in vivo *36*: 925-933 (2022)
doi:10.21873/invivo.12782

Oxalate Balance in Peritoneal Dialysis Patients: A Potential Role of Dialysis-related Peritonitis

NATALIA STEPANOVA, LESYA KOROL, LARYSA LEBID, LYUDMYLA SNISAR and SVITLANA SAVCHENKO

State Institution 'Institute of Nephrology of the National Academy of Medical Sciences', Kyiv, Ukraine

Abstract. *Background: Little evidence is available on oxalate balance in peritoneal dialysis (PD) patients. Patients and Methods: We performed a cross-sectional observational pilot study with 62 adult PD patients to document oxalate balance and explore its association with PD-related peritonitis. Plasma oxalate concentration, levels of oxalate excretion in 24-h urine, and peritoneal dialysis effluent were evaluated. The peritoneal oxalate transport status and renal and peritoneal oxalate clearances were calculated according to the PD-related peritonitis history. Results: PD patients with a history of peritonitis had a statistically significantly lower peritoneal oxalate clearance, daily peritoneal oxalate excretion, and overall oxalate removal rate compared with the peritonitis-free PD patients. They had a 4-fold risk of plasma oxalic acid increase, and even a single episode of dialysis-related peritonitis resulted in plasma oxalate elevation. Conclusion: Peritoneal oxalate clearance plays an important role in oxalate balance in PD patients and, therefore, dialysis-related peritonitis is a significant predictor for hyperoxalemia. Further well-designed clinical trials need to be undertaken before the association between peritonitis and oxalate balance in PD patients is more clearly understood.*

Oxalate is an ionized form of a potentially toxic oxalic acid formed from endogenously synthesized and exogenously ingested oxalates (1, 2). In physiological conditions, the bulk of circulating oxalate (90-95%) is excreted through the kidneys, whereas the remainder (5-10%) through the terminal parts of the small intestine and colon (1-4). A decline in kidney function leads to decreased oxalate clearance and, ultimately, hyperoxalemia in end-stage kidney disease (ESKD) (1, 5-7). The accumulation of oxalate is associated with oxidative stress and systemic inflammation (1, 8, 9), high cardiovascular risk (9-11), and increased mortality rate (1, 11) in patients with kidney stones and ESKD. Nevertheless, little evidence is available on oxalate balance in ESKD patients in general and peritoneal dialysis (PD) patients in particular; almost all scientific data on this issue were published during the 1980s and 1990s (6, 12-14).

Worldwide, PD is a key element of kidney replacement therapy (15-17). Nonetheless, peritonitis remains one of the major challenges associated with severe clinical complications of PD despite technological advances (17, 18). Detrimental effects of dialysis-related peritonitis on the characteristics of peritoneal transport and the alterations of the peritoneal membrane have been documented (19-21). However, the potential effect of dialysis-related peritonitis on oxalate balance in PD patients has never been evaluated before. We hypothesized that the alteration of the peritoneal membrane due to dialysis-related peritonitis could decrease the peritoneal clearance of oxalate and, consequently, its removal levels. To test this hypothesis, the present study aimed to define oxalate balance and explore its association with dialysis-related peritonitis in PD patients.

Patients and Methods

Study design. This cross-sectional observational pilot study was carried out in accordance with the Declaration of Helsinki and conducted between January 2019 and May 2020 at the State Institution 'Institute of Nephrology of the National Academy of Medical Sciences' (Kyiv, Ukraine). The study was part of the ongoing Institute project "Effect of oxalate and urate metabolism on the evolution of kidney disease" (ClinicalTrials.gov Identifier: NCT04399915; Domestic Trial Registration Number: 0119U000002). The study protocol was approved by the Ethics Committee of the Institute (Protocol Number: 8/2018; September 22, 2018). Written informed consent was obtained from all participants before enrollment in the study.

Sample size. The sample size was estimated using a *priori* power analysis (G*Power Software, version 3.1.9.4) (22) based on the study by Marangella *et al.* (6). A minimum of 42 participants (21

Correspondence to: Natalia Stepanova, MD, DSc, Ph.D., Professor of Medicine, Head of Department of Nephrology and Dialysis, State Institution 'Institute of Nephrology of the National Academy of Medical Sciences', Kyiv, Ukraine. Tel: +38 0965551555, +38 0442259386, e-mail: nmstep88@gmail.com

Key Words: Oxalate, peritoneal dialysis, dialysis-related peritonitis.

participants in each group) was found to be required to achieve 95% power for the detection of differences in plasma and urine oxalate concentrations between groups, with a significance level of 0.05, using the Student's *t*-test or the non-parametric Mann-Whitney test. Based on the fact that the reported incidence of peritonitis was significantly higher in a large unselected population of PD patients than that reported in single-center short-term studies (23, 24), the number of PD patients with a history of peritonitis was doubled. Therefore, we enrolled 62 adult ESKD patients from two dialysis centers who completed 3 months of continuous ambulatory PD.

Inclusion and exclusion criteria. Inclusion criteria for the enrollment in the study were: age >18 years, dialysis treatment for at least 3 months, and a stable clinical condition. The enrolled patients fulfilled the target weekly urea clearance level (Kt/V≥1.7) and did not take antibiotics for at least 3 months before the beginning of the study. Exclusion criteria were: hospitalization during the 3 months preceding the initiation of the study, history of systemic disease, malignancy, acute inflammation, and immunosuppressive treatment.

Study participants. Among the 62 enrolled patients, 33 (53%) were male and 29 (47%) female with an average age of 50.5±13.5 years and a PD vintage of 37±24 months. All PD patients were treated with a normal dwell time (4-5 h during daytime and 8-10 h at night) and received commercially available glucose-based Dianeal PD solution (Baxter Healthcare SA, Castlebar, Ireland) of different concentrations (1.36% and 2.27%) and Icodextrin (Baxter Healthcare SA, Castlebar, Ireland). Dialysis was targeted to achieve a value of Kt/V≥1.7 according to the Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Peritoneal Dialysis Adequacy of the National Kidney Foundation (25).

