frontiers | Research Topics

Advances and insights in peritoneal dialysis: a physiological perspective

Edited by
Guoshuang Xu, Ying-Yong Zhao, Lijie He and Bengt Lindholm

Published in
Frontiers in Physiology
Frontiers in Medicine

ISSN 1664-8714
ISBN 978-2-8325-5552-1
DOI 10.3389/978-2-8325-5552-1

About Frontiers

Frontiers is more than just an open access publisher of scholarly articles: it is a pioneering approach to the world of academia, radically improving the way scholarly research is managed. The grand vision of Frontiers is a world where all people have an equal opportunity to seek, share and generate knowledge. Frontiers provides immediate and permanent online open access to all its publications, but this alone is not enough to realize our grand goals.

Frontiers journal series

The Frontiers journal series is a multi-tier and interdisciplinary set of open-access, online journals, promising a paradigm shift from the current review, selection and dissemination processes in academic publishing. All Frontiers journals are driven by researchers for researchers; therefore, they constitute a service to the scholarly community. At the same time, the *Frontiers journal series* operates on a revolutionary invention, the tiered publishing system, initially addressing specific communities of scholars, and gradually climbing up to broader public understanding, thus serving the interests of the lay society, too.

Dedication to quality

Each Frontiers article is a landmark of the highest quality, thanks to genuinely collaborative interactions between authors and review editors, who include some of the world's best academicians. Research must be certified by peers before entering a stream of knowledge that may eventually reach the public - and shape society; therefore, Frontiers only applies the most rigorous and unbiased reviews. Frontiers revolutionizes research publishing by freely delivering the most outstanding research, evaluated with no bias from both the academic and social point of view. By applying the most advanced information technologies, Frontiers is catapulting scholarly publishing into a new generation.

What are Frontiers Research Topics?

Frontiers Research Topics are very popular trademarks of the *Frontiers journals series*: they are collections of at least ten articles, all centered on a particular subject. With their unique mix of varied contributions from Original Research to Review Articles, Frontiers Research Topics unify the most influential researchers, the latest key findings and historical advances in a hot research area.

Find out more on how to host your own Frontiers Research Topic or contribute to one as an author by contacting the Frontiers editorial office: frontiersin.org/about/contact

Advances and insights in peritoneal dialysis: a physiological perspective

Topic editors

Guoshuang Xu — Air Force Medical University, China
Ying-Yong Zhao — Northwest University, China
Lijie He — Air Force Medical University, China
Bengt Lindholm — Karolinska Institutet (KI), Sweden

Citation

Xu, G., Zhao, Y.-Y., He, L., Lindholm, B., eds. (2024). *Advances and insights in peritoneal dialysis: a physiological perspective*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-5552-1

Table of contents

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 10 May 2023
DOI 10.3389/fmed.2023.1132695

OPEN ACCESS

EDITED BY
Guoshuang Xu,
Fourth Military Medical University, China

REVIEWED BY
Tanawin Nopsopon,
Chulalongkorn University, Thailand
Jianhui Zhou,
Chinese PLA General Hospital, China

*CORRESPONDENCE
Shengmao Liu
✉ Liushengmao1968@163.com
Wenpeng Cui
✉ wenpengcui@163.com

RECEIVED 27 December 2022
ACCEPTED 12 April 2023
PUBLISHED 10 May 2023

CITATION
Guo S, Yang L, Zhu X, Zhang X, Meng L, Li X, Cheng S, Zhuang X, Liu S and Cui W (2023) Multidrug-resistant organism-peritoneal dialysis associated peritonitis: clinical and microbiological features and risk factors of treatment failure.
Front. Med. 10:1132695.
doi: 10.3389/fmed.2023.1132695

Multidrug-resistant organism-peritoneal dialysis associated peritonitis: clinical and microbiological features and risk factors of treatment failure

Shizheng Guo[1], Liming Yang[2], Xueyan Zhu[3], Xiaoxuan Zhang[4], Lingfei Meng[1], Xinyang Li[1], Siyu Cheng[1], Xiaohua Zhuang[1], Shengmao Liu[1]*and Wenpeng Cui[1]*

[1]Division of Nephrology, The Second Hospital of Jilin University, Changchun, China, [2]Division of Nephrology, First Hospital of Jilin University – The Eastern Division, Changchun, China, [3]Division of Nephrology, Jilin Central Hospital, Jilin, China, [4]Division of Nephrology, Jilin FAW General Hospital, Changchun, China

Background: Multidrug-resistant (MDR) bacterial infection causes difficulty in the therapy of peritoneal dialysis-associated peritonitis (PDAP); however, there are few studies on multidrug-resistant organism (MDRO)-PDAP. In view of growing concerns about MDRO-PDAP, the aim of this study was to investigate the clinical features, risk factors of treatment failure, and causative pathogens of MDRO-PDAP.

Methods: In total, 318 patients who underwent PD between 2013 and 2019 were included in this multicenter retrospective study. Clinical features, patient outcomes, factors related to treatment failure, and microbiological profiles associated with MDRO-PDAP were analyzed and risk factors for treatment failure associated with MDR-*Escherichia coli (E. coli)* were further discussed.

Results: Of 1,155 peritonitis episodes, 146 eligible episodes of MDRO-PDAP, which occurred in 87 patients, were screened. There was no significant difference in the composition ratio of MDRO-PDAP between 2013–2016 and 2017–2019 ($p>0.05$). *E. coli* was the most prevalent MDRO-PDAP isolate, with high sensitivity to meropenem (96.0%) and piperacillin/tazobactam (89.1%). *Staphylococcus aureus* was the second most common isolate and was susceptible to vancomycin (100%) and linezolid (100%). Compared to non-multidrug-resistant organism-PDAP, MDRO-PDAP was associated with a lower cure rate (66.4% vs. 85.5%), higher relapse rate (16.4% vs. 8.0%), and higher treatment failure rate (17.1% vs.6.5%). Dialysis age [odds ratio (OR): 1.034, 95% confidence interval (CI): 1.016–1.052, $p<0.001$] and>2 previous peritonitis episodes (OR: 3.400, 95% CI: 1.014–11.400, $p=0.047$) were independently associated with treatment failure. Furthermore, longer dialysis age (OR: 1.033, 95% CI: 1.003–1.064, $p=0.031$) and lower blood albumin level (OR: 0.834, 95% CI: 0.700–0.993, $p=0.041$) increased the risk of therapeutic failure for MDR-*E. coli* infection.

Conclusion: The proportion of MDRO-PDAP has remained high in recent years. MDRO infection is more likely to result in worse outcomes. Dialysis age and previous multiple peritonitis infections were significantly associated with treatment failure. Treatment should be promptly individualized based on local empirical antibiotic and drug sensitivity analyses.

KEYWORDS

peritoneal dialysis, peritonitis, multi-drug resistant, antimicrobial sensitivity pattern, risk factors

1. Introduction

The incidence of end-stage renal disease (ESRD) has been on the rise globally (1). Peritoneal dialysis (PD) is one of the most common renal replacement therapies; however, peritonitis remains a leading cause of technical failure in PD patients (2). Although prevention and treatment techniques have improved, peritonitis still plays a significant role in the mortality of PD patients (3, 4), and the occurrence of peritonitis has negative impacts on the survival of PD patients (5).

Infections caused by multi-drug resistant (MDR) bacteria are increasing (6), and the emergence of MDR-organism (MDRO) is a serious obstacle in the treatment of PD-associated peritonitis (PDAP). One of the main causes of antimicrobial resistance is the overuse of antibiotics (7). Furthermore, with the continuous adaptation and evolution of bacteria, it is becoming increasingly difficult to rationally choose antibiotics. Therefore, it is necessary to monitor the antimicrobial sensitivity patterns of MDROs to choose antibiotics more wisely.

Presently, studies on MDRO-PDAP are mainly limited to specific bacteria, such as *Acinetobacter* spp. (8), including *Acinetobacter baumannii* (9), and *Corynebacterium striatum* (10), and most of them are case reports or reviews. In previous studies, hypoproteinemia, malnutrition, sex, and diabetes have been identified as risk factors for adverse peritonitis outcomes (11, 12); however, the risk factors for poor MDRO-PDAP outcomes remain unclear. Furthermore, MDRO infection is a global health and economic threat with negative clinical consequences if not recognized and treated adequately (13). In summary, considering the growing problem of MDRO-PDAP, our major objective was to identify patient characteristics, predictors of treatment failure, and microbiological profiles to prevent antibiotic abuse and improve the clinical outcomes of MDRO-PDAP.

2. Methods

2.1. Patient selection and study design

We retrospectively screened 1,155 patients with peritonitis who underwent PD at the Second Hospital of Jilin University, Jilin Central Hospital, the First Hospital of Jilin University-the Eastern Division, and Jilin FAW General Hospital between January 1, 2013 and December 31, 2019. The inclusion criteria were the PDAP diagnostic criteria issued by the 2022 International Society for Peritoneal Dialysis (ISPD). The exclusion criteria were: (1) patients without complete data, (2) PD fluid that was not cultured, (3) negative PD culture, (4) PD fluid infected by multiple pathogens or fungi, and (5) drug sensitivity results could not be obtained.

Once a patient presented with peritonitis symptoms such as abdominal pain or cloudy dialysis fluid suspected to be caused by PDAP, the specimen of dialysis fluid was collected and sent for microbiological culture and sensitivity test, and then the patients was administered empirical intraperitoneal antibiotics. Most of the empirical treatment regimens were first-generation cephalosporins or vancomycin combined with third-generation cephalosporins or aminoglycoside drugs, and the corresponding antibiotic therapy plan was adjusted after obtaining the bacterial culture and drug sensitivity results. Finally, patients were treated according to the ISPD peritonitis treatment recommendations for 2–3 weeks, and clinicians decided whether to conduct catheter removal.

The study participants were divided into a MDRO group and a non-multidrug-resistant organism (NMDRO) group based on the results of microbial culture and drug sensitivity in the peritoneal dialysate fluid. Combined with patients' other clinical data, we mainly studied the clinical characteristics, microbiological overview, and risk factors of treatment failure. Additionally, we also analyzed the risk factors for treatment failure of MDR-*Escherichia coli* (*E. coli*)-PDAP specifically. This study was conducted in line with the Declaration of Helsinki. The Ethics Committee of the Second Hospital of Jilin University approved this study; ethics approval number: 2020026. Informed consent was not required due to the retrospective study design.

2.2. Data collection

All clinical data were obtained from patients' record review, including age, dialysis duration, sex, etiology of renal failure, comorbidities, past infections of MDRO-PDAP, number of previous episodes of peritonitis, and laboratory index (for white blood cell count, neutrophil percentage, and neutrophil count in blood, hemoglobin, albumin, potassium, calcium, phosphorus, blood urea nitrogen, serum creatinine, and dialysate white cell count on the first day of PDAP) before or at diagnosis of the index PDAP episode. Treatment outcomes were classified as the initial treatment evaluation, which was primary response and the follow-up treatment evaluation, which included clinical cure, relapse, catheter removal, and PDAP-related death. Drug sensitivity data were also recorded. Finally, we collected the microbiological results of peritoneal dialysate cultures taken from the patients on admission to identify gram-positive, gram-negative, anaerobic bacteria, *Mycobacterium tuberculosis*, fungi, and polymicrobial infections.

2.3. Definition

In accordance with the 2022 ISPD guidelines (14), when at least two of the following conditions were present, peritonitis was diagnosed: (1) abdominal pain and/or cloudy ascites, (2) white blood cells in the dialysate $>0.1\times10^9$/L or >100/μL (after at least 2 h dwell time), with >50% polymorphonuclear neutrophil cells, and (3) a positive dialysate pathogen culture. However, the surveillance and study of MDROs has been compromised by the lack of a complete consensus on the definition. Thus, MDRO was considered to be insensitivity to at least one agent in three or more antimicrobial categories following the joint

recommendations for epidemiologic studies from the European Center for Disease Prevention and Control (15). The guide also clearly defines common MDROs in healthcare systems, including *Staphylococcus aureus*, *Enterococcus* spp., *Enterobacteriaceae* (other than *Salmonella* and *Shigella*), *Pseudomonas aeruginosa*, and *Acinetobacter* spp. We have only conducted related studies on the above bacteria for reliability and unity of definitions. The effective primary response was identified, when the symptoms of PDAP were significantly alleviated, the dialysate fluid was cleared, and the white blood cell count of the fluid decreased significantly within 48–72 h of reasonable anti-infection treatment (16). Clinical cure implied reasonable antibiotic treatment for 2–3 weeks, complete relief of clinical peritonitis symptoms, clear peritoneal fluid, and white blood cell count in dialysis fluid $<0.1 \times 10^9$/L (14). PDAP-related death implied death occurring within 30 days of the onset of peritonitis or death due to peritonitis during hospitalization (14). Relapse implied an episode occurring within 4 weeks of therapy completion for a previous episode caused by the same organism (14). Recurrent implied a peritonitis episode occurring within 4 weeks of therapy completion for a previous episode caused by a different organism (14). Repeat implied a peritonitis episode occurring more than 4 weeks after therapy completion for a previous episode caused by the same organism (14). Treatment failure implied catheter removal or PDAP-related death (17).

