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Oxidative stress as the bridge between dyslipidemia and peritoneal ultrafiltration failure: A bi-center cross-sectional cohort study

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Abstract. *Oxidative stress and dyslipidemia are common concerns in patients undergoing peritoneal dialysis (PD) and are associated with adverse clinical outcomes. However, the interplay between these factors and their impact on peritoneal ultrafiltration (UF) remains poorly understood.*

Methods: In this bi-center cross-sectional cohort study, we examined the relationships between dyslipidemia, oxidative stress, and peritoneal UF in patients undergoing PD. A comprehensive set of oxidative stress markers, lipid profiles, and clinical variables were assessed.

Results. Among the 114 patients, aged 55 (48-65) years, with a dialysis vintage of 31 (14-50) months, 76 (66.7%) were diagnosed with dyslipidemia. Patients with dyslipidemia experienced significantly higher proportions of patients with peritoneal UF below 400 mL per day, suggesting ultrafiltration failure (UFF) ($\chi^2 = 4.9$, $p = 0.02$). An elevated D/P creatinine ratio was associated with higher levels of total cholesterol ($r = 0.39$, $p = 0.0005$), low-density lipoprotein cholesterol ($r = 0.26$, $p = 0.02$), triglycerides ($r = 0.33$, $p = 0.005$), and the atherogenic index of plasma (AIP) ($r = 0.27$, $p = 0.01$). UF rate displayed a positive correlation with high-density lipoprotein cholesterol ($r = 0.31$, $p = 0.003$) and a negative correlation with AIP ($r = -0.33$, $p = 0.004$). The ROC analysis revealed that an AIP value exceeding 4.3 could effectively predict UFF, with a sensitivity of 83.3% and a specificity of 73.4%

Dyslipidemia was significantly associated with increased intensity of oxidative stress, with elevated malondialdehyde (MDA) ($p = 0.0002$), oxidative stress index (OSI) ($p < 0.0001$), and reduced antioxidant markers. UFF was also associated with higher oxidative stress, as indicated by increased MDA ($p = 0.005$) and OSI ($p = 0.0009$). Patients with both dyslipidemia and UFF exhibited the highest levels of oxidative stress ($p < 0.0001$). Taking potential confounders into account in the ANCOVA analysis, a significant interaction effect of dyslipidemia ($F = 7.6$, $p = 0.007$) and UF rate ($F = 8.6$, $p = 0.004$) on oxidative stress was observed.

Conclusion. Dyslipidemia and UFF are independently associated with elevated oxidative stress in PD patients, and their coexistence exacerbates this oxidative burden. Understanding these relationships is crucial for developing interventions to improve clinical outcomes in this population. Targeted therapies addressing oxidative stress and dyslipidemia warrant further investigation.

Key words: *peritoneal dialysis, dyslipidemia, oxidative stress, peritoneal ultrafiltration.*

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Оксидативний стрес як посередник між дисліпідемією та недостатністю перитонеальної ультрафільтрації: двоцентрове одномоментне когортне дослідження

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Резюме. *Оксидативний стрес і дисліпідемія є поширеними характеристиками, асоційованими з несприятливими клінічними наслідками, у пацієнтів, які лікуються методом перитонеального діалізу (ПД). Однак взаємодія між цими факторами та їх сукупний вплив на перитонеальну ультрафільтрацію (УФ) залишаються не вивченими.*

Методи. У цьому двоцентровому одномоментному когортному дослідженні ми вивчали взаємозв'язок між дисліпідемією, оксидативним стресом і перитонеальною УФ у ПД пацієнтів. Аналізували маркери оксидативного стресу, ліпідного профілю та клініко-лабораторні показники.

Результати. Серед 114 пацієнтів віком 55 (48-65) років та тривалістю ПД 31 (14-50) місяців у 76 (66,7%) діагностовано дисліпідемію. У пацієнтів з дисліпідемією достовірно частіше визначалась УФ нижче 400 мл на день, що свідчило про недостатність перитонеальної УФ. Співвідношення D/P креатиніну мало прямий кореляційний зв'язок з рівнями загального холестерину (r = 0,39, p = 0,0005), холестерину ліпопротеїдів низької щільності (r = 0,26, p = 0,02), тригліцеридів (r = 0,33), p = 0,005) та індексом атерогенності (ІА) (r = 0,27, p = 0,01). Рівень перитонеальної УФ прямо асоціювався з холестерином ліпопротеїдів високої щільності (r = 0,31, p = 0,003) і мав негативний кореляційний зв'язок з ІА (r = -0,33, p = 0,004). ROC аналіз продемонстрував, що значення ІА понад 4,3 є незалежним предиктором недостатньої УФ з чутливістю 83,3% і специфічністю 73,4%

Дисліпідемія статистично значущо асоціювалась з підвищенням інтенсивності оксидативного стресу за показниками малонового діальдегіду (МДА) (p = 0,0002) та індексом оксидативного стресу (ІОС) (p < 0,0001), а також зниженням антиоксидантних маркерів. Рівень перитонеальної УФ також асоціювався з вищою інтенсивністю оксидативного стресу за показниками МДА (p = 0,005) та ІОС (p = 0,0009). Пацієнти як з дисліпідемією, так і з недостатністю УФ мали найвищу інтенсивність оксидативного стресу (p <0,0001). ANCOVA аналіз з контрелем потенційних ко-факторів визначив значний вплив взаємодії дисліпідемії (F = 7,6, p = 0,007) і рівня УФ (F = 8,6, p = 0,004) на оксидативний стрес.

Висновки. Дисліпідемія та недостатність перитонеальної УФ незалежно асоціювались з підвищенням інтенсивності оксидативного стресу у ПД пацієнтів, а їх співіснування посилювало цей прооксидантний тягар. Розуміння цих взаємозв'язків має вирішальне значення для розробки заходів щодо покращення клінічних наслідків у ПД пацієнтів. Цільова терапія, спрямована на корекцію дисліпідемії та оксидативного статусу, вимагає подальшого дослідження.