The recruited patients were divided into two groups according to PD-related peritonitis history: the peritonitis group included 41 patients with at least one past episode of PD-related peritonitis and the peritonitis-free group included 21 patients without any episode of peritonitis.

Clinical and laboratory measurements. The demographic data including age, gender, body mass index (BMI), body surface area (BSA), nosology of ESKD, PD vintage, all past peritonitis episodes, and diabetes status were collected from the medical records of the enrolled participants. BMI was calculated as weight (kg) divided by the square of the height (m^2). BSA was calculated using the DuBois & DuBois formula (26).

Dialysis-related peritonitis was defined as peritoneal dialysis effluent (PDE) containing >100 white cells/μl with >50% polynuclear leukocytes (27). Peritonitis rate was calculated as the number of infections in all patients divided by the number of patient-months on PD. Anuria was defined as a 24-h urine volume <100 ml.

Whole blood samples were collected from the patients after an overnight fasting period and processed immediately. Routine biochemical parameters including blood and daily dialysate concentrations of urea and creatinine, serum albumin, C-reactive protein, glucose, electrolytes, and lipid profile parameters were carried out using the automatic analyzer Flexor junior (Vital Scientific, Spankeren, the Netherlands). Hematological parameters of blood were determined using the ABX Micros-60 (Horiba Medical, Montpellier, France).

Dialysis adequacy in PD patients was determined by measuring the weekly peritoneal creatinine clearance (CrCl) (normalized to 1.73 m^2 of BSA) and Kt/V using the Watson formula for body water. Peritoneal Kt/V and renal Kt/V were estimated separately. The dialysate/plasma creatinine (D/P) ratio was calculated from the concentrations in 4-h dialysate and plasma creatinine. The peritoneal equilibration test proposed by Twardowski *et al*. (28) was used as a standardized procedure.

Oxalate balance measurements. The concentration of oxalic acid (POx) in plasma was measured spectrophotometrically using a commercially available kit (MAK_{315}, Sigma, Barcelona, Spain) according to the manufacturer's recommendations (29). The data were measured in μmol/L. However, the measurements were presented in both μmol/l and mg/l for better visualization of oxalate turnover.

Daily urinary oxalate (UOx) excretion and the PDE oxalate (PDEOx) concentration were determined using an oxalate oxidase/peroxidase reagent (BioSystems, Barcelona, Spain). To assess oxalate, 24-h PDE was collected on the day preceding the test.

The oxalate transport status was determined as the ratio of 4-h dialysate to plasma oxalate (D/P Ox). Renal oxalate clearance (ROxCL) and peritoneal oxalate clearance (PerOxCL) were calculated using the following formulas:

$$ROxCL\ (L/week/1.73\ m^2) = \frac{UOx\ (mg/l) \times 24-hour\ urine\ output\ (L) \times 7 \times 1.73}{POx\ (mg/l) \times BSA\ (m^2)}$$

$$PerOxCL\ (L/week/1.73\ m^2) = \frac{PDEOx\ (mg/l) \times 24-hour\ PDE\ output\ (L) \times 7 \times 1.73}{POx\ (mg/l) \times BSA(m^2)}$$

Statistical analysis. Statistical analysis was performed and all graphs were generated on MedCalc Statistical Software version 19.2.6 (Ostend, Belgium). The means (*M*), the standard deviations (*SD*), the median (*Me*), and the interquartile ranges [Q25-Q75] were calculated according to the distribution of the data. The Student's *t*-test and the nonparametric Mann-Whitney test (*U*-test) were used for the differences between groups. The Kruskal-Wallis (ANOVA) test was used to compare PerOxCL depending on the number of peritonitis episodes. Categorical variables were expressed as proportions and the Chi-square (χ^2) test was applied to compare the two groups. The Spearman's correlation test was used to evaluate the association between POx concentration, oxalate transport status, and PerOxCL.

Univariate linear regression analysis was performed to explore the independent effect of ROxCL and PerOxCL on POx concentration. The model's F-ratio, significance level, and residuals were presented using the Shapiro-Wilk test (*W*) for normal distribution. The data of ROxCL and PerOxCL were log-transformed before inclusion into the model because they did not fit the normal distribution.

Receiver operating characteristic (ROC) curve analysis and logistic regression analysis were performed to assess the overall discriminative ability of the number of peritonitis episodes on the predicting evaluation of the above-average POx concentration and calculate the odds ratios (OR) and 95% confidence interval (CI).

Results

Patient data. Among 62 enrolled PD patients, there were 41 (66%) patients who had experienced at least one episode of peritonitis and 21 (34%) who had never had peritonitis before

Table I. *Characteristics of the study participants according to peritonitis status.*