2.4. Statistical analysis

Sample size estimation was performed using PASS version 16.0 (NCCS LLC, Kaysville, Utah, USA), setting a power value of 0.80, an α of 0.05, and a ratio of 1:3 for the number of patients in the two groups, yielding a minimum ideal sample size of 139 cases in the MDRO group and 390 cases in the NMDRO group, respectively. All statistical data were analyzed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). For categorical variables, data were analyzed as frequencies and percentages; Pearson's chi-square and Fisher's exact tests were used to compare categorical variables between groups. For continuous variables, data were analyzed as interquartile ranges [M, (P_{25}, P_{75})], mean ± standard deviation ($\bar{x} \pm s$), using the independent *t*-test (normal distribution) and Wilcoxon rank-sum test (non-normal distribution) to compare continuous variables between groups. Poisson regression was used to compare the incidence of peritonitis. Risk factors influencing treatment failure were analyzed using logistic regression models. Variables with *p*-values <0.05 in the univariate analysis and factors that may influence treatment outcome (age > 60 years, diabetes mellitus) were included in the multivariate model for MDRO-PDAP treatment failure for correction. However, due to limitations in the positive sample size, only variables with *p*-values < 0.05 in the univariate analysis were supported for inclusion in the multivariate model of MDR-*E. coli*-PDAP treatment failure. Statistical significance was set at a *p*-value < 0.05. All probabilities were two-tailed. All figures were plotted using GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, United States).

3. Results

3.1. Clinical characteristics

A total of 1,155 PDAP episodes occurred in 670 individuals from January 1, 2013 to December 31, 2019. The screening process for including patients is shown in Figure 1. After applying the exclusion criteria, 318 individuals and 546 cases were finally included in the study, with 113 patients and 146 cases included in the MDRO group while 336 patients and 400 cases were included in the NMDRO group. During the study period, 93 patients experienced only one episode of MDRO-PDAP, 11 patients experienced only two episodes of MDRO-PDAP, 7 patients experienced only three episodes, 1 patient experienced only four episodes, and 1 patient experienced six episodes.

Comparisons of clinical characteristics between the two groups are presented in Table 1. Patients in the MDRO group had a higher percentage of blood neutrophils, were more likely to have past infections of MDRO-PDAP, more likely to show polycystic kidney as protopathy, and were more likely to be relapsing cases ($p < 0.05$) than those in the NMDRO group. Conversely, patients in the NMDRO group had higher blood albumin levels and were more likely to be initial cases than those in the MDRO group ($p < 0.05$). However, additional parameters showed no significant differences between the two groups. The details of each pathogenic bacteria studied are presented in Table 1.

3.2. Constituent ratio of MDRO-PDAP and pathogen distribution

A total of 146 cases of MDRO-PDAP accounted for 12.6% of the total 1,155 cases of PDAP over seven years. From 2013 to 2019, the average incidence of peritonitis was 0.225 episodes/patient-year, and the overall trend in incidence of MDRO-PDAP was decreasing ($p < 0.001$; Figure 2A); however, the composition ratio of MDRO-PDAP remained high from 2013–2015 (13.9%) to 2016–2019 (13.3%) ($p > 0.05$; Figure 2B). A total of 146 MDRO strains were isolated from 546 PDAP cases. Among these MDROs, gram-negative bacterial isolates ($n = 110$, 75.3%) were more common than gram-positive bacterial isolates ($n = 36$, 24.7%). MDR-*E. coli* ($n = 79$, 54.1%), followed by *Klebsiella pneumoniae* ($n = 10$, 6.8%), was the most common antimicrobial isolate among gram-negative strains, accounting for 78.2% (79/92) of all *E. coli* isolates. MDR-*S. aureus* ($n = 34$, 23.3%), followed by *Enterococcus* ($n = 2$, 1.4%), was the most common isolate among the gram-positive strains, accounting for 73.9% (34/46) of all *S. aureus* isolates (Table 2).

3.3. Antimicrobial susceptibility analysis

Figures 3A,B show the antibiotic sensitivity results with the two MDROs (*S. aureus* and *E. coli*) representing the largest proportion. All *S. aureus* strains showed susceptibility to vancomycin and linezolid (Figure 3A). The *enterococcus* spp. isolates were 100% susceptible to linezolid. Among gram-negative bacteria, *E. coli* strains were highly susceptible to meropenem (96.0%) and piperacillin/tazobactam (89.1%; Figure 3B). *P. aeruginosa* and *Acinetobacter* spp. were completely susceptible to meropenem and imipenem, respectively.

3.4. Evaluation of treatment outcome

Table 3 shows the treatment outcomes of the two groups. Compared to the NMDRO group, the MDRO group had a lower

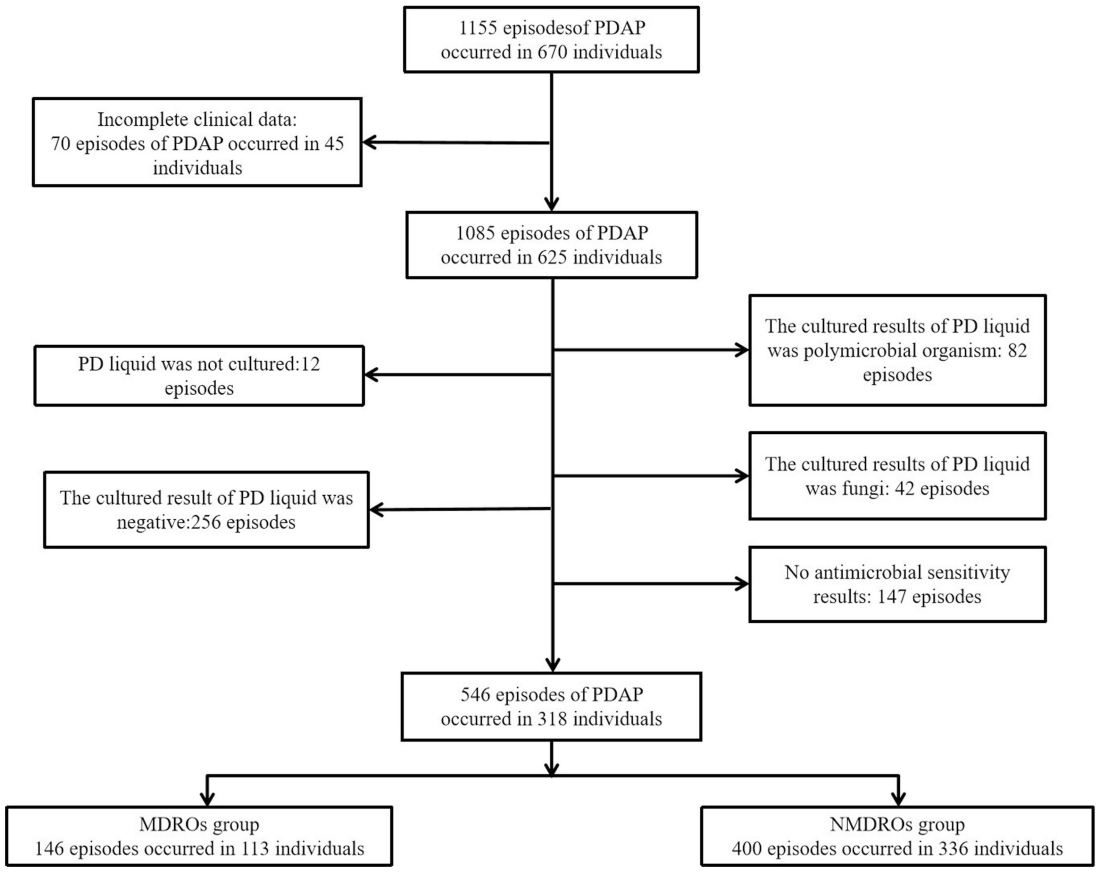


FIGURE 1
Flow chart. PD, peritoneal dialysis; PDAP, peritoneal dialysis-associated peritonitis; MDRO, multi-drug resistant organism; NMDRO, non-multi-drug resistant organism.

initial effective rate (70.5% vs. 88.5%, $p < 0.001$), lower cure rate (66.4% vs. 85.5%), higher relapse rate (16.4% vs. 8.0%), and higher treatment failure rate (17.7% vs. 6.5%, $p < 0.001$), which included a higher frequency of catheter removal (11.6% vs. 3.8%) and death (5.5% vs. 2.8%).

3.5. Risk factors for treatment failure

PD age and more than 2 previous PDAP episodes were suggested to be significant in the univariate analysis, and after adjusting for other confounding factors (age > 60 years, diabetes), a multifactorial logistic regression model identified the two independent risk factors for MDRO-PDAP treatment failure, namely PD age [odds ratio (OR): 1.034, 95% confidence interval (CI): 1.016–1.052, $p < 0.001$] and more than 2 previous PDAP episodes (OR: 3.400, 95% CI: 1.014–11.400, $p = 0.047$; Table 4). In addition, we also analyzed the risk factors for MDR-*E. coli*-PDAP treatment failure, with albumin levels and PD age showing significance in the univariate analysis. Putting the above indicators into a multifactorial regression analysis, it was determined that lower albumin levels (OR: 0.834, 95% CI: 0.700–0.993, $p = 0.041$) and PD age (OR: 1.033, 95% CI: 1.003–1.064, $p = 0.031$) increase the risk of MDR-*E. coli*-PDAP treatment failure (see Table 5).

4. Discussion

To our knowledge, this is the first multicenter retrospective study to explore the clinical characteristics, antimicrobial susceptibility, patient outcomes, and risk factors of treatment failure associated with MDRO-PDAP.

The average peritonitis rate was 0.225 episodes/patient-year in our study from 2013 to 2019, and per the ISPD recommendations updated in 2022, the requirement is no more than 0.4 episodes per patient-year, indicating that the incidence of peritonitis was relatively well controlled in the hospitals where this study was conducted. Another study from our center pointed out that the incidence of PDAP has decreased in recent years (18), and our study also observed that the incidence of MDRO-PDAP was similarly decreasing between 2013–2019. However, MDRO-PDAP remains a serious challenge for clinicians because of increasing drug resistance among bacteria. Considering that MDRO-PDAP incidence could be influenced by the overall incidence of peritonitis, we further studied the composition ratio of MDRO-PDAP in all PDAP cases. Not surprisingly, we observed that the proportion of MDRO-PDAP remained high in these years. During the study period, 93 patients with MDROs experienced only one episode of MDRO-PDAP, 11 patients experienced only two episodes, and 9 patients experienced more than two episodes. These

TABLE 1 Comparison of clinical characteristics between the MDRO and NMDRO groups.