Ключові слова: *перитонеальний діаліз, дисліпідемія, оксидативний стрес, перитонеальна ультрафільтрація.*

Introduction. In recent years, peritoneal dialysis (PD) has emerged as a viable kidney replacement therapy for patients suffering from end-stage kidney disease (ESKD) [1]. This modality offers advantages such as enhanced patient autonomy, improved quality of life, and reduced healthcare costs [2]. However, despite these benefits, patients treated with PD often face various complications, including peritoneal ultrafiltration failure (UFF), that can limit its long-term effectiveness [1, 3].

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UFF refers to a spectrum of changes within the peritoneal membrane, which includes peritoneal fibrosis and membrane thickening, clinically manifested by a high peritoneal solute transport rate and an ultrafiltration rate of less than 400 mL per day [3-5]. One of the pivotal factors contributing to these complications is oxidative stress, which has emerged as a central player in the pathophysiology of peritoneal membrane damage [6-8].

Oxidative stress arises from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to counteract their harmful effects through antioxidants [9, 10]. This imbalance can induce cellular dysfunction and result in oxidative damage to lipids and proteins, causing substantial harm to the peritoneal membrane, exacerbating UFF, and compromising the effectiveness of dialysis treatment [6-8]. Patients undergoing PD face a significant challenge in

managing oxidative stress due to the composition of PD solutions [11]. The unique characteristics of these solutions, including low pH, lactate buffering, heightened osmolarity, and elevated glucose concentration, collectively contribute to increased oxidative stress [6, 7, 11].

Furthermore, oxidative stress has gained increasing recognition as a central contributor to the development of dyslipidemia and its associated complications in individuals with chronic kidney disease (CKD) [12, 13]. Dyslipidemia, characterized by an imbalance in low-density lipoprotein cholesterol (LDL-C), triglycerides, and high-density lipoprotein (HDL-C), is frequently observed in patients undergoing PD [14]. Besides the uremic factors contributing to developing an atherogenic lipid profile, dyslipidemia in PD patients is further influenced by protein loss in the dialysate and the utilization of high glucose-based PD solutions [14]. Importantly, dyslipidemia not only significantly contributes to the elevated rates of cardiovascular and all-cause mortality in these patients [15, 16] but has also been demonstrated to be associated with PD adequacy and technique failure in our previous report [17]. However, despite this recognition, the association between dyslipidemia and oxidative stress in the context of PD remains unexplored [7]. Most studies investigating the interplay between dyslipidemia and oxidative stress have predominantly focused on the broader population of individuals with CKD [12, 13] or those undergoing hemodialysis [9, 18], leaving a substantial knowledge gap in patients on PD.

In this context, we hypothesized that dyslipidemia could exacerbate oxidative stress by impacting lipid peroxidation and inflammatory processes, thereby leading to peritoneal UFF. To address this significant research gap, we conducted a bi-center cross-sectional study to elucidate the relationship between dyslipidemia, peritoneal ultrafiltration (UF), and the intensity of oxidative stress in patients undergoing PD.

Patients and Methods. ***Study Design and Setting.*** This cross-sectional cohort study was conducted in collaboration between two dialysis centers: (i) the State Institution "Institute of Nephrology of the National Academy of Medical Sciences of Ukraine" and (ii) the Dialysis Medical Center LLC "Link-Medital," Odesa, Ukraine, spanning from 2019 to 2020. It was carried out as a part of the Institute's project titled "Exploring Novel Prognostic Factors that Negatively Impact Survival in Peritoneal Dialysis and Assess the Potential for Pharmacological Interventions," which is registered under the National Study Registration Number 0117U002122. Participation in the study was contingent upon all patients providing written informed consent. The study protocol received formal approval from the local Ethics Committee at the Institute (protocol number: 8, dated November 19, 2019). Throughout the study's duration, the research team diligently adhered to ethical principles and legal regulations governing biomedical research, including strict compliance with the Helsinki Declaration.

Study participants. The study included 114 patients undergoing PD for at least three months before their enrollment. The inclusion criteria for patients were as follows: age ranging from 18 to 75 years, a minimum of three months of peritoneal dialysis (PD) treatment, access to medical history information regarding statin usage, and, if prescribed, a minimum of 12 months of atorvastatin use before enrolling in the study. Additionally, patients needed to provide their informed consent to participate. Conversely, patients who met any of the following exclusion criteria were not included in the study: urine output <100 ml/day, recent hospitalization for any reason or PD-associated peritonitis in the month prior to the study, prior hemodialysis (HD) treatment, the presence of neoplasms at any site or other critical comorbid conditions, and the use of simvastatin, rosuvastatin, or their analogs.

All the patients were dialyzed using Dianeal PD4 with glucose concentrations of 1.36% and 2.27% (Baxter Healthcare Corporation, USA). Of them, 15 (13.2%) received a biocompatible PD solution containing icodextrin overnight.

Data collection and measurements. In addition to routine physical and clinical laboratory data, lipid profile parameters and PD adequacy were assessed during the initial patient visit, along with markers of lipid peroxidation and antioxidant status. Demographic data, including age, gender, body mass index (BMI), body surface area (BSA), diabetic status, duration of PD, and episodes of peritonitis in the medical history, were collected during the patient's initial visits. BMI was calculated using the formula: patient's weight (kg) divided by height (m2). BSA was calculated using the DuBois & DuBois formula. The frequency of PD-associated peritonitis was calculated as the number of infections per year divided by the years on PD for all patients at risk of developing peritonitis.