Clinical parameters	All (n=62)	Peritonitis Group (n=41)	Peritonitis-free Group (n=21)	*p*-Value
Clinical parameters				
Male gender, n (%)	33 (53%)	22 (53.6 %)	11 (52.2 %)	0.9
Age, years	50.5±13.5	49.7±11.7	53.2±18.3	0.07
ESKD course, n (%)				
Diabetes	27 (43.5%)	18 (43.9%)	9 (42.8%)	0.93
Arterial hypertension	15 (24.2%)	9 (22%)	6 28.6%)	0.56
Glomerulonephritis	13 (21%)	9 (22%)	4 (19%)	0.78
Other	7 (11.3%)	5 (12%)	2 (9.5%)	0.75
eGFR (ml/min/1.73m^2)	5.0 (4.0-6.0)	4.0 (4.0-5.0)	5.0 (4.0-7.0)	**0.004**
BMI, kg/m^2	25.4 (21.1-29.3)	24.2.0 (23-27.1)	25.9 (20.6-30.1)	0.74
Serum albumin, g/l	38.5 (34.4-40.8)	38.1 (32.8-40.2)	39.4 (34.4-40.9)	0.36
CRP, mg/l	9.8 (4.3-17.2)	10.5 (8.0-21)	8.8 (6.7-17.2)	0.26
Systolic blood pressure, mm Hg	128.4±14.2	127±10.2	129.3±14.8	0.73
Diastolic blood pressure, mm Hg	78±12.4	75±11.2	79±13.2	0.38
Hb, g/l	100 (96-113)	97 (92-101)	109 (101-110)	0.12
Glucose, mmol/l	5.6 (5.04-7.6)	5.6 (5.04-7.6)	5.3 (5.05-8.5)	0.62
Ferritin, ng/ml	245.6±109.4	248.9±114.3	241.8±107.7	0.80
Total cholesterol, mmol/l	5.6±1.57	5.9±1.6	5.3±1.2	**0.05**
Triglycerides, mmol/l	1.8±1.1	1.9±1.2	1.7±1.1	0.48
Calcium, mmol/l	2.34 (2.2-2.37)	2.34 (2.18-2.37)	2.37 (2.2-2.4)	0.36
Phosphorus, mmol/l	1.9 (1.57-2.2)	1.9 (1.63-2.3)	1.7 (1.45-1.92)	**0.05**
iPTH, ng/l	227.5 (31.7-457)	249 (83-578)	215 (63-329)	**0.04**
Peritoneal dialysis parameters				
Time on PD, months	37.4±22.2	40.3±22.7	30.2±19.7	0.08
Anuric patients, n (%)	21 (34%)	17 (41.5%)	4 (19%)	**0.05**
Urine volume, l/24 h	0.3 (0.05-0.65)	0.25 (0.1-0.65)	0.35 (0.15-0.95)	**0.04**
Daily peritoneal ultrafiltration, l	0.9 (0.5-1.6)	0.9 (0.4-1.6)	1.0 (0.7-1.1)	0.96
4-hour D/P creatinine ratio	0.73 (0.66-0.84)	0.78 (0.68-0.8)	0.72 (0.65-0.87)	0.68
Low-average transporters, n (%)	14 (22.6%)	7 (17.1%)	7 (31.3%)	0.22
High-average transporters, n (%)	27 (43.5%)	19 (46.3%)	8 (38.1%)	0.54
High transporters, n (%)	21 (33.9%)	15 (33.6%)	6 (28.6%)	0.53
Icodextrin, n (%)	16 (25.8%)	14 (34.2%)	2 (9.5%)	**0.03**
Renal weekly Kt/V	0.05 (0.02-0.22)	0.03 (0.02-0.06)	0.05 (0.02-0.22)	**0.04**
Peritoneal weekly Kt/V	1.91 (1.47-2.27)	1.63 (1.42-1.89)	1.92 (1.47-2.3)	**0.01**
Total Kt/V	2.04 (1.82-2.32)	1.9 (1.71-2.14)	2.05 (1.93-2.49)	**0.004**
Peritoneal weekly CrCl, L/week/1.73m^2	49.4 (44.5-58.7)	47.4 (42.9-51.5)	56.6 (52.2-64.4)	**0.0001**

Values are expressed as mean±standard deviation (M±SD) or as median and interquartile range [Me (Q25-Q75)]. Values are compared between groups using the Chi-square test, the Student's *t*-test and the Mann-Whitney *U*-test as appropriate. BMI, Body mass index; CrCl, creatinine clearance; CRP, C-Reactive Protein; D/P creatinine ratio, dialysate/plasma creatinine ratio; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; iPTH, intact parathyroid hormone; total Kt/V, total weekly Kt/Vurea. Significant *p*-Values are shown in bold.

inclusion and completion of the study. The peritonitis group had suffered 79 peritonitis episodes (1-5 episodes per patient). Twenty-three (56%) patients had experienced more than one episode throughout the PD treatment period of 2108 patient-months. The overall incidence of peritonitis was 0.45 episodes per patient-year or 1 episode per 26.7 patient-months during the PD treatment. Table I shows the baseline characteristics of the participants according to their peritonitis status. These data were obtained during routine clinical practice immediately after enrollment of the patients in the study.

As seen in Table I, both groups had similar ages, percentages of males and diabetics, and ESKD causes. No differences were observed between the groups in most clinical characteristics. However, the patients of the peritonitis group had a significantly lower estimated glomerular filtration rate (eGFR) and 24-h urine volume, and higher serum phosphate and parathyroid hormone levels compared to the peritonitis-free group. In addition, the peritonitis group had lower PD adequacy indicators, a larger number of anuric patients, and more Icodextrin users compared to the peritonitis-free group.

Table II. *Oxalate balance patterns according to peritonitis status in PD patients with preserved diuresis.*

Oxalate balance pattern	All (n=41)	Peritonitis Group (n=24)	Peritonitis-free Group (n=17)	*p*-Value
POx, μmol/l	39.2±1.9	49.1±17.0	30.0±10.6	<0.001
POx, mg/l	3.5±1.4	4.4±1.5	2.7±0.9	<0.001
UOx, mg/d	33.8 (16.1-49.2)	33.8 (16.1-46.8)	46.1 (33.2-50.5)	0.07
PDEOx, mg/d	16.1 (10.7-25.3)	11.7 (9.0-25.7)	23.9 (16.1-58.6)	0.001
Overall oxalate removal level, mg/d	44.0 (21.1-53.7)	39.6 (16.4-54.9)	52.1 (26.5-64.1)	0.03
4-hour D/P Ox	1.06 (0.6-1.3)	0.8 (0.5-1.2)	1.2 (1.07-1.7)	0.01
ROxCL, L/week/1.73 m^2	56.6 (35.9-102.7)	63.6 (39.7-122.6)	45.6 (31.9-60.1)	0.05
PerOxCL, L/week/1.73 m^2	40.6 (15.0-53.8)	29.9 (12.4-48.8)	53.8 (30.7-68.0)	<0.001

Values are expressed as mean±standard deviation (M±SD) or as the median and interquartile range [Me (Q25-Q75)]. Values are compared between the groups using the Student's *t*-test and the Mann-Whitney *U*-test as appropriate. D/P Ox, Dialysate to plasma oxalate ratio; POx, plasma oxalic acid; UOx, urinary oxalate; PDEOx, peritoneal dialysis effluent oxalate; ROxCL, renal oxalate clearance; PerOxCL, peritoneal oxalate clearance. Significant *p*-Values are shown in bold.