Clinical variables	MDRO group (n=146)	NMDRO group (n=400)	$t/X^2/Z$	p-value	MDRO[a]				
					Staphylococcus aureus (n=34)	Enterobacteriaceae (n=101)	Acinetobacter spp. (n=7)	Pseudomonas aeruginosa[b] (n=2)	Enterococcus spp.[b] (n=2)
Age [year, (M, P_{25}, P_{75})]	62.0 (48.0, 70.0)	58.0 (46.0, 68.0)	2.632	0.105	61.0 (47.8, 66.0)	63.0 (48.0, 70.0)	67.5 (47.8, 79.5)	58.5	71.5
Gender [men (n, %)]	78 (53.4%)	210 (52.5%)	0.037	0.848	22 (64.7%)	49 (48.5%)	6 (85.7%)	1 (50.0%)	0 (0%)
Dialysis age [month, (M, P_{25}, P_{75})]	17.5 (4.0, 33.5)	16.0 (7.0, 30.0)	0.133	0.715	13.5 (4.8, 22.3)	20.0 (5.0, 46.0)	20.0 (1.5, 44.8)	3.5	1.5
Past infection of MDRO (n, %)	33 (22.6%)	21 (14.4%)	36.140	<0.001	12 (35.3%)	19 (18.8%)	0 (0%)	0 (0%)	0 (0%)
Protopathy									
Chronic glomerulonephritis (n, %)	62 (42.5%)	153 (38.3%)	0.796	0.372	12 (35.3%)	48 (47.5%)	1 (14.3%)	1 (50.0%)	0 (0%)
Diabetic nephropathy (n, %)	15 (10.3%)	66 (16.5%)	3.282	0.070	16 (47.1%)	17 (16.8%)	1 (14.3%)	0 (0%)	1 (50.0%)
Interstitial nephritis (n, %)	9 (6.1%)	12 (3%)	2.896	0.089	2 (5.9%)	7 (6.9%)	0 (0%)	1 (50.0%)	0 (0%)
Hypertensive nephropathy (n, %)	35 (24.0%)	110 (27.5%)	0.682	0.409	2 (5.9%)	11 (10.9%)	1 (14.3%)	0 (0%)	1 (50.0%)
Polycystic kidney (n, %)	13 (8.8%)	17 (4.3%)	4.462	0.035	1 (2.9%)	17 (16.8%)	1 (14.3%)	0 (0%)	0 (0%)
Accompanying disease									
Hypertension (n, %)	119 (81.5%)	351 (87.8%)	3.479	0.062	30 (88.2%)	82 (81.2%)	4 (57.1%)	1 (50.0%)	2 (100.0%)
Diabetes (n, %)	45 (30.8%)	157 (39.2%)	3.260	0.071	16 (47.1%)	27 (26.7%)	1 (14.3%)	0 (0%)	0 (0%)
Laboratory index									
WBC count [*10^9/L, (M, P_{25}, P_{75})]	8.26 (6.25, 12.16)	8.46 (6.29, 11.39)	0.031	0.860	8.25 (6.62, 12.37)	8.23 (5.93, 11.97)	8.75 (5.63, 18.44)	15.63	12.41
NEU percentage [%, (M, P_{25}, P_{75})]	85.95 (79.55–90.65)	82.40 (75.01–88.0)	12.327	<0.001	87.50 (79.91, 91.23)	85.40 (79.50, 90.15)	83.25 (81.30, 91.55)	85.57	74.15
NEU count [*10^9/L, (M, P_{25}, P_{75})]	7.34 (4.87–10.20)	6.92 (4.72–9.85)	0.935	0.334	7.38 (5.60, 10.52)	7.20 (4.71, 10.12)	7.47 (4.62, 17.05)	13.67	9.66
Hb [g/L, ($\overline{x} \pm s$)]	100.33 ± 17.05	98.16 ± 20.13	−1.249	0.213	89.97 ± 12.14	104.29 ± 17.13	89.00 (74.50, 109.00)	94.50	104.00
Alb [g/L, ($\overline{x} \pm s$)]	27.83 ± 6.38	29.21 ± 5.90	2.362	0.019	26.86 ± 7.25	27.98 ± 5.78	31.49 ± 10.13	14.55	22.55
Potassium [mmol/L, (M, P_{25}, P_{75})]	3.74 (3.30, 4.24)	3.79 (3.30, 4.27)	0.086	0.770	3.91 (3.53, 4.68)	3.71 (3.24, 4.20)	3.5 (3.04, 3.83)	3.33	3.17
Calcium [mmol/L, (M, P_{25}, P_{75})]	2.11 (1.98, 2.29)	2.17 (2.01, 2.31)	2.422	0.120	2.03 (1.90, 2.28)	2.13 (2.00, 2.30)	2.11 (2.06, 2.42)	2.35	1.94
Phosphorus [mmol/L, (M, P_{25}, P_{75})]	1.22 (0.99, 1.51)	1.28 (1.05, 1.55)	2.448	0.118	1.26 (1.07, 1.54)	1.22 (0.97, 2.30)	1.05 (0.79, 1.70)	1.28	1.41
BUN [mmol/L, (M, P_{25}, P_{75})]	25.44 (11.61, 20.73)	15.88 (12.02, 19.84)	0.081	0.777	16.21 (12.34, 24.87)	14.77 (11.39, 20.44)	17.06 (14.96, 18.21)	12.84	23.17
Scr [μmol/L, (M, P_{25}, P_{75})]	707.94 (529.68, 907.31)	738 (543.13, 920.03)	0.884	0.347	729.21 (578.85, 829.42)	703.30 (528.45, 910.50)	708.37 (335.71, 1047.83)	522.77	430.91
Nature of peritonitis									
Initial PDAP (n, %)	75 (51.4%)	244 (61.0%)	4.084	0.043	18 (52.9%)	47 (46.5%)	6 (85.7%)	2 (100.0%)	2 (100.0%)
Relapsing PDAP (n, %)	17 (11.6%)	26 (6.5%)	3.901	0.048	7 (20.6%)	10 (9.9%)	0 (0%)	0 (0%)	0 (0%)
Recurrent PDAP (n, %)	9 (6.2%)	20 (5.0%)	0.288	0.591	1 (2.9%)	8 (7.9%)	0 (0%)	0 (0%)	0 (0%)
Repeat PDAP (n, %)	9 (6.2%)	30 (7.5%)	0.288	0.592	4 (11.8%)	5 (5.0%)	0 (0%)	0 (0%)	0 (0%)

WBC, white blood cell; NEU, neutrophil; Hb, hemoglobin; Alb, albumin; BUN, blood urea nitrogen; Scr, serum creatinine; PDAP, peritoneal dialysis-associated peritonitis; MDRO, multi-drug resistant organism; NMDRO, non-multi-drug resistant organism.

[a]In addition to describing the differences between the two groups, we also presented baseline information for each type of MDRO we studied for reference.

[b]Because there were only two cases of this bacterium, the continuous variables were described using the mea

10.3389/fmed.2023.1132695

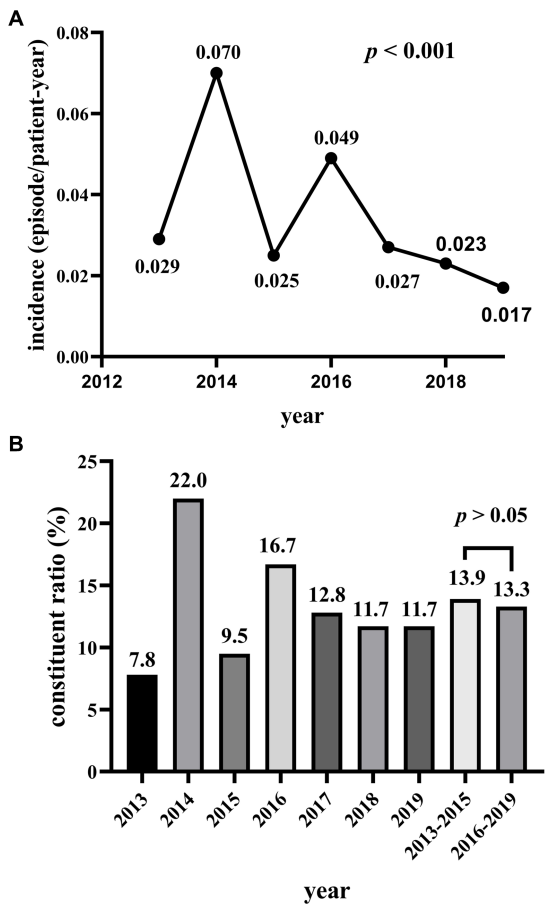


FIGURE 2
(A) The incidence of MDRO-PDAP from 2013 to 2019.
(B) The constituent ratio of MDRO-PDAP from 2013 to 2019.

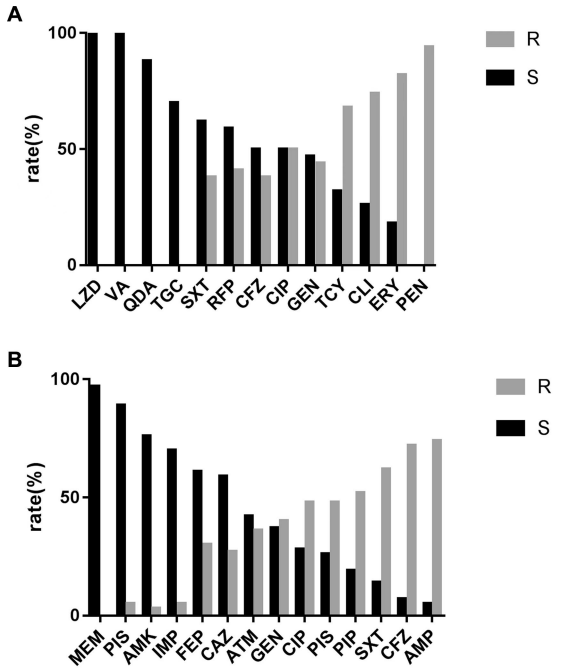


FIGURE 3
(A) Antimicrobial sensitivity result of MDR-*Staphylococcus aureus*. LZD, linezolid; VA, vacomycin; QDA, quinupristin-dalfopristin; TGC, tigecycline; SXT, trimethoprim-sulphamethoxazole; RFP, rifampicin; CFZ, cephazolin; CIP, ciprofloxacin; GEN, gentamicin; TCY, tetracucline; CLI, clindamyxin; ERY, erythrocin; PEN, penicillin.
(B) Antimicrobial sensitivity result of MDR-*Escherichia coli* MEM, meropenem; PIS, piperacillin/tazobactam; AMK, amikacin; IMP, imipenem; FEP, cefepime; CAZ, ceftazidime; ATM, aztreonam; GEN, gentamicin; CIP, ciprofloxacin; SAM, ampicillin/sulbactam; PIP, peperacillin; SXT, trimethoprim-sulphamethoxazole; CFZ, cephazolin; AMP, ampicillin.

TABLE 2 The distribution of causative organisms in patients infected with MDRO.

Pathogenic microorganisms	*n* (%)
Gram-positive bacteria	36 (24.7%)
Staphylococcus aureus	34 (23.3%)
Enterococcus spp.	2 (1.4%)
Gram-negative bacteria	110 (75.3%)
Enterobacteriaceae	101 (69.2%)
Escherichia coli	79 (54.1%)
Klebsiella pneumoniae	10 (6.8%)
Others	12 (8.2%)
Pseudomonas aeruginosa	2 (1.3%)
Acinetobacter spp.	7 (4.8%)
Baumannii	4 (2.7%)
Others	3 (2.1%)
Total	146 (100%)

MDRO, multi-drug resistant organism.

results support the notion that, because of the seriousness of the problem presented by MDRO, the vigilance for MDROs should be improved and further research conducted on the microbiological profiles and risk factors of MDRO-PDAP to fill the current gap in research.

We observed that the percentage of neutrophils was higher in the MDRO group than in the NMDRO group, with higher expression levels of inflammatory mediators, resulting in a stronger inflammatory response and a more severe degree of disease in the MDRO group; this finding is supported by an article demonstrating elevated expression of inflammatory mediators in endophthalmitis patients infected with MDR-*P. aeruginosa* (19). Another study (20) from China clarified that elevated neutrophil levels are a sensitive systemic inflammatory marker associated with high mortality in patients with ESRD. Furthermore, several studies (21, 22) have associated hypoalbuminemia with the development of PDAP. In our study, the MDRO group had low albumin levels. Serum albumin level is often used to assess patient nutritional condition, although hypoalbuminemia may also be linked to inflammation. Malnutrition affects immunity and causes immune dysfunction, which in turn affects the resistance to infection. Besides, some studies (13, 23) have noted that having a history of MDROs is associated with positive MDRO isolation on admission; this could partially explain why the MDRO group in our study were more likely to have a history of MDRO colonization.

Compared to the NMDRO group, the MDRO group had more relapsing cases, which required medical professionals to pay closer

TABLE 3 Evaluation of treatment between MDRO group and NMDRO group.