Physical and clinical laboratory examinations included the assessment of arterial pressure, urine output levels, complete blood and urine analyses, determination of total protein and albumin levels, creatinine, urea, serum electrolytes (Ca, K, P), C-reactive protein (CRP), glucose, uric acid, and blood parathormone levels. Whole blood samples were collected after an overnight fasting period and processed immediately. Hematological and biochemical parameters were analyzed using the "ABX Micros-60" (Horiba Medical, Montpellier, France) and "Flexor Junior" (Vital Scientific, Spankeren, Netherlands) analyzers.

The adequacy of PD was assessed by measuring plasma urea and creatinine concentrations in dialysate and urine collected over a 24-hour period. Using these parameters, weekly creatinine clearance (CrCl), normalized to BSA, peritoneal (pKt/V), renal (rKt/V), and total weekly urea clearances (Kt/V) were calculated. The volume of urea distribution (V) was calculated using the Watson formula. The creatinine dialysate/plasma ratio (D/P Cr) was calculated based on creatinine concentrations in effluent and plasma after a 4-hour

exchange of PD. A standardized peritoneal equilibrium test proposed by Twardowski et al. was used. The patients were categorized based on their peritoneal transport rate into the following groups: high transporters (4-hour D/P ratio above 0.82), high-average transporters (0.66–0.81), low-average transporters (0.51–0.65), or low transporters (0.35–0.50). UFF was defined as low peritoneal UF capacity, which is indicated by a volume of less than 400 mL (3.86% glucose/4.25% dextrose) or <100 mL (2.27% glucose /2.5% dextrose) over a 24-hour period, particularly in patients with a high peritoneal transport rate [4].

The investigation of the lipid profile included the determination of total cholesterol (TC), HDL-C, LDL-C, triglycerides (TG), and the calculation of very low-density lipoprotein cholesterol (VLDL-C) using the formula (TG/2.22). We also calculated the atherogenic index of plasma (AIP) using the formula (TC-HDL-C / HDL-C). Atherogenic dyslipidemia was diagnosed in cases where a low level of HDL-C in plasma (≥2.59 mmol/L) was combined with an elevated TG level (≥2.26 mmol/L), in accordance with KDIGO Clinical Practice Guideline for Lipid Management in CKD [19].

Lipid peroxidation was evaluated by measuring malondialdehyde (MDA) levels in serum and erythrocytes using the previously described methods [20]. The panel of antioxidant markers included serum ceruloplasmin, transferrin, the count of sulfhydryl groups (SH-groups), and total peroxidase activity in erythrocytes, following established procedures [21, 22]. Additionally, based on these markers, we calculated the oxidative stress index (OSI) as the ratio of the total changes in the activity of oxidative processes to the total antioxidant activity according to the formula described in prior studies [20, 22].

Statistical analysis. Statistical analysis was performed using the MedCalc Statistical Software version 22.007 (MedCalc Software Ltd, Ostend, Belgium) taking into account the verification of data for normal distribution using the Kolmogorov-Smirnov test. For normally distributed data, the mean values (M) and standard deviations (SD) were calculated, and the Student's t-test was used for comparisons. In cases where the data did not follow a normal distribution, the median (Me) and interquartile range (Q25-Q75) were used for description, and the non-parametric Mann-Whitney U-test was employed for comparisons.

Differences in frequencies between groups were assessed using Fisher's exact test (χ^2). Differences between the 3 groups of patients' peritoneal statuses were compared using the Kruskal–Wallis H test. The correlation analysis was done using the Spearmen test. Receiver operating characteristic (ROC) analysis was employed to assess the predictive accuracy of the AIP and OSI in identifying UFF. Finally, as a sensitivity analysis, we utilized analysis of covariance (ANCOVA) to examine the interaction effects of dyslipidemia and UF rate on oxidative stress while adjusting for potential confounding variables such as the patient's age, sex, diabetes status, PD duration, and the number of peritonitis episodes experienced. To normalize the distribution of OSI and mitigate any biases associated with extreme values, a Box–Cox transformation function was applied.

Results. ***Baseline characteristics of the study cohort.*** Among the 114 patients enrolled in the study, 75 (65.8%) were males, and 39 (34.2%) were females of similar age, with mean ages of 54 ± 12.5 and 51.7 ± 11.9 years, respectively (p = 0.48). Most patients, 77 (67.5%), had non-diabetic kidney disease, while 37 (32.5%) had type 1 and type 2 diabetes (n = 18 and n = 19, respectively). Importantly, there were no significant age or disease duration differences between patients with non-diabetic and diabetic kidney diseases (50.6 ± 10.8 vs. 47.6 ± 11.3 years; p = 0.51 and 29 (15.1-41.3) vs. 27.3 (13.7-36.05) months; p = 0.36, respectively).

Dyslipidemia was identified in 76 out of 114 (66.7%) patients, comprising 18 out of 37 (48.6%) with diabetes mellitus and 58 out of 77 (75.3%) with non-diabetic kidney disease (χ^2 = 7.9; p = 0.005). As anticipated, within the group of patients with dyslipidemia, there was a higher proportion of males, older individuals, and those with hypertension and excessive body weight. Patients diagnosed with dyslipidemia exhibited lower levels of hemoglobin (Hb) and blood calcium, alongside higher concentrations of glucose, phosphorus, and parathyroid hormone (PTH) compared to their dyslipidemia-free counterparts. Furthermore, individuals with dyslipidemia had a lengthier history of PD treatment, lower daily peritoneal ultrafiltration, and higher D/P creatinine ratio, resulting in reduced dialysis adequacy compared to those without dyslipidemia. It's noteworthy that both groups were similar concerning the medications used. The detailed demographic and clinical characteristics of the patients, categorized by the presence of dyslipidemia, are presented in Table 1.