Oxalate balance patterns according to peritonitis status. The PD patients of the peritonitis group had a significantly lower level of oxalate transport status (4-h D/P Ox), PerOxCL, daily PDEOx excretion, and overall oxalate removal levels compared with the peritonitis-free patients (Table II). It should be noted, that the peritoneal oxalate transport status has a direct association with creatinine transport status in the PD patients (r=0.57, p<0.001). Moreover, the peritonitis group tended to have less UOx excretion with statistically higher ROxCL compared to the peritonitis-free group.

Effects of renal and peritoneal oxalate clearance on pox concentration in PD patients with preserved diuresis. ROxCL was correlated with residual diuresis (r=0.71, p<0.001) and weekly renal Kt/V (r=0.57, p<0.001), while PerOxCL was directly associated with the daily peritoneal ultrafiltration rate (r=0.57, p<0.0001), CrCL (r=0.6, p<0.0001), and D/P Ox ratio (r=0.46, p=0.0003). In addition, residual diuresis was directly correlated with the overall oxalate removal levels (r=0.66, p<0.0001). Low UOx excretion was associated with high PDEOx concentration (r=–0.36, p=0.007). However, neither residual diuresis (r=–0.13, p=0.27) nor overall oxalate removal levels (r=–0.11, p=0.34) were associated with POx concentration in PD patients. It is worth noting that POx was not correlated with eGFR (r=0.008, p=0.95) or the daily peritoneal ultrafiltration rate (r=0.23, p=0.12). However, it was inversely correlated with oxalate transport status (Figure 1a) and the weekly PerOxCl (Figure 1b).

Bearing in mind that there was no statistically significant association between PerOxCL and ROxCL (r=–0.17, p=0.24), univariate linear regression analysis was performed to determine their particular contribution to oxalate balance. Only PerOxCL was found to be an explanatory factor for POx in PD patients regardless of age and gender (W=0.99, F-ratio 17.7, p=0.0001) (Figure 2).

Oxalate balance in anuric PD patients. Among the enrolled PD patients, 21 (34%) patients presented anuria and 17 (81%) of them had experienced at least one episode of dialysis-related peritonitis (see Table I). The anuric PD patients independently of the peritonitis status had lower PerOxCL [20.2 (11.2-35.7) *versus* 40.6 (15.0-53.8) L/week/1.73m^2, p=0.009] and overall oxalate removal levels [33.7 (14.9-56.6) *versus* 46.9 (25.3-62.4) mg/d, p=0.04] compared to the patients with preserved residual diuresis. In anuric conditions, POx concentration had a direct strong association with PDEOx levels (r=0.84, p<0.0001) and 24-h D/P Ox ratio (r=0.52, p=0.003) and was inversely correlated with the weekly peritoneal Kt/V (r=–0.45, p=0.01).

Association between the number of peritonitis episodes and oxalate balance in PD patients. A direct association was observed between the number of peritonitis episodes and POx concentration (r=0.52, p<0.001). However, a negative association was found between the number of peritonitis episodes and the D/P creatinine ratio (r=–0.37, p=0.01), CrCL (r=–0.35, p=0.02), D/P Ox (r=–0.58, p<0.001), and PerOxCL (r=–0.58, p<0.001). Figure 3 clearly demonstrates the association between the decreasing tendency in PerOxCL and the increasing number of PD-related peritonitis episodes. Moreover, an inverse association was found between the number of peritonitis episodes and the weekly plasma Kt/V (r=–0.51, p<0.001) and, consequently, the weekly total Kt/V (r=–0.33, p=0.04).

ROC analysis was performed for further assessment of the impact of dialysis-related peritonitis on POx elevation above the average level in our cohort (>39.2 μmol/l or 3.5 mg/L). We observed that the area under the curve (AUC) of the number of peritonitis episodes was 0.86 [95% CI=0.75-0.94] demonstrating the ability to discriminate different POx concentrations. The optimal cut-off value of the number of peritonitis episodes as a predictor of POx

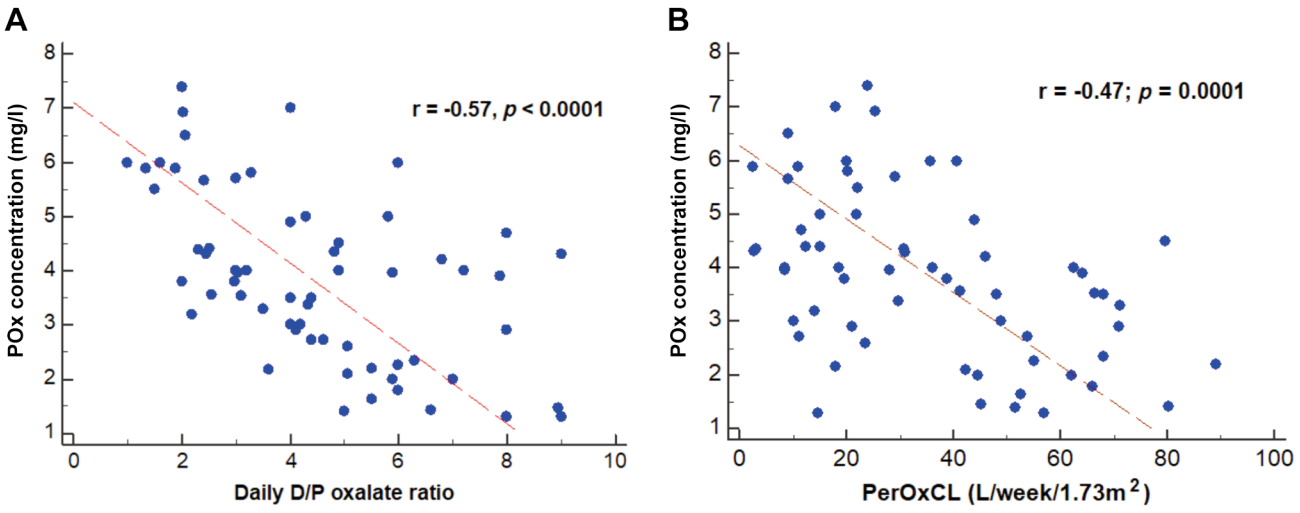

Figure 1. *Association between POx concentration and (A) oxalate transport status, and (B) PerOxCL in PD patients. D/P oxalate ratio, Dialysate to plasma oxalate ratio; PerOxCL, peritoneal oxalate clearance; POx, plasma oxalate concentration.*