Therapeutic evaluation	MDRO group (n=146)	NMDRO group (n=400)	X^2	p-value	MDRO[a]			
					Staphylococcus aureus (n=34)	Enterococcus spp. (n=101)	Acinetobacter spp. (n=7)	Pseudomonas aeruginosa (n=2)	Enterobacteriaceae (n=2)
Effective initial treatment (n, %)	103 (70.5%)	354 (88.5%)	25.265	<0.001	28 (82.4%)	67 (66.3%)	5 (71.4%)	2 (100.0%)	1 (50.0%)
Evaluation of follow-up treatment			25.921	<0.001	–	–	–	–	–
Cure (n, %)	97 (66.4%)	342 (85.5%)	–	–	22 (64.7%)	68 (67.3%)	5 (71.4%)	1 (50.0%)	1 (50.0%)
Relapse (n, %)	24 (16.4%)	32 (8.0%)	–	–	8 (23.5%)	14 (13.9%)	1 (14.3%)	0 (0%)	1 (50.0%)
Catheter removal (n, %)	17 (11.6%)	15 (3.8%)	–	–	4 (11.8%)	12 (11.9%)	1 (14.3%)	0 (0%)	0 (0%)
Death associated with peritonitis (n, %)	8 (5.5%)	11 (2.8%)	–	–	0 (0%)	7 (6.9%)	0 (0%)	1 (50.0%)	0 (0%)
Treatment failure [b]	25 (17.1%)	26 (6.5%)	14.254	<0.001	4 (11.8%)	19 (18.8%)	1 (14.3%)	1 (50.0%)	0 (0%)

MDRO, multi-drug resistant organism; NMDRO, non-multi-drug resistant organism.

[a]In addition to describing the differences between the two groups, we also presented baseline information for each type of MDRO we studied for reference.

[b]Treatment failure including catheter removal and peritonitis-related death.

attention to patients with relapsing peritonitis because they are more prone to infections by MDROs. A systematic review (24) indicated that previous antibiotic use was related to the likelihood of MDRO isolation, possibly because prior antimicrobial treatment strongly modified the abdominal microbiota and was associated with an increased risk of drug-resistant microbial infection. Interestingly, there were no significant differences in the recurrent and repeat cases between the case and control groups. Besides, the MDRO group had a lower initial treatment effective rate and higher treatment failure rate compared with the NMDRO group. Reportedly, a poor prognosis was more common in patients with peritonitis due to methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant *enterococci*, and extended spectrum β-lactamase (ESBL)- and metallo-β-lactamase-producing bacteria (25, 26), which supported our conclusion to some extent that MDRO-PDAP tended to have poor outcomes. Therefore, it is necessary to adjust the poor treatment plan of MDRO-PDAP on the basis of the drug sensitivity results and attempt to reduce the related risk to prevent poor prognosis whenever possible.

In our multivariate study, PD age and more than 2 previous PDAP episodes were independently associated with MDRO-PDAP treatment failure. Our previous study showed that long dialysis age was a risk factor for treatment failure of first peritonitis (27). The thickness of the submesothelial layer increases gradually and is accompanied by peritoneal fibrosis and neovascularization in the peritoneum of patients with long-term PD. Thus, these patients have a higher incidence of ultrafiltration failure (28). In this study, we observed a 2.4-fold increase in the risk-of-failure of the current peritonitis treatment when there were more than 2 previous PDAP episodes. Repeated episodes of peritonitis cause aggregation of inflammatory cells such as mononuclear macrophages and release transforming growth factor-β (TGF-β), a major molecule in the course of peritoneal fibrosis, and the overexpression of TGF-β is linked to worse PD outcomes (29). We further inferred that the effect of empirical antimicrobial therapy could be compromised based on the above pathological basis if the patient had an infection caused by MDROs, with treatment delay increasing the likelihood of treatment failure. In our study, non-first-episode peritonitis with the same pathogen cultured in the previous peritonitis episode accounted for 74.3% (26/35) of all non-first-episode peritonitis cases. This also suggests that in patients who are repeatedly hospitalized for peritonitis in a short period, clinicians should choose the initial treatment regimen in conjunction with their previous culture and drug susceptibility results. There are few studies related to the risk factors for treatment failure in MDR-*S. aureus* and MDR-*E. coli*; however, to avoid statistical bias caused by the few cases of *S. aureus* treatment failure, we only studied *E. coli*, which is the most prevalent species in the *Enterobacteriaceae* family. We observed that lower albumin levels and longer PD age increased the risk of treatment failure, similar to the results of another study (30) conducted in our center on the treatment outcome of *E. coli* infection. Therefore, for *E. coli*-PDAP, especially those infected with MDROs, it could be beneficial for clinical outcomes to raise albumin levels.

Previous studies (31, 32) showed that the most common microorganisms isolated from patients with PDAP were gram-positive bacteria, among which coagulase-negative *Staphylococcus* was the most prevalent, followed by *S. aureus*. Furthermore, *E. coli* was the most common gram-negative bacterium, followed by *Klebsiella pneumoniae* and *P. aeruginosa*. However, because coagulase-negative

TABLE 4 Risk factors of treatment failure in patients with MDROs group.

Variables	Univariate			Multivariate		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age>60 (years)	1.061	0.446–2.524	0.894	1.105	0.429–2.846	0.836
Male	0.882	0.371–2.099	0.777	–	–	–
Dialysis age (years)	1.034	1.016–1.052	0.000	1.034	1.016–1.052	<0.001
>2 previous peritonitis episodes	3.158	1.043–9.558	0.042	3.400	1.014–11.400	0.047
Accompanying disease						
Hypertension	1.232	0.386–3.937	0.725	–	–	–
Diabetes	0.849	0.327–2.205	0.737	0.780	0.269–2.261	0.836
Laboratory index						
NEU percentage (%)	1.026	0.974–1.080	0.339	–	–	–
NEU count (*109/L)	0.999	0.920–1.085	0.977	–	–	–
WBC count (*109/L)	0.992	0.915–1.075	0.768	–	–	–
Hb (g/L)	1.004	0.979–1.029	0.768	–	–	–
Alb (g/L)	0.956	0.891–1.026	0.214	–	–	–
Potassium (mmol/L)	0.915	0.511–1.637	0.764	–	–	–
Phosphorus (mmol/L)	0.655	0.259–1.653	0.370	–	–	–
Calcium (mmol/L)	2.659	0.457–15.457	0.276	–	–	–
Nature of peritonitis	–	–	0.685	–	–	–
Relapsing	0.712	0.251–2.203	0.524	–	–	–
Repeating	1.275	0.317–5.127	0.732	–	–	–
Recurrent	2.071	0413–10.395	0.376	–	–	–
Initial	0.000	0.000–	0.999	–	–	–
Others	Reference					
Bacteria	–	–	0.712	–	–	–
Staphylococcus aureus	Reference					
Enterococcus spp.	1.738	0.547–5.524	0.349	–	–	–
Enterobacteriaceae	0.000	0.000–	0.999	–	–	–
Pseudomonas aeruginosa	7.500	0.388–144.973	0.182	–	–	–
Acinetobacter spp.	1.250	0.118–13.240	0.853	–	–	–
Protopathy	–	–	0.804	–	–	–
Chronic glomerulonephritis	2.115	0.245–188.271	0.496	–	–	–
Diabetic nephropathy	2.750	0.248–30.512	0.410	–	–	–
Interstitial nephritis	5.500	0.464–65.162	0.177	–	–	–
Hypertensive nephropathy	2.276	0.245–21.120	0.469	–	–	–
Polycystic kidney disease	2.000	0.157–25.404	0.593	–	–	–
Others	Reference					
Dialysate white cell count,1st day of PDAP (*10^6)	1.000	1.000–1.000	0.716	–	–	–

WBC, white blood cell; NEU, neutrophil; Hb, hemoglobin; Alb, albumin; BUN, blood urea nitrogen; Scr, serum creatinine; PDAP, peritoneal dialysis-associated peritonitis; MDRO, multi-drug resistant organisms; OR, odds ratio; 95% CI, 95% confidence interval.

Staphylococcus was not included in the MDRO group in our study, the microbiological distribution of MDROs in our study was slightly different from the results of the PDAP population. Therefore, as shown in Table 2, gram-positive MDROs were mainly *S. aureus* and *E. coli*, followed by *Klebsiella pneumoniae*, and *Baumannii* was the most common gram-negative bacterium.

Owing to the small number of strains of other MDROs, including *P. aeruginosa*, *Enterococcus* spp., and *Acinetobacter* spp., we did not perform detailed drug susceptibility analysis of the above pathogens to avoid a small sample size distorting study results but instead focused on MDR-*S. aureus* and MDR-*E. coli*. The causative organism that produced more severe outcomes in MDR-*S. aureus* PDAP was MRSA,

TABLE 5 Risk factors of treatment failure in patients with MDR-*E. coli*-PDAP.

Variables	Univariate			Multivariate		
	OR	95%CI	*p*-value	OR	95%CI	*p*-value
Age > 60 (years)	0.750	0.173–3.249	0.701	–	–	–
Male	1.784	0.413–7.706	0.438	–	–	–
Dialysis age (years)	1.036	1.006–1.067	0.018	1.033	1.003–1.064	0.031
Previous peritonitis episodes	0.552	0.937–2.570	0.088	–	–	–
Accompanying disease						
Hypertension	0.798	0.148–4.296	0.793	–	–	–
Diabetes	0.767	0.14604.023	0.754	–	–	–
Laboratory index						
NEU percentage (%)	1.046	0.942–1.077	0.339	–	–	–
NEU count (*109/L)	1.007	0.942–1.071	0.832	–	–	–
WBC count (*109/L)	1.047	0.939–1.169	0.408	–	–	–
Hb (g/L)	0.997	0.957–1.039	0.892	–	–	–
Alb (g/L)	0.841	0.719–0.983	0.030	0.834	0.700–0.993	0.041
Potassium (mmol/L)	0.796	0.315–2.012	0.623	–	–	–
Phosphorus (mmol/L)	0.716	0.189–2.709	0.623	–	–	–
Calcium (mmol/L)	1.275	0.070–23.121	0.869	–	–	–
Nature of peritonitis	–	–	0.881	–	–	–
Relapsing	0.463	0.094–2.278	0.344	–	–	–
Repeating	0.875	0.082–9.376	0.912	–	–	–
Recurrent	1.313	0.115–15.032	0.827	–	–	–
Initial	0.000	0.000–	0.999	–	–	–
Others	Reference					
Protopathy	–	–	0.727	–	–	–
Chronic glomerulonephritis	Reference					
Diabetic nephropathy	2.188	0.339–14.095	0.410	–	–	–
Interstitial nephritis	4.375	0.599–31.934	0.146	–	–	–
Hypertensive nephropathy	0.729	0.074–7.181	0.787	–	–	–
Polycystic kidney disease	0.000	0.000–	0.999	–	–	–
Others	0.000	0.000–	0.999	–	–	–
Dialysate white cell count,1st day of PDAP (*10^6)	1.000	1.000–1.000	0.557	–	–	–

WBC, white blood cell; NEU, neutrophil; Hb, hemoglobin; Alb, albumin; BUN, blood urea nitrogen; Scr, serum creatinine; PDAP, peritoneal dialysis-associated peritonitis; MDRO, multi-drug resistant organisms; OR, odds ratio; 95% CI, 95% confidence interval.

which are usually more severe than peritonitis caused by methicillin-susceptible *S. aureus*, with significantly increased frequency of hospitalization and length of treatment time, as well as increased frequency of extubation and death (33). Severe negative outcomes were more likely to occur when vancomycin was not used in the regimen of treatment for MRSA peritonitis (33). In our study, all the MDR-*S. aureus* strains were susceptible to vancomycin, reflecting the importance of vancomycin in the treatment of MDR-*S. aureus*-infection. Producing extended-spectrum beta-lactamases (ESBLs) is the most vital resistance mechanism in *Enterobacteriaceae*. In a study of MDROs from Hong Kong (6), *E. coli* accounted for 85.6% of all ESBL-producing isolates. Unfortunately, owing to the limitations of this retrospective study, ESBL-producing organisms could not be accurately detected. Carbapenems are ideal therapeutic agents against this bacterium (34). The 2022 ISPD guidelines also state that for *Enterobacteriaceae*, treatment regimens should be based on resistance patterns. Intraperitoneal application of meropenem could be an option for ESBL-producing Enterobacteriaceae (ESBL-E) (14). The treatment recommendations were also supported by our finding that almost all MDR-*E. coli* cultured *in vitro* are susceptible to meropenem. However, it is worth noting that except for ESBL-E, *Enterobacteriaceae* had evolved to resist carbapenems (6), causing mortality rates of up to 70% (35) which are rising globally (36). Above all, our results showed that the local antimicrobial susceptibility patterns of MDR-*E. coli* and MDR-*S. aureus* were consistent with the therapeutic antibiotics recommended by the guidelines. Nevertheless,

the final treatment plan should still be carefully selected according to the drug susceptibility results to prevent more resistance caused by antibiotic abuse.