Table 1

Characteristics of patients undergoing PD stratified by the presence of dyslipidemia

Indicators	All patients (n = 114)	Patients with dyslipidemia (n = 76)	Patients without dyslipidemia (n = 38)	*P*-value
Demographic and clinical data				
Men, n (%)	75 (65.8%)	49 (64.5%)*	26 (68,4%)	0.01*
Diabetes, n (%)	37 (32.5%)	18 (23.7%)	19 (50 %)	0.11
Age, years	55 (48-65)	58 (49-68)	52 (45-62)	0.04

Continuation of Table 1

Indicators	All patients (n = 114)	Patients with dyslipidemia (n = 76)	Patients without dyslipidemia (n = 38)	*P*-value
BMI, kg/m^2	25.8 ± 3.8	27.8 ± 3.47	23.4 ± 3.5	0.03
Serum albumin, g/Ll	38.8 (36.5-42)	40.8 (37.3-42.8)	37.8 (35.9-41.3)	0.0007
CRP, mg/L	8.9 (1.7-5.3)	4.2 (1.7-4.5)	2.4 (1.1-10.3)	0.67
Systolic blood pressure, mm Hg	129 ± 14.2	131 ± 13.2	119.3 ± 9.8	0.02
Diastolic blood pressure, mm Hg	78 ±12.4	82 ±11.2	77 ± 13.2	0.45
Hb, g/L	101.6 ± 20.6	96.8 ± 18.2	112.2 ± 11.7	0.01
Glucose, mmol/L	5.07 (4.6-5.4)	5.14 (4.8-8.2)	4.9 (4.3-5.3)	0.01
Calcium, mmol/L	2.18 (2.0 – 2.36)	2.1 (1.9-2.3)	2.27 (2.08-2.4)	0.02
Phosphorus, mmol/L	1.79 ± 0.42	2.1 ± 0.66	1.6 ± 0.71	0.03
PTH, pg/mL	602 (275-718)	617.5 (423-784.5)	400.5 (300-700)	0.003
PD parameters				
Dialysis vintage, months.	31 (14-50)	46 (19–55)	27 (9.2-46.5)	0.001
Diuresis, mL/d	550 (250-900)	400 (150-1000)	500 (1500-800)	0.74
D/P creatinine ratio	0.74 ± 0.13	0.86 ± 0.14	0.67 ± 0.12	<0.0001
Icodexrin, n (%)	15 (13.2%)	10 (13.2%)	5 (13.3%)	0.89
rKt/V	0.44 (0.08-0.97)	0.42 (0.06-0.81)	0.67 (0.42-0.69)	0.07
pKt/V	2.09 (1.58-2.64)	1.94 (1.38-2.92)	2.15 (1.87-2.5)	0.04
Kt/V	2.09 (1.74-2.9)	2.1 (1.7-2.2)	2.35 (1.76-3.25)	0.001
CrCl, ml/1.73 m^2/week	45.7 (39.0-52.2)	43.1 (41.8-55.5)	47.2 (40.1-57.4)	0.03
Peritoneal ultrafiltration, mL/d	740 (515-1050)	550 (420-925)	905 (730-1230)	<0.0001
Number of PD peritonitis, 1/patient-month	1/23.9	1/35.4	1/10.8	0.002
Lipid profile markers				
Total cholesterol, mmol/L	5.7 ± 1.3	6.1 ± 1.3	5.5 ± 2.3	0.35
Triglycerides, mmol/L	1.58 (1.09-2.21)	2.62 (2.3-2.9)	1.14 (0.87-1.5)	<0.0001
LDL-C, mmol/L	4.07 (3.19-5.02)	4.7 (3.04-5.05)	3.2 (3.1-4.7)	0.002
VLDL-C, mmol/L	0.63 (0.43-0.87)	0.75 (0.063-1.2)	0.46 (0.39-0.56)]	<0.0001
HDL-C, mmol/L	1.18 (0.9-1.57)	0.98 (0.87-1.18)	1.6 (1.2-2.1)	<0.0001
AIP	3.7 (2.4-4.8)	4.5 (3.9-6.0)	2.3 (1.7-2.9)	<0.0001
Prescribed medicines, n (%)				
Atorvastatin	54 (47.4 %)	39 (51.3%)	15 (39.5%)	0.23
ACE inhibitors / RAAS blockers	93 (81.6%)	65 (85.5%)	28 (73.7%)	0.13
Iron remedies	59 (51.7%)	41 (53.9%)	18 (47.4%)	0.51
Erythropoietins	56 (49.2%)	35 (46.0%)	21 (55.3%)	0.35
Beta-blockers	46 (40.3%)	31 (40.8%)	15 (39.5%)	0.89
Calcium channel blockers	68 (59.6%)	42 (55.2%)	26 (68.4%)	0.17
Diuretics	35 (30.7%)	20 (26.3%)	15 (39.5%)	0.15

Notes: *The data is presented as M±SD or Me (Q25-Q75) as appropriate. * – p-value compared to women.*

Abbreviations: *ACE, angiotensin-converting enzyme; AIP, atherogenic index of plasma; BMI, body mass index; CrCl, weekly creatinine clearance; CRP, C-reactive protein; D/P, dialysate/plasma; Hb, hemoglobin; HDL-C, high-density lipoprotein; Kt/V, total weekly urea clearances; LDL-C, low-density lipoprotein cholesterol; pKt/V, peritoneal clearance; rKt/V, renal clearance; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; VLDL-C, very low-density lipoprotein cholesterol.*

Dyslipidemia and clinically suspected UFF in patients undergoing PD. Within the studied cohort, none of the patients fell into the low transporter category. There were 23 patients (20.2%) classified as low-average transporters, 59 patients (51.8%) as high-average transporters, and 32 patients (28.1%) as high transporters. It's worth noting that among patients with dyslipidemia, there was a statistically significant lower number of low-average transporters and a higher proportion of high transporters compared to those without dyslipidemia (Fig. 1).