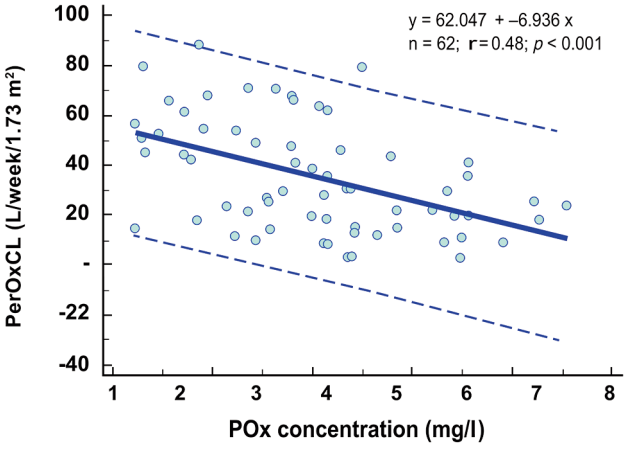

Figure 2. *Association between POx concentration and PerOxCL in univariate linear regression analysis in PD patients. PerOxCL, Peritoneal oxalate clearance; POx, plasma oxalate concentration.*

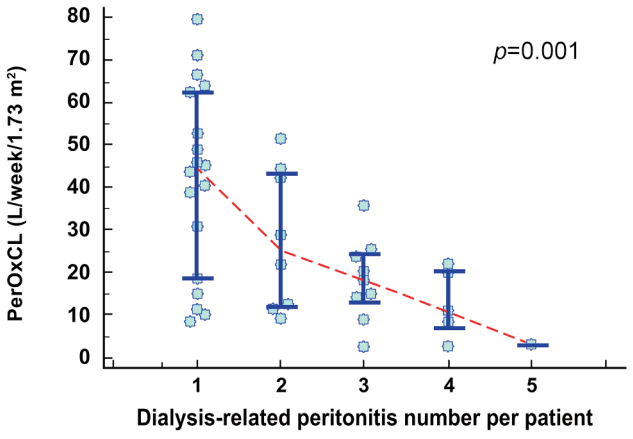

Figure 3. *The distribution of PerOxCL levels according to the number of peritonitis episodes. p=0.001 using Kruskal-Wallis test. PerOxCL, Peritoneal oxalate clearance.*

concentrations >3.5 mg/l was determined to be >1 (sensitivity of 72.4% and specificity of 85.7%) (Figure 4).

The logistic regression analysis confirmed a 4-fold risk of elevation in POx in the peritonitis group compared with the peritonitis-free group (χ^2=27.5, p<0.001; OR=4.06, 95% CI=2.0-8.3).

Discussion

Hyperoxalemia in PD patients has been described in early clinical studies (6, 7, 14). However, current reports in the field of oxalate balance in ESKD patients are limited and mostly focused on the hemodialysis population (5, 30). Furthermore, the association between dialysis-related peritonitis and oxalate balance in PD patients had never been analyzed before. We have suggested 2 possible pathways of how dialysis-related peritonitis affects oxalate balance in PD patients: 1) the alteration of the peritoneal membrane could decrease the peritoneal clearance of oxalate and, consequently, its removal level, and 2) the use of antibiotics could increase intestinal oxalate absorption and hyperoxalemia (31-34). The present study focused on the effect of dialysis-related peritonitis on oxalate balance through the reduction of the peritoneal oxalate removal rate in PD patients. For this, we evaluated the contribution of residual renal and peritoneal oxalate clearances, as well as the

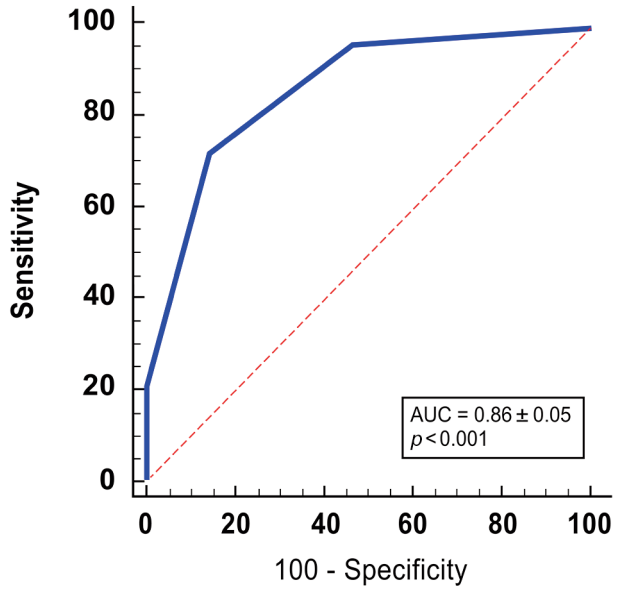

Figure 4. *ROC curve revealing the cut-off value of the number of dialysis-related peritonitis episodes that predict POx concentration of >3.5 mg/l. AUC, Area under the curve.*

effect of peritonitis on oxalate balance in PD patients, providing several new findings. First, this research showed significantly higher concentrations of POx in PD patients with a history of peritonitis compared with the peritonitis-free patients. Also, the peritonitis patients demonstrated a significantly lower 4-h D/P oxalate ratio, PerOxCL, daily PDEOx excretion, and overall oxalate removal levels compared with the peritonitis-free patients. Second, we identified that PerOxCL but not ROxCL largely affected oxalate balance in PD patients. Third, a strong association was observed between the number of peritonitis episodes, PerOxCL, and POx concentration. According to our results, PD patients with a history of peritonitis had a 4-fold risk of POx increase, and even a single episode of peritonitis was associated with an increase in POx concentration (>3.5 mg/l).