This study had some limitations. Firstly, the retrospective nature of the study resulted in the presence of some unavoidable biases. For example, the results of this study cannot be extrapolated to the general population because of the confined location from which patients were included and the treatment regimens in each region. What's more, we excluded cases with mixed bacterial infections due to concerns that they would interfere with the analysis of treatment failure of MDR-PDAP, but mixed infections are more likely to develop antibiotic resistance than isolated infections (37), which might introduce selection bias. Secondly, we were unable to identify MRSA or ESBL-E based on the collected drug sensitivity results; therefore, our efforts to analyze the antibiotic sensitivity pattern in more detail were limited. Finally, the number of MDROs for some species was too few to be analyzed categorically, so larger prospective studies are warranted in the future.

5. Conclusion

In summary, MDRO-PDAP has remained a major issue in recent years, resulting in poor treatment outcomes. Special attention should be paid to patients with more than two previous peritonitis episodes, and those who have been undergoing dialysis for a long time because treatment for such patients is more likely to fail. Although the treatment regimens recommended by the current guidelines for infections caused by MDR-*S. aureus* and MDR-*E. coli* are appropriate in the area where we are conducting our study; they should be modified promptly in accordance with drug susceptibility to reduce the adverse outcomes caused by delays in MDRO-PDAP treatment.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Second Hospital of Jilin University (No. 2020026). The ethics committee waived the requirement of written informed consent for participation.

Author contributions

LMY, XYZ, and XXZ provided the data. LFM, XYL, SYC, and XHZ collected the data. SZG performed the statistical analysis and wrote the manuscript. WPC and SML designed the study and reviewed this manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by the Research Project of the Branch of Blood Purification Center of the Chinese Hospital Association (Project No. CHABP 2021-20) and the Science and Technology department of Jilin Province (Project No. YDZJ202201ZYTS110).

Acknowledgments

The authors thank all the staff of the four PD centers for their contribution of this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Saran R, Li Y, Robinson B, Ayanian J, Balkrishnan R, Bragg-Gresham J, et al. Us renal data system 2014 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Diseases*. (2015) 66:S1–305. doi: 10.1053/j.ajkd.2015.05.001

2. Jeloka TK, Abraham G, Bhalla A, Balasubramaniam J, Dutta A, Gupta A, et al. Continuous ambulatory peritoneal dialysis peritonitis guidelines - consensus statement of peritoneal dialysis Society of India - 2020. *Ind J Nephrology*. (2021) 31:425–34. doi: 10.4103/ijn.IJN_73_19

3. Tian Y, Xie X, Xiang S, Xin Y, Chen J. Risk factors and outcomes of high peritonitis rate in continuous ambulatory peritoneal dialysis patients: a retrospective study. *Medicine*. (2016) 95:e5569. doi: 10.1097/MD.0000000000005569

4. Pindi G, Kawle V, Sunkara RR, Darbha MS, Garikaparthi S. Continuous ambulatory peritoneal dialysis peritonitis: microbiology and outcomes. *Indian J Med Microbiol*. (2020) 38:72–7. doi: 10.4103/ijmm.IJMM_20_251

5. Bustillo E, Borrás F, Gómez-Roldán C, Pérez-Contreras FJ, Miguel A. Impact of peritonitis on long-term survival of peritoneal dialysis patients. *Nefrología Publicación Oficial De La Sociedad Espaola Nefrologia*. (2011) 31:723–32. doi: 10.3265/Nefrologia.pre2011.Oct.10987

6. Kwok KO, Chan E, Chung PH, Tang A, Wei WI, Zhu C, et al. Prevalence and associated factors for carriage of Enterobacteriaceae producing Esbls or Carbapenemase and methicillin-resistant staphylococcus Aureus in Hong Kong community. *J Infect*. (2020) 81:242–7. doi: 10.1016/j.jinf.2020.05.033

7. Shaaban MT, Ghaly MF, Fahmi SM. Antibacterial activities of Hexadecanoic acid methyl ester and green-synthesized silver nanoparticles against multidrug-resistant bacteria. *J Basic Microbiol*. (2021) 61:557–68. doi: 10.1002/jobm.202100061

8. Li PH, Cheng VC, Yip T, Yap DY, Lui SL, Lo WK. Epidemiology and clinical characteristics of acinetobacter peritoneal dialysis-related peritonitis in Hong Kong-with a perspective on multi-drug and carbapenem resistance. *Perit Dial Int*. (2017) 37:177–82. doi: 10.3747/pdi.2016.00123

9. Zhang W, Wu Y-G, Qi X-M, Dai H, Lu W, Zhao M. Peritoneal dialysis-related peritonitis with acinetobacter baumannii: a review of seven cases. *Perit Dial Int*. (2014) 34:317–21. doi: 10.3747/pdi.2012.00198

10. Kitayama S, Saito K, Sato Y. Peritoneal dialysis-related peritonitis due to corynebacterium striatum: an emerging multidrug-resistant pathogen. *Ther Apher Dial*. (2021) 25:254–5. doi: 10.1111/1744-9987.13564

11. Tsai CC, Lee JJ, Liu TP, Ko WC, Wu CJ, Pan CF, et al. Effects of age and diabetes mellitus on clinical outcomes in patients with peritoneal dialysis-related peritonitis. *Surg Infect*. (2013) 14:540–6. doi: 10.1089/sur.2012.195

12. Chen H-L, Tarng D-C, Huang L-H. Risk factors associated with outcomes of peritoneal dialysis in Taiwan: an analysis using a competing risk model. *Medicine*. (2019) 98:e14385. doi: 10.1097/MD.0000000000014385

13. Menéndez R, Méndez R, Polverino E, Rosales-Mayor E, Amara-Elori I, Reyes S, et al. Risk factors for multidrug-resistant pathogens in bronchiectasis exacerbations. *BMC Infect Dis*. (2017) 17:659. doi: 10.1186/s12879-017-2754-5

14. Li PK-T, Chow KM, Cho Y, Fan S, Figueiredo AE, Harris T, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. *Perit Dial Int*. (2022) 42:110–53. doi: 10.1177/08968608221080586

15. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and Pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect*. (2012) 18:268–81. doi: 10.1111/j.1469-0691.2011.03570.x

16. Yu X, Liao Y, Chen M, Lin H, Ni Z, Wang L, et al. Guidelines for the prevention and treatment of peritoneal dialysis-associated infections. *Chinese J Nephrol*. (2018) 34:139–48. doi: 10.3760/cma.j.issn.1001-7097.2018.02.010

17. Muthucumarana K, Howson P, Crawford D, Burrows S, Swaminathan R, Irish A. The relationship between presentation and the time of initial administration of antibiotics with outcomes of peritonitis in peritoneal dialysis patients: the prompt study. *Kidney Int Rep*. (2016) 1:65–72. doi: 10.1016/j.ekir.2016.05.003

18. Liu S, Yang L, Zhu X, Zhang X, Meng L, Li X, et al. Clinical features and risk factors of catheter removal among 1062 episodes of peritoneal dialysis-associated peritonitis: a multicenter 7-year study. *Ther Apher Dial*. (2022). doi: 10.1111/1744-9987.13956 [Epub ahead of print].

19. Naik P, Singh S, Rudraprasad D, Dave VP, Kumar A, Joseph J. Multidrug-resistant pseudomonas aeruginosa triggers differential inflammatory response in patients with endophthalmitis. *Transl Vis Sci Technol*. (2021) 10:26. doi: 10.1167/tvst.10.9.26

20. Zhang L, Nie Y, Guo M, Wang L, Ji J. Neutrophil to lymphocyte ratio as a predictor of long-term outcome in peritoneal dialysis patients: a 5-year cohort study. *Blood Purif*. (2021) 50:772–8. doi: 10.1159/000510552

21. Hu J, Zhang H, Yi B. Peritoneal transport status and first episode of peritonitis: a large cohort study. *Ren Fail*. (2021) 43:1094–103. doi: 10.1080/0886022X.2021.1949350

22. Ong LM, Ch'ng CC, Wee HC, Supramaniam P, Zainal H, Goh BL, et al. Risk of peritoneal dialysis-related peritonitis in a multi-racial Asian population. *Perit Dial Int*. (2017) 37:35–43. doi: 10.3747/pdi.2015.00141

23. Otter JA, Herdman MT, Williams B, Tosas O, Edgeworth JD, French GL. Low prevalence of Meticillin-resistant staphylococcus aureus carriage at hospital admission: implications for risk-factor-based vs. universal screening. *J Hosp Infect*. (2013) 83:114–21. doi: 10.1016/j.jhin.2012.10.008

24. Sulis G, Sayood S, Katukoori S, Bollam N, George I, Yaeger LH, et al. Exposure to who aware antibiotics and isolation of multi-drug resistant bacteria: a systematic review and meta-analysis. *Clin Microbiol Infect*. (2022) 28:1193–202. doi: 10.1016/j.cmi.2022.03.014

25. Prasad KN, Singh K, Rizwan A, Mishra P, Tiwari D, Prasad N, et al. Microbiology and outcomes of peritonitis in northern India. *Peritoneal Dialysis Int: J Int Soc Peritoneal Dialysis*. (2014) 34:188–94. doi: 10.3747/pdi.2012.00233

26. Szeto C-C, Chow K-M, Kwan BC-H, Law M-C, Chung K-Y, Yu S, et al. Staphylococcus aureus peritonitis complicates peritoneal dialysis: review of 245 consecutive cases. *Clin J Am Soc Nephrol*. (2007) 2:245–51. doi: 10.2215/CJN.03180906

27. Zhao J, Yang L, Zhu X, Zhang X, Li X, Liu S, et al. Clinical characteristics and treatment outcomes of first peritonitis in patients receiving long-term peritoneal dialysis: a multicenter study. *J Southern Med Univ*. (2020) 40:1740–6. doi: 10.12122/j.issn.1673-4254.2020.12.07

28. Smit W, Schouten N, Berg N, Langedijk MJ, Krediet RT. Analysis of the prevalence and causes of ultrafiltration failure during long-term peritoneal dialysis: a cross-sectional study. *Perit Dial Int*. (2004) 24:562–70. doi: 10.1177/089686080402400616

29. Aroeira LS, Aguilera A, Sanchez-Tomero JA, Bajo MA, Peso GD, Jimenez-Heffernan JA, et al. Epithelial to mesenchymal transition and peritoneal membrane failure in peritoneal dialysis patients: pathologic significance and potential therapeutic interventions. *J Am Soc Nephrol*. (2007) 18:2004–13. doi: 10.1681/ASN.2006111292

30. Cheng S-Y, Yang L-M, Zhu X-Y, Zhang X-X, Meng L-F, Guo S-Z, et al. Risk factors for the occurence and treatment failure of peritonral dialysis-associated E-coli peritonitis. *Chinese J Clin Infect Diseases*. (2021) 14:6. doi: 10.3760/cma.j.issn.1674-2397.2021.03.002

31. Moola Y, Musoke J, Bailey A, Kajee U, Parlato A, Moola I, et al. The prevalence and bacterial distribution of peritonitis amongst adults undergoing continuous ambulatory peritoneal dialysis at Universitas hospital. *South Afr J Infect Dis*. (2020) 35:1–5. doi: 10.4102/sajid.v35i1.104

32. Wang H-H, Huang C-H, Kuo M-C, Lin S-Y, Hsu C-H, Lee C-Y, et al. Microbiology of peritoneal dialysis-related infection and factors of refractory peritoneal dialysis related peritonitis: a ten-year single-center study in Taiwan. *J Microbiol Immunol Infect*. (2019) 52:752–9. doi: 10.1016/j.jmii.2018.10.013

33. Govindarajulu S, Hawley CM, Mcdonald SP, Brown FG, Rosman JB, Wiggins KJ, et al. Staphylococcus aureus peritonitis in Australian peritoneal dialysis patients: predictors, treatment, and outcomes in 503 cases. *Perit Dial Int*. (2010) 30:311–9. doi: 10.3747/pdi.2008.00258