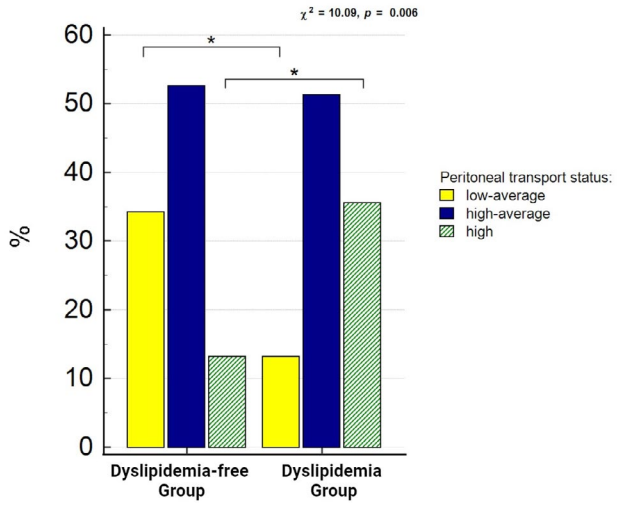

Fig. 1. Distribution of the study cohort according to peritoneal transport status.

Note: * - statistically significant differences between the groups (p < 0.001).

A total of 14 patients (12.3%) exhibited a peritoneal ultrafiltration of less than 400 mL per day, raising clinical suspicion of UFF. Out of these individuals, 13 patients (17.1%) were ultimately diagnosed with dyslipidemia, while only 1 patient (2.63%) did not show any indications of dyslipidemia ($\chi^2 = 4.9$, p = 0.02).

As expected, there was a negative association between the D/P creatinine ratio and the daily peritoneal ultrafiltration rate (r = -0.27, p = 0.003) and diuresis (r = -0.31, p = 0.001). However, interestingly, an increase in the D/P creatinine ratio was linked to higher levels of total cholesterol (r = 0.39, p = 0.0005), LDL-C (r = 0.26, p = 0.02), triglycerides (r = 0.33, p = 0.005), and the AIP (r = 0.27, p = 0.01).

Peritoneal UF was positively correlated with HDL-C (r = 0.31, p = 0.003) and negatively with AIP (r = -0.33, p = 0.004). Moreover, it showed a negative correlation between the number of peritonitis episodes experienced by the patient (r = -0.38, p = 0.001) and the duration of PD treatment (r = -0.39, p = 0.0001). The ROC analysis revealed that an AIP value exceeding 4.3 could effectively predict UFF, with a sensitivity of 83.3% and a specificity of 73.4% (Fig. 2).

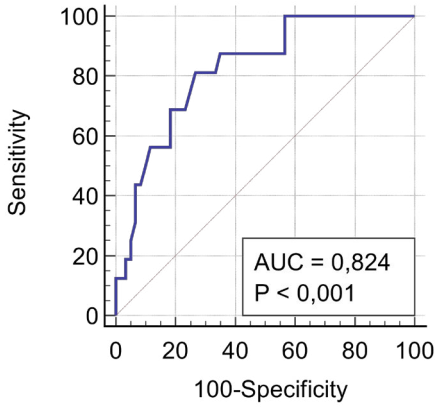

Fig. 2. The ROC curve for the cut-off value of AIP for predicting peritoneal UFF in patients undergoing PD.

Dyslipidemia and oxidative stress in patients undergoing PD. The intensity of oxidative processes was significantly higher in the entire group of patients undergoing PD with dyslipidemia compared to those without dyslipidemia. This was indicated by elevated OSI and MDA levels in both serum and erythrocytes, along with statistically significant reductions in antioxidant markers (Table 2).

Table 2

Comparison of oxidant-antioxidant markers in patients undergoing PD stratified by the presence of dyslipidemia

Markers	Dyslipidemia Group (n = 76)	Dyslipidemia-free Group (n = 38)	*P*-value
MDAs, μmol/L	475.8 (385.5-590.3)	384.6 (292.6-512.8)	0.0002
MDAe, μmol/L	870.4 (578.7-1031.3)	680.4 (494.4-967.8)	< 0.0001
Transferrin, g/L	1.23 (0.9-2.6)	2.5 (0.9-5.9)	0.03
Ceruloplasmin, g/L	0.12 (0.08-0.27)	0.22 (0.11-0.31)	0.02
SH-groups, mmol/L	1.56 (1.32-1.84)	1.43 (1.23-1.45)	0.68
TPA, μmol/min/g Hb	440.4 (269.3-1061.8)	534.6 (295.8-1145.2)	0.004
OSI, CU	5.07 (3.42-7.15)	3.78 (2.16-5.1)	< 0.0001

Abbreviations: MDAs, serum malondialdehyde; MDAe, erythrocytes malondialdehyde; OSI, oxidative stress index; SH-groups, sulfhydryl groups; TPA, total peroxidase activity.

Blood cholesterol levels demonstrated a positive correlation with OSI (r = 0.37; p = 0.0001) and the concentration of MDA in both serum (r = 0.38; p = 0.003) and erythrocytes (r = 0.21; p = 0.04). Conversely, HDL-C levels showed an inverse relationship with MDAs (Fig. 3A) and a positive correlation with blood catalase (r = 0.74; p = 0.0001). LDL-C, on the other hand, exhibited a negative correlation with transferrin (r = -0.31; p = 0.002) and a positive correlation with OSI (r = 0.39; p = 0.005). Elevated blood triglyceride levels were associated with reduced concentrations of transferrin (r = -0.37; p = 0.007) and catalase (r = -0.81; p < 0.0001), as well as increased levels of MDAs (r = -0.36; p = 0.001) and OSI (Fig. 3B).