In accordance with previous results, the present study demonstrated that UOx excretion or overall oxalate removal levels in all PD patients were within reference intervals for healthy subjects and similar to the previously reported average of UOx excretion in ESKD patients (3, 5, 6, 8, 13, 35). Nonetheless, the levels of urine output in the participants of the present study were at least four times lower than those of healthy subjects (2, 35), meaning that PD patients had hyperoxaluria. This phenomenon is a result of inadequate Ox clearance, which balances between the peritoneal and renal routes depending on the peritoneal and residual kidney functions (RKF). Therefore, high POx concentrations in PD patients could not be explained by insufficient renal excretion only. Decreased PerOxCL due to dialysis-related peritonitis could potentially result in hyperoxaluria. Our data on the negative association between UOx excretion and PDEOx levels confirms this hypothesis. Moreover, in a recent study, Perinpam *et al.* (35) have demonstrated increased POx concentrations and UOx excretion concomitantly with eGFR decline in patients with primary hyperoxaluria, enteric hyperoxaluria, and kidney stone disease. These are in agreement with the present study, where we reported increased ROxCL in patients with high POx concentration. In our view, the higher ROxCL in the peritonitis group compared with the peritonitis-free group originated in decreased PerOxCL and elevated POx concentrations. The decreasing tendency of the UOx excretion despite high ROxCL in this group can be explained by the lower levels of daily urine volume compared to the peritonitis-free group.

It has been demonstrated that the number of peritonitis episodes is correlated with RKF decline (18, 36). Our results are in agreement with this since RKF measured by both renal urea clearance (renal Kt/V) and the presence of anuria was significantly lower in the peritonitis group compared with the peritonitis-free patients. However, contrary to our expectations, neither residual diuresis nor overall oxalate removal levels and eGFR were associated with POx concentration in PD patients. Our findings are in agreement with data provided by Marangella *et al.* (6) that demonstrated a higher level of dialysate oxalate excretion compared to urinary excretion. This means that the effect of peritoneal clearance on POx concentration might become evident in the absence of RKF. In other words, we believe that not only does the impaired kidney function lead to an increase in POx but also PerOxCL plays a crucial role in the oxalate dyshomeostasis in PD patients. In this context, peritoneal transport and altered functioning associated with peritonitis could be the main cause of hyperoxalemia in PD patients.

Peritonitis is an established risk factor for structural and functional alterations in the peritoneal membrane, eventually leading to peritoneal fibrosis, technique failure, and increased mortality (20, 37-39). In the early study by Wiggins *et al.* (40), the acceleration in membrane transport was observed one year after peritonitis. Recently, van Esch and van Diepen *et al.* demonstrated in a series of studies (19-21) that even a single episode of peritonitis leads to an increase in small solute transport and a decrease in the ultrafiltration rate. In turn, high peritoneal small solute transport status is associated with increased glucose absorption, protein loss, peritoneal and capillary surface area, inflammation, mortality, and technique failure in PD patients (37, 38). Similarly, in the present study, we observed worse dialysis adequacy in PD patients with peritonitis history compared with the peritonitis-free patients. In our view, both low CrCL and PerOxCL could result in high POx concentrations. The observed identity between creatinine and

oxalate peritoneal clearance could be explained by their similar molecular weights (113 g/mol for creatinine and 90.3 g/mol for oxalic acid). The absence of a difference in daily ultrafiltration levels between the groups was most likely caused by a high percentage of Icodextrin users among peritonitis patients.

Other reasonable explanations for the strong association between high POx concentration and peritonitis history, which we were unable to analyze in the present study, are: 1) the effect of peritonitis on gut microbiota and oxalate gastrointestinal absorption due to the long-term use of antibiotics, and 2) dietary restrictions, malnutrition, and high protein intake due to the loss of protein associated with PD-related peritonitis. Further research on the effects of gut microbiota correction or dietary restrictions on oxalate balance may open up a new path to improve PD-related peritonitis outcomes.

The findings presented here are subject to at least three limitations. First, it was a cross-sectional study, and the oxalate balance profile was measured at only one point during the research period; therefore, causality could not be established. Second, the sample size was relatively small and the study population represented a group of patients in a stable clinical condition within the target levels of Kt/V. Contrary to expectations, the selection criteria could render our findings exaggerated. Third, we did not evaluate the effects of other factors potentially associated with POx elevation: different PD modalities or PD solution composition, glucose absorption, oxalate and/or protein dietary intake, phosphate binders, use of antibiotics and other medications that could influence intestinal oxalate absorption.

Notwithstanding these limitations, our study is the first to our knowledge that reports a strong association between dialysis-related peritonitis and elevated POx in PD patients. Although the clinical significance of hyperoxalemia in PD patients remains unclear, recent studies have demonstrated that oxalate is involved in the activation of oxidative stress, chronic inflammation, and atherogenesis (1, 8, 9, 11), which may explain the high cardiovascular and overall mortality in PD-related peritonitis. Quite possible that further research to investigate the effect of dietary oxalate restriction or the gut microbiota correction may open up a new pathway to improve PD-related peritonitis outcomes. Thus, we believe that our hypothesis would be reflected in further research to clarify the interaction mechanisms and the role of PD-related peritonitis in impaired oxalate balance in PD patients.

Conclusion

The results of the present pilot study indicate an important role of PerOxCL in oxalate balance in PD patients. Moreover, dialysis-related peritonitis was associated with decreased peritoneal oxalate transport status, PerOxCL, daily PDEOx excretion, and overall oxalate removal levels. Finally, dialysis-related peritonitis was a significant predictor of POx elevation. This research has resulted in new questions that need to be addressed in future investigations. Therefore, further controlled clinical trials are necessary to deeply understand the association between peritonitis and oxalate balance in PD.

Data Availability Statement

The datasets generated and analyzed for the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

The Authors have no potential conflicts of interest, financial or otherwise.