34. Szeto CC, Chow CY, Chow KM, Lai WM, Li KT. Enterobacteriaceae peritonitis complicating peritoneal dialysis: a review of 210 consecutive cases. *Kidney Int*. (2006) 69:1245–52. doi: 10.1038/sj.ki.5000037

35. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella Pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev*. (2012) 25:682–707. doi: 10.1128/CMR.05035-11

36. Weinstein RA. Carbapenem-resistant Enterobacteriaceae: epidemiology and prevention. *Clin Infect Diseases: Off Publ Infect Diseases Soc Am*. (2011) 53:60–7. doi: 10.1093/cid/cir202

37. Wolcott R, Costerton J, Raoult D, Cutler S. The polymicrobial nature of biofilm infection. *Clin Microbiol Infect*. (2013) 19:107–12. doi: 10.1111/j.1469-0691.2012.04001.x

frontiers | Frontiers in Physiology

TYPE Review
PUBLISHED 15 May 2023
DOI 10.3389/fphys.2023.1187207

OPEN ACCESS

EDITED BY
Guoshuang Xu,
Fourth Military Medical University, China

REVIEWED BY
Yuan Gui,
University of Connecticut, United States
Quan Hong,
Chinese PLA General Hospital, China

*CORRESPONDENCE
Hua-feng Liu,
hf-liu@263.net

†These authors have contributed equally to this work

RECEIVED 15 March 2023
ACCEPTED 03 May 2023
PUBLISHED 15 May 2023

CITATION
Su H-y, Yang J-j, Zou R, An N, Chen X-c, Yang C, Yang H-j, Yao C-w and Liu H-f (2023), Autophagy in peritoneal fibrosis. *Front. Physiol.* 14:1187207. doi: 10.3389/fphys.2023.1187207

Autophagy in peritoneal fibrosis

Hong-yong Su†, Jia-jie Yang†, Rong Zou, Ning An, Xiao-cui Chen, Chen Yang, Hai-juan Yang, Cui-wei Yao and Hua-feng Liu*

Guangdong Provincial Key Laboratory of Autophagy and Major Chronic Non-communicable Diseases, Key Laboratory of Prevention and Management of Chronic Kidney Disease of Zhanjiang City, Institute of Nephrology, Affiliated Hospital of Guangdong Medical University, Zhanjiang, Guangdong, China

Peritoneal dialysis (PD) is a widely accepted renal replacement therapy for patients with end-stage renal disease (ESRD). Morphological and functional changes occur in the peritoneal membranes (PMs) of patients undergoing long-term PD. Peritoneal fibrosis (PF) is a common PD-related complication that ultimately leads to PM injury and peritoneal ultrafiltration failure. Autophagy is a cellular process of "self-eating" wherein damaged organelles, protein aggregates, and pathogenic microbes are degraded to maintain intracellular environment homeostasis and cell survival. Growing evidence shows that autophagy is involved in fibrosis progression, including renal fibrosis and hepatic fibrosis, in various organs. Multiple risk factors, including high-glucose peritoneal dialysis solution (HGPDS), stimulate the activation of autophagy, which participates in PF progression, in human peritoneal mesothelial cells (HPMCs). Nevertheless, the underlying roles and mechanisms of autophagy in PF progression remain unclear. In this review, we discuss the key roles and potential mechanisms of autophagy in PF to offer novel perspectives on future therapy strategies for PF and their limitations.

KEYWORDS

autophagy, human peritoneal mesothelial cells, peritoneal dialysis, peritoneal fibrosis, peritoneal dialysis-related peritonitis

1 Introduction

To date, more than 2 million people suffer from end-stage renal disease (ESRD), and this prevalence continues to increase year by year, leading to a significant economic burden (Howell et al., 2019; Masola et al., 2022). More than 272,000 patients, approximately 11% of the dialysis population, undergo peritoneal dialysis (PD) worldwide (Balzer, 2020). PD is a common renal replacement therapy for patients with ESRD. Owing to advantages such as simple operation, protection of residual renal function, and lower risk of cross-infection, PD offers a higher quality of life and more cost savings than does hemodialysis for patients with ESRD (Mehrotra et al., 2011; Yeates et al., 2012). During the COVID-19 pandemic, the importance of PD was revealed, especially in children or patients from low-income areas. The peritoneum is the first barrier preventing microbial invasion during the peritoneal fluid exchange. Owing to their large surface and dense vascularization, peritoneal membranes (PMs) can facilitate high solute and water transport to the intraperitoneal region and thus are a natural choice for membrane filtration and removal of excess water and uremic and other solutes (Balzer, 2020).

In patients undergoing long-term PD, the peritoneum is repeatedly exposed to a non-physiological environment with high glucose, high permeability, and low pH. Over time, it develops inflammation, fibrosis, and other peritoneal complications, leading to morphological and functional changes in the PMs, resulting in PM injury and ultrafiltration failure (UF) (Davies et al., 1996; Smit et al., 2004; Masola et al., 2022). UF

gradually declines within 2–4 years after the initiation of PD (Davies et al., 1996; Smit et al., 2004; Hayat et al., 2021). Initially, the primary causes of PD failure are peritonitis and catheter-related complications (Li et al., 2016a; Hayat et al., 2021). However, the bio-incompatibility of peritoneal dialysis solution (PDS) in the long term, accompanied by impairment of peritoneal integrity and functionality, becomes the main concern (Bajo et al., 2017). In 50%–80% of the patients undergoing long-term PD, the primary signs of peritoneal fibrosis (PF) are detected within 1–2 years (Strippoli et al., 2016). Inhibition of fibrosis and inflammation can prolong the life of PD therapy. Although many mechanisms have been proposed, effective interventions and treatment strategies for PF are lacking (Zhang et al., 2018a). Thus, there is an urgent need to explore the mechanisms underlying PF progression and develop effective prevention strategies.

Autophagy, a process that degrades single proteins and large organelles, is an integral part of all eukaryotic cell types. It is considered a true health modifier (Morishita and Mizushima, 2019; Klionsky et al., 2021) and serves as the primary regulator of cellular and tissue adaptation to various endogenous and exogenous pressures (Morishita and Mizushima, 2019). Autophagy pathways are physiologically correlated, even under basal and non-stressful conditions. In multiple experimental models, pharmacological and genetic interventions that impair autophagy were found to promote or exacerbate diseases (Klionsky et al., 2021). Autophagy plays a critical role in the progression of fibrosis in various organs, such as the kidneys (Dai et al., 2022), liver (Sun et al., 2021), and lungs (Araya et al., 2013). However, the causal connection between autophagy and PF and the pathophysiological mechanisms remains unclear.

Currently, many researches have proved that autophagy is involved in the process of PD and in PD-related complications, and novel interventions targeting autophagy may have clinical transformability. In this review, we highlight the current knowledge about the key roles and potential mechanisms of autophagy in PF. Furthermore, we discuss novel underlying mechanisms of autophagy modulators, which may contribute to developing new clinical therapies for PF.

2 Effect of autophagy in peritoneal fibrosis

PF is one of the most common complications in patients undergoing long-term PD and one of the leading causes of PD failure (Krediet and Struijk, 2013; Krediet, 2018). Epithelial-mesenchymal transition (EMT) of peritoneal mesothelial cells (PMCs), also called mesothelial-mesenchymal transition (MMT), is wildly accepted as the main cause of PF (Strippoli et al., 2016; Zhou et al., 2016; Zhang et al., 2018a; Hayat et al., 2021). Furthermore, in submesothelial areas, transformed mesothelial cells can generate extracellular matrix (ECM) and cause fibrosis, demonstrating their invasive capacity (Yáñez-Mó et al., 2003). Moreover, during PF and MMT, the key fibrogenic molecular machinery, mainly transforming growth factor-β (TGF-β)/Smad-dependent signaling (Margetts et al., 2005; Patel et al., 2010; Loureiro et al., 2011; Yoshizawa et al., 2015) and TGF-β/Smad-independent signaling (Matsuo et al., 2006; Patel et al., 2010; Liu et al., 2012; Fan et al., 2013; Kitterer et al., 2015; Wynn and Vannella, 2016; Padwal et al., 2018), triggers the transcription factors that act on the promoter regions of the cell matrix genes to activate their transcription via specific downstream intracellular signaling.

PF is commonly observed in patients with mild fibrosis undergoing PD (Di Paolo and Sacchi, 2000). However, encapsulating peritoneal sclerosis (EPS), which has low morbidity and high mortality, is an uncommon form of PF (Strippoli et al., 2016). It is a life-threatening complication that may progress even in patients who have discontinued PD.

2.1 Effect of autophagy in peritoneal fibrosis

As a complex and necessary metabolic process, autophagy exists in most mammalian cells. Autophagy is closely related to fibrosis in multiple organs, such as the kidney (Zhao et al., 2019), heart (Zhao et al., 2018), lungs (Cabrera et al., 2015), and liver (Meng et al., 2018). Additionally, high-glucose (HG) levels can modulate autophagy in multiple disease models (Wei et al., 2014; Chang et al., 2015; Lu et al., 2015). However, the potential effects of autophagy during the development of PF remain ambiguous, as some studies suggest that autophagy reduces PF, whereas others show the opposite trend (Figure 1).

On the one hand, autophagy is believed to contribute to PF progression. First, autophagy inhibition was observed in the peritoneum of an HG-induced peritoneal injury mouse model (Li et al., 2019a). Simultaneously, studies suggest that blocking autophagy with 3-methyladenine (3-MA) and Beclin-1 or ATG5 small interfering RNA (siRNA) not only enhances the continuous activation of the inflammatory factor nod-like receptor 3 (NLRP3)/interleukin-1β (IL-1β) induced by the stimulation of long-term HGPDS but also promotes MMT progression in the PMs of patients undergoing PD (Li et al., 2017). Moreover, as an autophagy inducer, trehalose has been shown to ameliorate PF by promoting the generation of autophagosomes and suppressing MMT in PMCs (Mayer et al., 2016; Sakai et al., 2017; Miyake et al., 2020) through activating AMP-activated protein kinase (AMPK) pathway, phosphorylating unc-52-like kinase-1 (ULK1) at Ser317, and AMPK/mammalian target of rapamycin (mTOR)pathway, dephosphorylating the inhibitory site of ULK1 (Ser757) (DeBosch et al., 2016; Mayer et al., 2016). Under HG conditions, autophagy inhibition has been observed in peritoneal mesothelial cells and mouse models, with reduction in the expression of light chain 3 (LC3)-II, p62, and Beclin-1; contrastingly, 1,25(OH)2D3 alleviates autophagy inhibition in PMCs through the mTOR pathway (Yang et al., 2017). Increasing evidence has shown that regulation of autophagy through the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling contributes to the occurrence and pathological progression of diabetic nephropathy and PF (Li et al., 2016b; Lu et al., 2019; Yang et al., 2020a; Jia et al., 2022). In this research, treatment with the mTOR inhibitor rapamycin (RAPA) and PI3K inhibitor LY294002 activated autophagy and alleviated PF *in vivo* and *in vitro*, thereby upregulating E-cadherin and zonula occludens-1 (ZO-1) and downregulating alpha-smooth muscle actin (α-SMA) and ferroptosis suppressor protein 1 (Jia et al., 2022). In addition, RAPA, which can induce autophagy by inhibiting