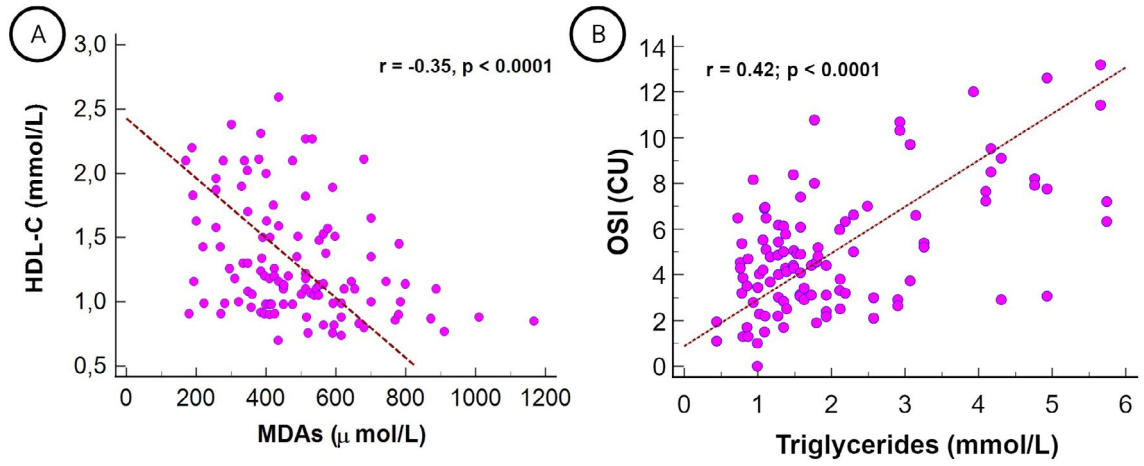

Fig. 3. The correlation between HDL-C levels and MDAs (A) and triglycerides and OSI (B) in patients undergoing PD.

UFF and oxidative stress in patients undergoing PD. Patients with UF rate < 400 mL/24-h exhibited higher concentrations of MDA in both erythrocytes and serum, elevated OSI, and lower ceruloplasmin and transferrin levels compared to patients with UF rate> 400 mL/24-h (Table 3).

Table 3

Comparison of oxidant-antioxidant markers in patients undergoing PD stratified by the clinically suspected UFF

Markers	Patients with UF rate < 400 mL/24-h (n = 14)	Patients with UF rate > 400 mL/24-h (n = 100)	*P*-value
MDAs, μmol/L	512.8 (432.6-607.8)	343.0 (257.2-562.2)	0.005
MDAe, μmol/L	825.4 (555.9-1211.4)	673.3 (494.4-1044.8)	0.008
Transferrin, g/L	1.0 (0.7-1.65)	1.6 (0.8-3.8)	0.03
Ceruloplasmin, g/L	0.13 (0.06-0.27)	0.21 (0.11-0.33)	0.04
SH-groups, mmol/L	1.49 (1.27-1.45)	1.52 (1.34-1.79)	0.86
TPA, μmol/min/g Hb	938.6 (453.5-1158.0)	857.9 (289.7-1281.2)	0.94
OSI, CU	6.3 (5.3-8.7)	4.3 (3.09-5.9)	0.0009

Abbreviations: MDAs, serum malondialdehyde; MDAe, erythrocytes malondialdehyde; OSI, oxidative stress index; SH-groups, sulfhydryl groups; TPA, total peroxidase activity.

A trend was observed in the increase of both MDAs and OSI in accordance with rising peritoneal transport rates (Fig. 4). Additionally, peritoneal UF showed an inverse correlation with OSI (r = -0.41, p <0.0001) and MDAs (Fig. 5A), as well as a direct correlation with transferrin concentrations (Fig. 5B) in patients undergoing PD.

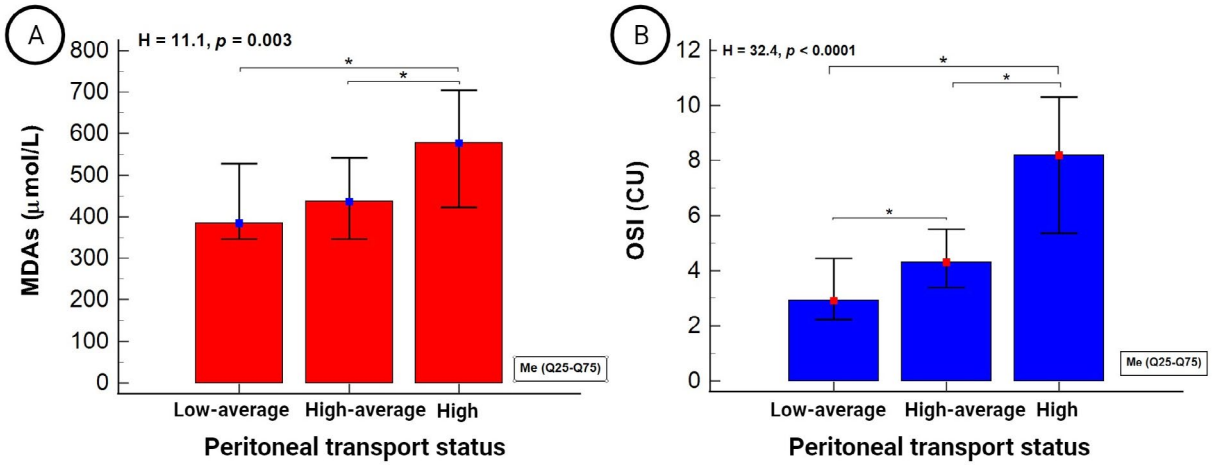

Fig. 4. Concentrations of MDAs (A) and OSI values (B) according to peritoneal transport status in patients undergoing PD.
Note: compared with the Kruskal-Wales test; * - p < 0.001.

