meter.[32,33] However, measurements of ECV and TBW are influenced by both body composition and hydration status. Thus these variables or ratios between these variables cannot accurately separate hydration changes from changes in other aspects of body composition.[31] Furthermore, body composition measurements using the analysis in PD patients are affected by the presence of dialysate in abdomen.[32]

There are several limitations of this study. First, the study was cross-sectional and the potential causal relationship between inflammation and hypervolemia cannot be concluded. Second, the number of patients in the study was relatively low. To better clarify that issue, further studies with great numbers are warranted. Third, there was a lack of usage of detailed inflammation markers.

In conclusion, inflammation is closely associated with hypervolemia in PD patients. One of the benefits of strict volume control in these patients is also a positive effect on inflammation. Residual renal functions play an important role to maintain euvolemia in PD patients.

Declaration of interest

The authors declare that they have no conflict of interest.

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