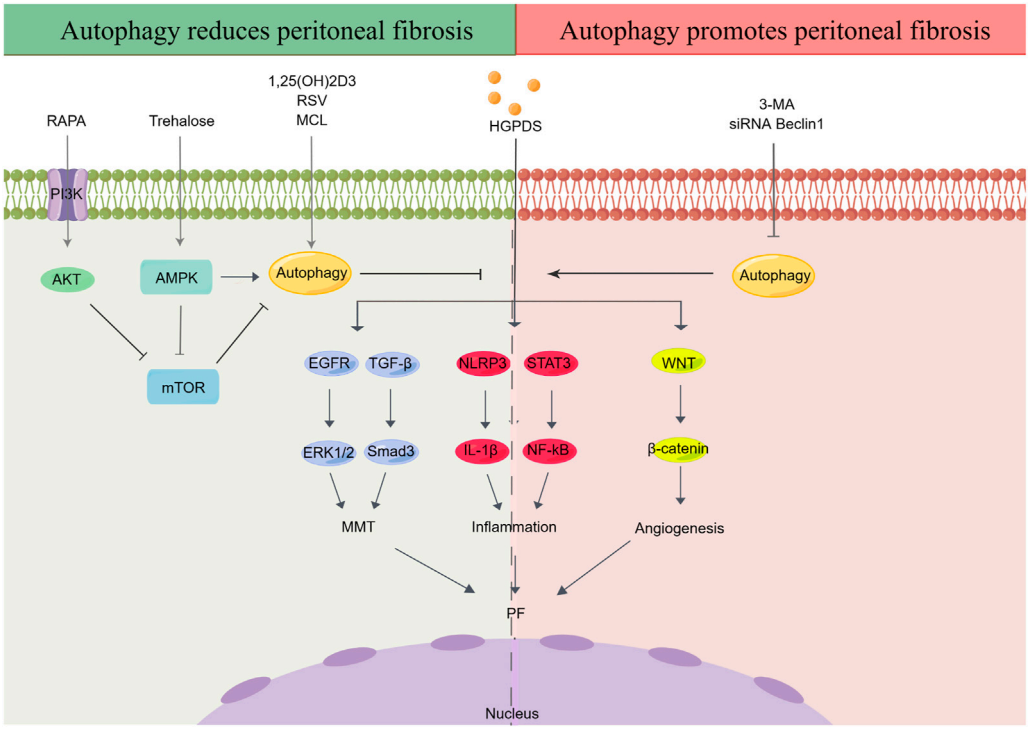


FIGURE 1
Effect of autophagy in peritoneal fibrosis. HGPDS contributes to MMT, inflammation and angiogenesis in peritoneal mesothelial cells, eventually cause PF. Some studies suggest that activation of autophagy reduces PF, whereas some evidences demonstrate that autophagy promotes PF. RAPA: rapamycin, RSV: resveratrol, MCL: michelilide, HGPDS: high-glucose peritoneal dialysis solution, 3-MA: 3-methyladenine, PI3K: phosphatidylinositide 3-kinases, AMPK: AMP-activated protein kinase, mTOR: mammalian target of rapamycin, EGFR: epidermal growth factor receptor, ERK1/2: extracellular signal-regulated kinase 1/2, TGF-β: transforming growth factor-β, NLRP3: nod-like receptor 3, IL-1β: interleukin-1β, STAT3: signal transducer and activator of transcription 3, NF-κB: nuclear factor kappa-B, MMT: mesothelial-mesenchymal transition.

MTORC1 expression, relieved peritoneal thickening, angiogenesis, lymphangiogenesis, MMT, and endothelial-to-mesenchymal transition (Endo-MT) and improved UF in a mouse PD model (González-Mateo et al., 2015). Finally, micheliolide (MCL), a natural guaianolide sesquiterpene lactone, which promoted autophagy in db/db mice at a low dose, inhibited TGF-β1-induced ECM accumulation by activating autophagy in PF mouse models and the HPMC cell line (HMrSV5) (Zhong et al., 2018; Li et al., 2019b).

Limited evidence has demonstrated that autophagy promotes PF. Apigenin, a dietary flavonoid synthesized in multiple plants, effectively inhibits PF in a HG-induced mouse model, accompanied by a corresponding alteration of autophagy biomarkers (Zhang et al., 2018a). Moreover, significant activation of autophagy was observed in the PMCs of both two PF rat models induced by PDS and chlorhexidine gluconate (CG) (Shi et al., 2021). However, in above PF rat models and cultured HPMCs, treatment with 3-MA effectively delayed MMT and prevented PF by TGF-β/Smad3 signaling pathway and alleviated peritoneal angiogenesis by downregulation of β-catenin signaling pathway (Shi et al., 2021). Autophagy inhibition significantly reduced MMT, fibrosis, and apoptosis in HPMCs (Wu et al., 2018)(Table 1).

Similar dual characteristics of autophagy have been demonstrated in renal (Liang et al., 2022) and hepatic fibrosis (Sun et al., 2021; Hou et al., 2022). The effect of autophagy activation in the process of PF is complex and multifactorial, and its molecular impact may vary from specific targets in autophagy regulation. Furthermore, different experimental PF models, cell categories, drugs, doses and timing of autophagy inducers, and the diversified molecular mechanisms could result in varying effects of autophagy on PF. It is generally accepted that autophagy functions differently in diverse diseases and at different stages of the same disease. Over-activation of autophagy promotes fibrosis of multiple organs, whereas inhibition of autophagy aggravates cell damage and promotes the occurrence of PF. Nevertheless, further studies are needed to explore whether the different factors mediating autophagy play different roles at different stages of PF. Autophagy activation is usually considered effective in acute pathological damage to maintain cell homeostasis. In contrast, sustained autophagy induced by some chronic diseases may be harmful, causing apoptosis by damaging important organelles.

Furthermore, mitophagy may be involved in PF. With the production of reactive oxygen species (ROS), mitochondrial DNA is more prone to mutations than nuclear DNA, which makes mitochondria more susceptible to damage. Thus, maintaining an intact population of mitochondria via quality control mechanisms, including mitophagy, is essential for cell survival under pathological stress conditions (Lemasters, 2005; Youle and Narendra, 2011). Many studies have shown that HPMCs stimulated with HGPDS can undergo oxidative stress, mitochondrial DNA damage, and even

apoptosis (Hung et al., 2014; Ramil-Gómez et al., 2021). However, insufficient or excessive autophagy of mitochondria results in the accumulation of damaged mitochondria, which eventually leads to the disruption of mitochondrial quality control and bioenergy metabolism and even cell death (Kubli and Gustafsson, 2012; Namba et al., 2014; Kawakami et al., 2015). The mitochondrial dysfunction subsequently participates in the occurrence and development of fibrosis (Li et al., 2020). Under long-term hypertonic and HGPDS, HPMCs exhibit progressive PF, and MMT of HPMCs caused by mitochondrial dysfunction is one of the possible mechanisms (Shin et al., 2017; Ramil-Gómez et al., 2021). Furthermore, metformin and other AMPK inhibitors could delay the phenotypic transition of PMCs and PF via modulating oxidative stress, suggesting that AMPK could be a novel therapeutic target to prevent PF. However, there is no direct evidence that mitophagy can inhibit the progression of PF, which requires further experimental proof (Shin et al., 2017).

2.2 Effect of autophagy in encapsulating peritoneal sclerosis

Autophagy may have a potential connection with EPS, a rare but severe complication of patients undergoing PD (Pepereke et al., 2022). EPS, a clinical syndrome characterized by the formation of a fibrous cocoon in the peritoneal cavity, has a high mortality rate of 42% 1 year after diagnosis (Brown et al., 2009). Although there are few treatment methods, and their efficacy is poor. Anti-inflammatory therapy with steroids and antifibrotic therapy with tamoxifen are most commonly used for treating EPS (Lo and Kawanishi, 2009; Garosi et al., 2013; Pepereke et al., 2022).

Recently, mTOR inhibitors (everolimus and sirolimus), widely used as immunosuppressive/antiproliferative agents in renal transplantation and oncology field, have been suggested as a novel treatment for EPS. Two *in vivo* experiments indicated that oral mTOR inhibitors (everolimus and sirolimus) significantly reduced the progression of PF, including peritoneal thickness, vascularity, and fibrosis score, in a rat model induced by CG (Duman et al., 2008; Ceri et al., 2012). Furthermore, mTOR inhibitors may protect the peritoneum from PF by inhibiting MMT, with an upregulation of the E-cadherin and downregulation of α-SMA (Aguilera et al., 2005). In addition, multiple clinical studies have proposed the therapeutic role of mTOR inhibitors in the management of EPS owing to the antifibrotic and anti-angiogenesis effects. Due to the rarity of EPS, most studies come from case reports rather than systematic research. In particular, Ghadimi et al. reviewed the effects of mTOR inhibitors (everolimus and sirolimus) in the therapy of EPS using 13 case reports (Ghadimi et al., 2016). In one-third of the patients with EPS, mTOR inhibitors were found to allay EPS and reduce mortality. Moreover, 5-aminoimidazole-4-carboxyamide ribonucleoside (AICAR), a classical AMPK agonist that reduces inflammation, fibrosis, and cellular ROS injury and promotes autophagy, inhibits postoperative adhesion formation *in vivo* and *in vitro* by inhibiting inflammation and oxidative stress response and accelerating peritoneal mesothelial cell repair (Wu et al., 2022).

The therapeutic effects and mechanism of autophagy against EPS have not been fully confirmed, and more evidence is needed.

3 Effect of autophagy in PD-related peritonitis

PF encompasses two synergistic actions: the fibrosis process itself and inflammation. These two processes are usually bidirectional, with one triggering another (Yáñez-Mó et al., 2003; Loureiro et al., 2011; Yoshizawa et al., 2015; Zhou et al., 2016). PF often progresses after acute and chronic PD-related inflammatory (Kobayashi et al., 2018). Thus, the effects of autophagy on PD-related peritonitis must be elucidated (Figure 2).

Recently, PD-related peritonitis, the common and serious complication of PD, has attracted increasing public attention. More than 40% of patients experience UF owing to PD-related peritonitis after 3 years of PD therapy (Baroni et al., 2012). Mild systemic inflammation is usually observed in patients with chronic kidney disease (Stenvinkel and Alvestrand, 2002). PD-related peritonitis can be primarily classified into infection-related and non-infectious peritonitis.

On the one hand, a single microorganism is the main cause of the infection-related peritonitis, with half of these infections come from gram-positive bacteria (Peterson et al., 1987; Golper et al., 1996; Gokal, 2002; Yung and Chan, 2012). According to the comprehensive recommendations on the prevention and treatment of PD-related peritonitis by the International Society for PD, appropriate and adequate antimicrobial treatment is still the most important and main therapy for infection-related peritonitis (Szeto and Li, 2019). However, despite apparent clinical remission of peritonitis, the inflammatory factors and fibrotic mediators persistently increased in the peritoneal cavity cause continuous stimulation to PMCs (Yung and Chan, 2012). In addition, evidence indicates that pro-inflammatory factors are continuously released for at least 6 weeks even after the clinical resolution of PD-related peritonitis (Lai et al., 2000; Lai et al., 2007). On the other hand, when repeatedly exposed to a non-physiological condition of HGPDS, PMCs raise an inflammatory response in the peritoneal cavity, which causes non-infectious peritonitis (Lai and Leung, 2010). Research has established that non-infectious peritonitis also results in PF, neoangiogenesis, and UF (Lai et al., 2000; Myers, 2004; De Vriese, 2005; Zareie et al., 2005; De Vriese et al., 2006; Leung et al., 2006; Aroeira et al., 2007; Guo et al., 2007; Lai et al., 2007; Leung et al., 2009).

3.1 Effect of autophagy in infection-related peritonitis

Several studies have suggested that autophagy has a strong relationship with both infection-related and non-infectious peritonitis, suggesting that autophagy might act as a novel therapeutic target for patients with PD-related peritonitis.