Authors' Contributions

NS conceived the presented concept, designed the study, analyzed and interpreted the patient data, wrote and edited the manuscript. LK performed the laboratory oxalate measurements. LL and LS collected the data and contributed to the manuscript preparation. SS performed the laboratory measurements. All Authors read and approved the manuscript.

References

1 Ermer T, Eckardt KU, Aronson PS and Knauf F: Oxalate, inflammasome, and progression of kidney disease. Curr Opin Nephrol Hypertens *25(4)*: 363-371, 2016. PMID: 27191349. DOI: 10.1097/MNH.0000000000000229

2 Robijn S, Hoppe B, Vervaet BA, D'Haese PC and Verhulst A: Hyperoxaluria: a gut-kidney axis? Kidney Int *80(11)*: 1146-1158, 2011. PMID: 21866092. DOI: 10.1038/ki.2011.287

3 Abratt VR and Reid SJ: Oxalate-degrading bacteria of the human gut as probiotics in the management of kidney stone disease. Adv Appl Microbiol *72*: 63-87, 2010. PMID: 20602988. DOI: 10.1016/S0065-2164(10)72003-7

4 Barnett C, Nazzal L, Goldfarb DS and Blaser MJ: The presence of oxalobacter formigenes in the microbiome of healthy young adults. J Urol *195(2)*: 499-506, 2016. PMID: 26292041. DOI: 10.1016/j.juro.2015.08.070

5 Ermer T, Kopp C, Asplin JR, Granja I, Perazella MA, Reichel M, Nolin TD, Eckardt KU, Aronson PS, Finkelstein FO and Knauf F: Impact of regular or extended hemodialysis and hemodialfiltration on plasma oxalate concentrations in patients with end-stage renal disease. Kidney Int Rep *2(6)*: 1050-1058, 2017. PMID: 29270514. DOI: 10.1016/j.ekir.2017.06.002

6 Marangella M, Bagnis C, Bruno M, Petrarulo M, Gabella P and Linari F: Determinants of oxalate balance in patients on chronic peritoneal dialysis. Am J Kidney Dis *21(4)*: 419-426, 1993. PMID: 8465823. DOI: 10.1016/s0272-6386(12)80271-x

7 Tomson CR, Channon SM, Ward MK and Laker MF: Plasma oxalate concentration, oxalate clearance and cardiac function in patients receiving haemodialysis. Nephrol Dial Transplant *4(9)*: 792-799, 1989. PMID: 2516611.

8 Korol L, Stepanova N, Vasylchenko V, Snisar L, Lebid L and Kolesnyk M: Plasma oxalic acid as a trigger for oxidative processes in end-stage renal disease patients. Ukrainian Journal of Nephrology and Dialysis *1(69)*: 46-53, 2021. DOI: 10.31450/ukrjnd.1(69).2021.07

9 Stepanova N, Driianska V, Korol L, Snisar L and Lebed L: Plasma oxalic acid and cardiovascular risk in end-stage renal disease patients: a prospective, observational cohort pilot study. Korean J Intern Med, 2021. PMID: 34167288. DOI: 10.3904/kjim.2020.561

10 Arafa A, Eshak ES and Iso H: Oxalates, urinary stones and risk of cardiovascular diseases. Med Hypotheses *137*: 109570, 2020. PMID: 31972450. DOI: 10.1016/j.mehy.2020.109570

11 Stepanova N: Role of impaired oxalate homeostasis in cardiovascular disease in patients with end-stage renal disease: an opinion article. Front Pharmacol *12*: 692429, 2021. PMID: 34122117. DOI: 10.3389/fphar.2021.692429

12 McConnell KN, Rolton HA, Modi KS and Macdougall AI: Plasma oxalate in patients with chronic renal failure receiving continuous ambulatory peritoneal dialysis or hemodialysis. Am J Kidney Dis *18(4)*: 441-445, 1991. PMID: 1928062. DOI: 10.1016/s0272-6386(12)80111-9

13 Costello JF, Sadovnic MJ and Cottington EM: Plasma oxalate levels rise in hemodialysis patients despite increased oxalate removal. J Am Soc Nephrol *1(12)*: 1289-1298, 1991. PMID: 1912391. DOI: 10.1681/ASN.V1121289

14 Borland WW, Payton CD, Simpson K and Macdougall AI: Serum oxalate in chronic renal failure. Nephron *45(2)*: 119-121, 1987. PMID: 3561621. DOI: 10.1159/000184091

15 Kolesnyk M, Stepanova N, Dudar I, Bagdasarova I and Fomina S: Nephrology in Ukraine. Nephrology Worldwide: 675-685, 2021. DOI: 10.1007/978-3-030-56890-0_50

16 Vasylchenko VS, Korol LV, Kuchmenko OB and Stepanova NM: The oxidative status in patients with chronic kidney disease. Ukr Biochem J *92(5)*: 70-77, 2020. DOI: 10.15407/ubj92.05.070

17 Shifris IM, Dudar IO, Driyanska VE and Shymova AU: Activation of chronic inflammation and comorbidity in end-stage renal disease patients treated with continuous ambulatory peritoneal dialysis. Medicni Perspektivi (Medical perspectives) *25(2)*: 108-1018, 2020. DOI: 10.26641/2307-0404.2020.2.206381

18 Szeto CC and Li PK: Peritoneal dialysis-associated peritonitis. Clin J Am Soc Nephrol *14(7)*: 1100-1105, 2019. PMID: 31068338. DOI: 10.2215/CJN.14631218

19 van Esch S, van Diepen AT, Struijk DG and Krediet RT: The mutual relationship between peritonitis and peritoneal transport. Perit Dial Int *36(1)*: 33-42, 2016. PMID: 25395498. DOI: 10.3747/pdi.2014.00115

20 van Diepen AT, van Esch S, Struijk DG and Krediet RT: The first peritonitis episode alters the natural course of peritoneal membrane characteristics in peritoneal dialysis patients. Perit Dial Int *35(3)*: 324-332, 2015. PMID: 24711641. DOI: 10.3747/pdi.2014.00277

21 van Esch S, Struijk DG and Krediet RT: The natural time course of membrane alterations during peritoneal dialysis is partly altered by peritonitis. Perit Dial Int *36(4)*: 448-456, 2016. PMID: 26526046. DOI: 10.3747/pdi.2014.00215

22 Faul F, Erdfelder E, Lang AG and Buchner A: G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods *39(2)*: 175-191, 2007. PMID: 17695343. DOI: 10.3758/bf03193146

23 Davenport A: Peritonitis remains the major clinical complication of peritoneal dialysis: the London, UK, peritonitis audit 2002-2003. Perit Dial Int *29(3)*: 297-302, 2009. PMID: 19458302.