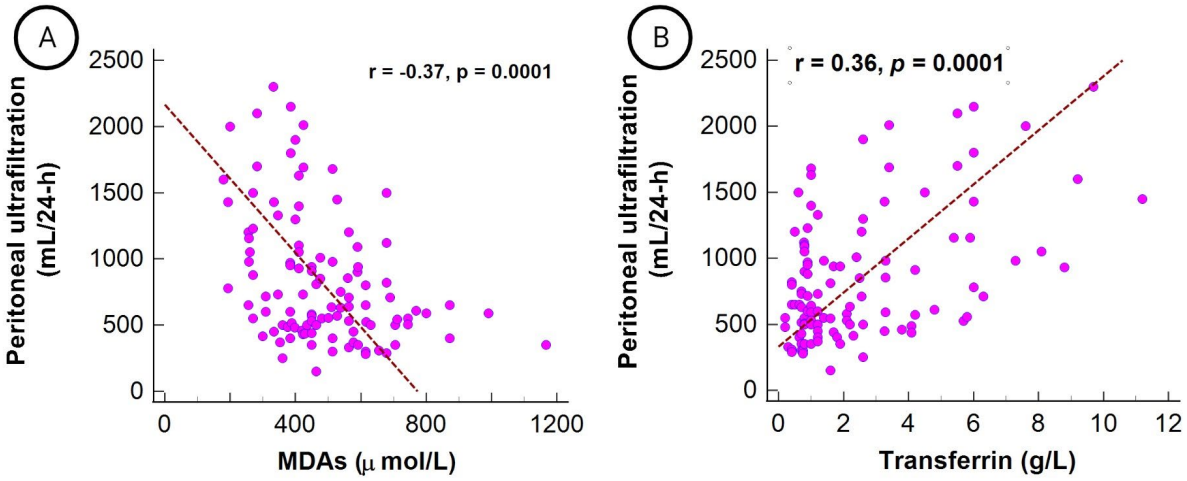

Fig. 5. The association between daily peritoneal UF rates and MDAs (A) and transferrin (B) concentrations in patients undergoing PD.

The ROC analysis, employing OSI as the comprehensive indicator of oxidative stress intensity, revealed that an OSI value surpassing 4.8 could effectively predict UFF, demonstrating a sensitivity of 89.5% and a specificity of 69.3% (Fig. 6).

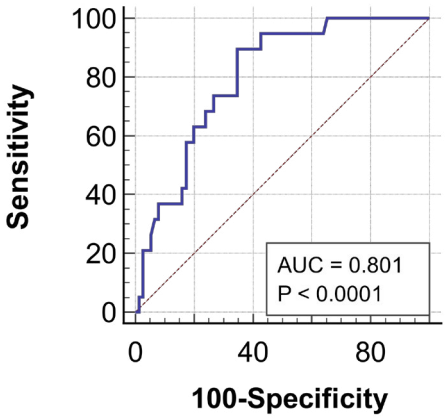

Fig. 6. The ROC curve for the cut-off value of OSI for predicting UFF in patients undergoing PD.

Oxidative stress as a link between dyslipidemia and UFF. To validate the significant differences in oxidative status associated with dyslipidemia and UFF while considering potential confounding variables, we conducted ANCOVA analysis, incorporating Box-Cox transformation for the OSI variable. The analysis accounted for patient age, sex, diabetes, daily diuresis, PD duration, atorvastatin usage, and the number of peritonitis episodes. The results consistently showed that patients with both dyslipidemia and UFF had the highest OSI values. Notably, a significant main effect of dyslipidemia ($F = 7.6$, $p = 0.007$) and UFF ($F = 8.6$, $p = 0.004$) on the intensity of oxidative stress in patients undergoing PD was observed (Fig. 7).

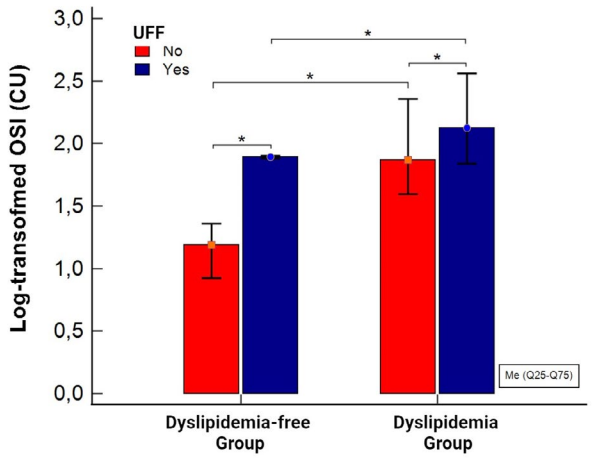

Fig. 7. Log-transformed values of OSI in patients undergoing PD stratified by the presence of dyslipidemia and UFF.

Abbreviation: *PMD, peritoneal membrane dysfunction.*
Note: ** - statistically significant interactions ($p < 0.001$).*

Discussion. In this study, we set out to explore the intricate relationship between oxidative stress, dyslipidemia, and peritoneal UF rates in patients undergoing PD. Our findings unveiled a multitude of significant insights into the complex interactions among these factors. First and foremost, patients with dyslipidemia exhibited elevated levels of glucose, phosphorus, and PTH and lower hemoglobin levels, reaffirming the well-established connection between dyslipidemia and CKD-associated disorders. Furthermore, they had longer periods of PD treatment, lower daily peritoneal ultrafiltration rates, and higher D/P creatinine ratios. This combination of factors contributed to reduced dialysis adequacy compared to their counterparts without dyslipidemia. Consistent with our findings, prior research has highlighted the association between dyslipidemia and adverse renal outcomes in the broader CKD population [23–25] as well as in specific studies focusing on clinical outcomes in patients undergoing PD [15, 16, 26]. These observations emphasize the significance of addressing dyslipidemia in the context of PD to enhance patient outcomes and minimize the risk of UFF.