24 Nieto-Ríos JF, Díaz-Betancur JS, Arbeláez-Gómez M, García-García Á, Rodelo-Ceballos J, Reino-Buelvas A, Serna-Higuita LM and Henao-Sierra JE: Peritoneal dialysis-related peritonitis: twenty-seven years of experience in a Colombian medical center. Nefrologia *34(1)*: 88-95, 2014. PMID: 24336639. DOI: 10.3265/Nefrologia.pre2013.Nov.12002

25 Peritoneal Dialysis Adequacy 2006 Work Group: Clinical practice guidelines for peritoneal adequacy, update 2006. Am J Kidney Dis *48 Suppl 1*: S91-S97, 2006. PMID: 16813997. DOI: 10.1053/j.ajkd.2006.05.016

26 Du Bois D and Du Bois EF: A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition *5(5)*: 303-11; discussion 312-3, 1989. PMID: 2520314.

27 Piraino B, Bernardini J, Brown E, Figueiredo A, Johnson DW, Lye WC, Price V, Ramalakshmi S and Szeto CC: ISPD position statement on reducing the risks of peritoneal dialysis-related infections. Perit Dial Int *31(6)*: 614-630, 2011. PMID: 21880990. DOI: 10.3747/pdi.2011.00057

28 Twardowski ZJ, Nolph KD and Khanna R: Peritoneal equilibration test. Perit Dial Bull *7*: 138-147, 1987.

29 Oxalate Assay Kit Catalog. Safety Data Sheet, 2020. Available at: https://www.sigmaaldrich.com/UA/en/sds/sigma/mak315 [Last accessed on June 2, 2021]

30 Gulhan B, Turkmen K, Aydin M, Gunay M, Cıkman A and Kara M: The relationship between serum oxalic acid, central hemodynamic parameters and colonization by oxalobacter formigenes in hemodialysis patients. Cardiorenal Med *5(3)*: 164-174, 2015. PMID: 26195968. DOI: 10.1159/000381219

31 Kharlamb V, Schelker J, Francois F, Jiang J, Holmes RP and Goldfarb DS: Oral antibiotic treatment of Helicobacter pylori leads to persistently reduced intestinal colonization rates with Oxalobacter formigenes. J Endourol *25(11)*: 1781-1785, 2011. PMID: 22017284. DOI: 10.1089/end.2011.0243

32 Stepanova N, Tolstanova G, Korol L, Akulenko I, Savchenko O and Kolesnyk M: A potential role of fecal oxalate-degrading activity in oxalate homeostasis in end-stage renal disease patients; a descriptive pilot study. Journal of Renal Injury Prevention *10(3)*: e19-e19, 2021. DOI: 10.34172/jrip.2021.19

33 Ticinesi A, Nouvenne A and Meschi T: Gut microbiome and kidney stone disease: not just an Oxalobacter story. Kidney Int *96(1)*: 25-27, 2019. PMID: 31229040. DOI: 10.1016/j.kint.2019.03.020

34 Ramirez J, Guarner F, Bustos Fernandez L, Maruy A, Sdepanian VL and Cohen H: Antibiotics as major disruptors of gut microbiota. Front Cell Infect Microbiol *10*: 572912, 2020. PMID: 33330122. DOI: 10.3389/fcimb.2020.572912

35 Perinpam M, Enders FT, Mara KC, Vaughan LE, Mehta RA, Voskoboev N, Milliner DS and Lieske JC: Plasma oxalate in relation to eGFR in patients with primary hyperoxaluria, enteric hyperoxaluria and urinary stone disease. Clin Biochem *50(18)*: 1014-1019, 2017. PMID: 28764885. DOI: 10.1016/j.clinbiochem.2017.07.017

36 Liao CT, Shiao CC, Huang JW, Hung KY, Chuang HF, Chen YM, Wu KD and Tsai TJ: Predictors of faster decline of residual renal function in Taiwanese peritoneal dialysis patients. Perit Dial Int *28 Suppl 3*: S191-S195, 2008. PMID: 18552254.

37 Heaf JG: Peritoneal transport: getting more complicated. Nephrol Dial Transplant *27(12)*: 4248-4251, 2012. PMID: 23042708. DOI: 10.1093/ndt/gfs385

38 Cueto-Manzano AM: Rapid solute transport in the peritoneum: physiologic and clinical consequences. Perit Dial Int *29 Suppl 2*: S90-S95, 2009. PMID: 19270240.

39 Ma X, Shi Y, Tao M, Jiang X, Wang Y, Zang X, Fang L, Jiang W, Du L, Jin D, Zhuang S and Liu N: Analysis of risk factors and outcome in peritoneal dialysis patients with early-onset peritonitis: a multicentre, retrospective cohort study. BMJ Open *10(2)*: e029949, 2020. PMID: 32060152. DOI: 10.1136/bmjopen-2019-029949

40 Wiggins KJ, Blizzard S, Arndt M, O'Shea A, Watt R, Hamilton J, Cottingham S, Campbell SB, Isbel NM and Johnson DW: Increases in peritoneal small solute transport in the first month of peritoneal dialysis predict technique survival. Nephrology (Carlton) *9(6)*: 341-347, 2004. PMID: 15663634. DOI: 10.1111/j.1440-1797.2004.00325.x

Received November 2, 2021
Revised November 23, 2021
Accepted December 10, 2021