Second, we observed a distinct association between dyslipidemia and UF rates. A substantial majority of patients with clinically suspected UFF had dyslipidemia. The study revealed that an elevated D/P creatinine ratio was associated with higher levels of total cholesterol, LDL-C, triglycerides, and AIP. Conversely, peritoneal ultrafiltration displayed a positive correlation with HDL-C and a negative association with AIP. AIP value exceeding 4.3 was a significant risk factor for peritoneal ultrafiltration failure. While there is a paucity of studies directly addressing this specific relationship, our findings align with the results from our previous study involving other PD patient cohorts [17]. Moreover, recent research conducted by Lu et al. contributes to our understanding of this association [27]. The authors demonstrated that a decreased apolipoprotein A (apoA)/HDL-C ratio was significantly linked to a rapid decline in peritoneal function. Additionally, they found that D-4F, one of the apoA-I mimic peptides, reduced peritoneal fibrosis in PD rats by regulating the epithelial-to-mesenchymal transformation [27]. They concluded that apoA-I exerts a protective effect on peritoneal ultrafiltration function by suppressing multiple profibrotic signaling pathways, mitigating oxidative stress, and dampening inflammatory responses [27]. These findings underscore the intricate relationship between peritoneal UF, oxidative stress, and specific lipid profile markers in patients undergoing PD.

Third, we established a robust association between dyslipidemia and the intensity of oxidative stress. Patients with dyslipidemia exhibited elevated levels of MDA in both serum and erythrocytes. They also showed higher OSI values and reduced concentrations of antioxidant markers such as ceruloplasmin, transferrin, and TPA. As anticipated, the heightened oxidative stress observed in patients with dyslipidemia was mirrored in those with UFF. Patients afflicted with UFF showcased elevated MDA and OSI levels, coupled with decreased levels of ceruloplasmin and transferrin, emphasizing the intricate connection between peritoneal UF rate and oxidative stress. Our findings align with previous research demonstrating the mutual association of oxidative stress with redox status in VLDL-C, LDL-C, and HDL-C in the plasma of CKD patients [13, 28]. Miljkovic and colleagues demonstrated that patients with CKD exhibit distinctive distribution patterns of advanced oxidation protein products (AOPP) among their lipoprotein fraction [13]. Their study revealed that the VLDL-C fraction is characterized by the highest concentration of AOPP. Additionally, the LDL-C fraction displays elevated AOPP levels compared to the HDL-C fraction. These findings underscore that oxidative stress markers, including AOPP, are particularly prominent in the VLDL-C and LDL-C fractions in CKD patients [13]. Moreover, a noteworthy finding in this context is the observed positive correlation between AOPP levels within the LDL-C fraction and the degree of injury score. This correlation underscores the intricate relationship between dyslipidemia and oxidative stress, suggesting its role in the pathophysiology of oxidative stress in these individuals [13].

However, the pathophysiological relationship between oxidative stress and dyslipidemia is multifaceted, with each factor influencing the other in a bidirectional manner [29]. Oxidative stress induced by PD can disrupt lipid metabolism, contributing to the development of dyslipidemia. This disruption is a consequence of processes such as the oxidation of lipoproteins, alterations in the activity of lipid metabolism enzymes, and changes in the expression of genes related to lipid homeostasis [6, 30].

Oxidative stress has further implications for UFF. Ramil-Gómez et al., have revealed that oxidative stress triggers a sequence of events that can ultimately lead to peritoneal membrane dysfunction [8]. For instance,

mitochondrial ROS production increases significantly, and there is a loss of mitochondrial membrane potential in mesothelial cells with a fibroblast phenotype found in PD effluent-derived human mesothelial cells when compared to those maintaining an epithelial morphology. This study also indicates that mitochondrial ROS plays a role in the epithelial-to-mesothelial transformation in omentum-derived mesothelial cells [8]. Moreover, a substantial body of experimental and clinical studies indicates that oxidative stress plays a role in activating various growth and transcriptional factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells, vascular endothelial growth factor, monocyte chemotactic peptide-1, and tumor growth factor-β. Activation of these factors, in turn, contributes to the increased build-up of extracellular matrix, a process that leads to fibrosis in the peritoneal membrane [6, 7, 31]. Over time, this fibrosis results in the deterioration and loss of ultrafiltration capacity in the peritoneal membrane [31].

Limitations and Future Directions. This study used a cross-sectional design, which is valuable for identifying associations but cannot demonstrate causality. Longitudinal or intervention studies are needed to confirm causal associations between dyslipidemia, oxidative stress, and UFF. In addition, the study sample size was relatively modest, which may limit the generalizability of the results to a broader population. Larger cohorts could further validate the observed associations. In addition, the study measured biomarkers and clinical parameters at a single time point, which may not capture dynamic changes. Furthermore, despite the statistical adjustments in the analysis, it is possible that other unmeasured or unknown confounders may influence the observed associations. Variability in treatment regimens, including medications, may have influenced the observed associations. For example, we did not examine the effect of lipid-lowering interventions on oxidative stress and UF rate. A more detailed analysis of the effects of specific medications on dyslipidemia and oxidative stress would be valuable.

Clinical Implications. Our findings have potential clinical implications for managing patients undergoing PD. Dyslipidemia, a modifiable risk factor, may serve as a target for therapeutic interventions aimed at mitigating oxidative stress and, consequently, UFF. Controlling lipid profiles in this patient population may not only reduce cardiovascular risk but also potentially preserve peritoneal membrane function.

Conclusions. Our findings collectively highlight the intricate relationships between dyslipidemia, oxidative stress, and peritoneal UF in patients undergoing PD. Both dyslipidemia and UFF are independently associated with elevated oxidative stress intensity, and their coexistence magnifies this oxidative burden. In this context, dyslipidemia may serve pivotal player in the development of UFF, with oxidative stress acting as the bridge connecting these two factors. These findings emphasize the importance of addressing dyslipidemia and oxidative stress as integral components of patient care, with the potential to improve peritoneal membrane function and enhance overall patient outcomes.

Conflict of interest statement. The authors declare no conflict of interest

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The authors' contribution.

N. Stepanova: Conceptualization, data analysis and interpretation, manuscript review;

L. Korol: Biochemical assay, manuscript review;

O. Burdeyna: Data collection, formal manuscript writing;

L. Snisar, A. Rysyev, V. Filonov, and I. Poperechny: Data collection.

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