HPMCs are considered as the first barrier to prevent against invading pathogens in patients on PD. Autophagy plays a key role in innate immunity and cell homeostasis (Gutierrez et al., 2004; Nakagawa et al., 2004; Thurston et al., 2009; Sir et al., 2010; Anand et al., 2011). After bacterial invasion, autophagy is activated, degrading bacteria via the autophagy-lysosomal pathway, thus protecting the host against pathogen colonization (Ligeon et al., 2011; Choi et al., 2013). Autophagy activation plays a critical role in the recovery of mesothelium following acute inflammation in a rat model by removing damaged cytoplasmic organelles (Balogh et al., 2015). Lipopolysaccharide (LPS), the active constituent of endotoxins in gram-negative bacteria, is a potential

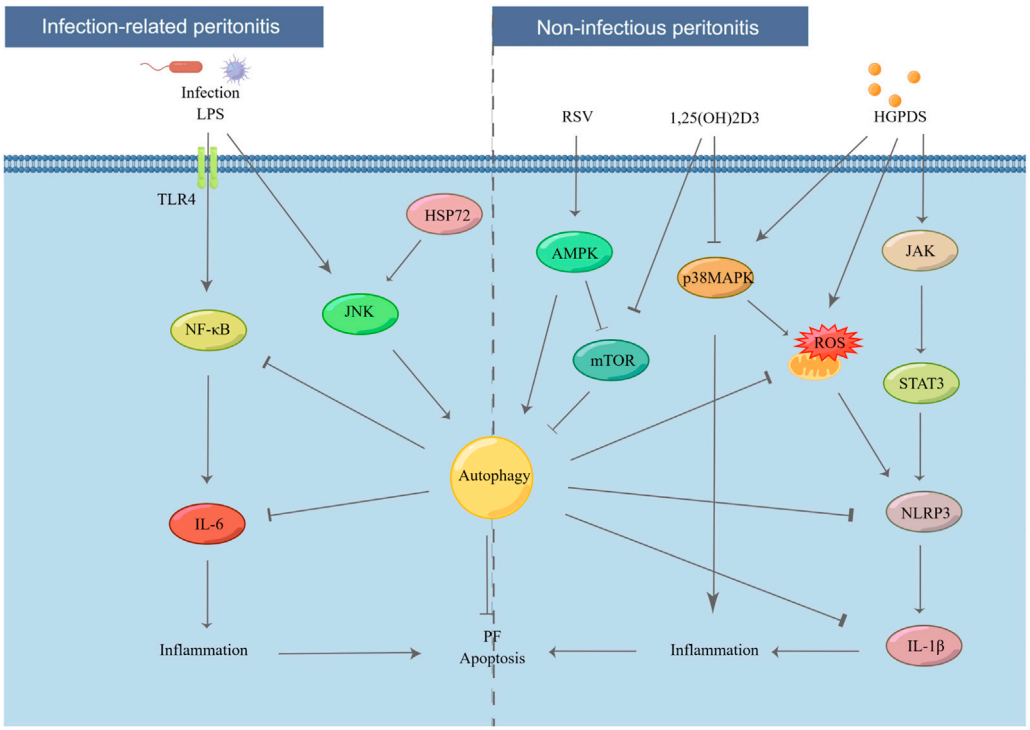


FIGURE 2
Effect of autophagy in PD-related peritonitis. Infectious factors lead to infection-related peritonitis via NF-κB/IL-6 pathway. In addition, under long-term stimulation of HGPDS, HPMCs suffer from non-infectious peritonitis by NLRP3/IL-1β pathway. However, these processes are blocked by the activation of autophagy. LPS: lipopolysaccharide, TLR4: toll like receptor 4, IL-6: interleukin-6, JNK: c-Jun N-terminal kinase, HSP72: heat shock protein 72, p38 MAPK: p38 mitogen activated protein kinases, JAK: Janus kinase.

inducer of autophagy in PMCs and macrophages (Xu et al., 2007; Doyle et al., 2011; Meng et al., 2012). In particular, autophagy is induced by LPS in HMrSV5 in a dose- and time-dependent manner, as demonstrated by an increase in the expression of Beclin-1 and LC3-II, number of autophagic vacuoles, and intracellular bactericidal activity (Li et al., 2011). However, these processes in the peritoneal cavity are blocked by autophagy inhibitors, such as 3-MA, Beclin-1 siRNA, or wortmannin, via TLR4 signaling (Wang et al., 2013). A study suggested that heat shock protein 72 (HSP72) protects peritoneal mesothelial cells against LPS-induced mesothelial cell injury by activating c-Jun N-terminal kinase (JNK)-dependent autophagy and partially inhibiting apoptosis (Li et al., 2011). Furthermore, peroxisome proliferator-activated receptor-γ (PPAR-γ) may act as a potential therapeutic target for peritonitis (Zhang et al., 2018b). With the stimulation of LPS, upregulating the expression of nuclear factor kappa-B (NF-κB) activity, *ICAM-1*, and interleukin (IL)-6 was observed in rat PD models (Zhang et al., 2015). Although fungal peritonitis is rare compared to bacterial peritonitis, accounting for only 1%–12% of PD-related peritonitis (Chavada et al., 2011; Tobudic et al., 2013; Nadeau-Fredette and Bargman, 2015), it has higher morbidity and catheter-related mortality (Levallois et al., 2012; Li et al., 2016a; Giacobino et al., 2016; Xu et al., 2022). *Candida* species are the most common pathogens involved in most fungal peritonitis cases, with approximately 70%–90% frequency (Kazancioglu et al., 2010; Nadeau-Fredette and Bargman, 2015). In addition, scientific evidence suggests that caspase recruitment domain-containing protein 9 (Card9), an adapter protein, protects against fungal peritonitis by regulating the mucosa-associated lymphoid tissue lymphoma translocation 1 (Malt1)-mediated activation of autophagy in macrophages (Xu et al., 2022).

3.2 Effect of autophagy in non-infectious peritonitis

Autophagy also contributes to non-infectious peritonitis. PMs develop chronic inflammation during long-term PD as a result of bioincompatible PDS with low pH, high concentrations of glucose, and high osmolality (Hayat et al., 2021). IL-6 is a crucial inflammatory factor in patients with PD, and repeated inflammatory activation can lead to fibrotic injury in the peritoneum via the JAK/Signal Transducer And Activator Of Transcription 3 (STAT3) signaling pathway (Fielding et al., 2014; Xiao et al., 2017; Yang et al., 2020b; Yang et al., 2021). Moreover, evidence indicates that the upregulation of IL-17 family cytokines protects the host from infections and chronic inflammation during PD-associated peritoneal injury (Schroder and Tschopp, 2010; Helmke et al., 2021). Long-term continuous exposure to HG PDS leads to mitochondrial ROS production in HPMCs, which subsequently triggers NLRP3 inflammasome activation and IL-1β secretion (Witowski et al., 2001; Yáñez-Mó et al., 2003; Schroder and Tschopp, 2010; Li et al., 2017). However, ROS can induce autophagy, a self-clearance process that reduces oxidative damage via engulfing and

TABLE 1 Autophagy in peritoneal fibrosis.

Patients	Animals	Cells	Perineal fibrosis models	Fibrosis	Drugs/compound to modulate autophagy	Autophagy activity	References
NO	-	HMrSV5	HGPDS	↓	RSV,3-MA, ATG5 siRNA, Beclin1 siRNA	↑	Li et al. (2017)
NO	C57BL/6 mice	-	CG	↓	Trehalose	↑	Miyake et al. (2020)
NO	Kunming Mice	HPMCs	HGPDS	↓	$1,25(OH)_2D_3$	↑	Yang et al. (2017)
NO	Rats	Rat PMCs	HGPDS	↓	PI3K inhibitor LY294002 and rapamycin	↑	Jia et al. (2022)
NO	C57BL/6 mice	Patients MCs	HGPDS	↓	Rapamycin	↑	González-Mateo et al. (2015)
NO	C57BL/6 mice	HMrSV5	HGPDS	↓	MCL, rapamycin, ATG7 siRNA	↑	Li et al. (2019b)
NO	BALB/c mice	Mice MCs	HGPDS	↓	Apigenin	↓	Zhang et al. (2018a)
NO	Sprague-Dawley rats	HPMCs	HGPDS and CG	↓	3-MA	↓	Shi et al. (2021)
YES	-	MET-5A	HGPDS	↓	Beclin1 siRNA	↓	Wu et al. (2018)

degrading the oxidized substances (Wu et al., 2016; Li et al., 2021). Timely initiation of autophagy could block the activation of NLRP3-IL-1β signaling, providing a theoretical basis for a potential therapeutic strategy to suspend inflammation and PF (Li et al., 2017). Resveratrol-induced mitophagy/autophagy by the AMPK pathway may protect against ROS-NLRP3-mediated inflammatory injury in HPMCs (Wu et al., 2016). Research has conclusively demonstrated that HG treatment leads to apoptosis, ROS production, inflammatory activation, and MMT in PMCs via the MAPK/P38 signaling pathway, while 1,25(OH) 2D3 blocks the above-mentioned changes (Zhang et al., 2012; Yang et al., 2016). A recent study found that 1,25(OH)2D3 plays a protective role in HG-induced peritoneal injury by increasing autophagy, possibly via the mTOR signaling pathway (Yang et al., 2017). However, opposing views exist. The blockade of autophagy with 3-MA considerably reduced the inflammatory response and macrophage infiltration via the STAT3/NF-κB pathway in both PDS and CG-induced rat models (Shi et al., 2021).

4 Conclusion and perspective

In the last decades, many researchers have suggested a strong relationship between the process of PF and autophagy, but the roles and potential mechanisms are not completely clear, probably due to the versatility of autophagy.

Owing to the continuous research on the role of autophagy in the prevention and treatment of diseases, some drugs targeting autophagy have been used for the treatment of cancer, infection-related diseases, and neuropathy. Meanwhile, drugs targeting autophagy, such as mTOR inhibitors (evolutionus and sirolimus), have also been used in the treatment of EPS. However, most of the clinical data on EPS comes from case reports, while the registries and treatments of EPS provide low-quality evidence owing to its rarity, making it difficult to carry out large-scale systematic research on the role of autophagy in EPS. Histone deacetylase (HDAC) inhibitors or lysosomal acidification inhibitors (such as chloroquine and hydroxychloroquine) may also be used for the regulation of autophagy and are often used in immunotherapy in kidney diseases. However, there is less clinical evidence in PF or peritonitis.

There are several potential aspects of autophagy research in PF. First, the specific mechanism of autophagy in PF and peritonitis needs to be clarified. Selective autophagy, such as mitophagy and macrophagy, may also be involved in PF. Additionally, potential autophagy markers are also attractive. For example, owing to the objective advantages such as simple operation, small invasion, and fast recovery, the 'pull technology' for PD catalyst removal is more popular among doctors and patients than the traditional open surgery, which makes it hard to obtain tissue samples. With the simpler, more economical, easier to obtain, and repeatable advantages, peritoneal dialysis fluid, rather than peritoneal tissue, can continuously and remarkably detect autophagy activity and peritoneal fibrosis. Additionally, the application of intervention drugs is equally important. Some autophagy activators can be added to peritoneal dialysis fluid for preventing peritoneal complications. Effective measures should be implemented to promote the transformation of experimental data into clinical practice. Autophagy modulators that can be used to develop novel clinical therapeutic strategies for allaying PF need to be developed to reveal the mechanism of autophagy pathways in PF.

Author contributions

HS, and JY designed and wrote the manuscript. RZ, NA, XC and HY revised the manuscript. HS and CY designed the figures. HS, NA, CY, C-wY, and HL obtained funding. All authors contributed to the article and approved the submitted version

Funding

This work was supported by the Funds for the National Natural Science Foundation of China (grant numbers 81700627, 81670654,

and 81974095), National Clinical Key Specialty Construction Project (Institute of Nephrology, Affiliated Hospital of Guangdong Medical University), Science and Technology Innovation Strategy of Guangdong Province (grant numbers 2019A1515010678 and 2018A030313231), Science and Technology Planning Project of Zhanjiang City (grant numbers 2021A05067 and 2021A05083), and Science Foundation of Guangdong Medical University (grant number GDMUM2020009).

Acknowledgments

We thank Editage (www.editage.cn) for English language editing and Figdraw (www.figdraw.com) for figure drawing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Aguilera, A., Aroeira, L. S., Ramirez-Huesca, M., Perez-Lozano, M. L., Cirugeda, A., Bajo, M. A., et al. (2005). Effects of rapamycin on the epithelial-to-mesenchymal transition of human peritoneal mesothelial cells. *Int. J. Artif. Organs* 28, 164–169. doi:10.1177/039139880502800213

Anand, P. K., Tait, S. W., Lamkanfi, M., Amer, A. O., Nunez, G., Pagès, G., et al. (2011). TLR2 and RIP2 pathways mediate autophagy of Listeria monocytogenes via extracellular signal-regulated kinase (ERK) activation. *J. Biol. Chem.* 286, 42981–42991. doi:10.1074/jbc.M111.310599

Araya, J., Kojima, J., Takasaka, N., Ito, S., Fujii, S., Hara, H., et al. (2013). Insufficient autophagy in idiopathic pulmonary fibrosis. *Am. J. Physiol. Lung Cell Mol. Physiol.* 304, L56–L69. doi:10.1152/ajplung.00213.2012

Aroeira, L. S., Aguilera, A., Sánchez-Tomero, J. A., Bajo, M. A., Del, P. G., Jiménez-Heffernan, J. A., et al. (2007). Epithelial to mesenchymal transition and peritoneal membrane failure in peritoneal dialysis patients: Pathologic significance and potential therapeutic interventions. *J. Am. Soc. Nephrol.* 18, 2004–2013. doi:10.1681/ASN.2006111292

Bajo, M. A., Del, P. G., and Teitelbaum, I. (2017). Peritoneal membrane preservation. *Semin. Nephrol.* 37, 77–92. doi:10.1016/j.semnephrol.2016.10.009

Balogh, P., Szabó, A., Likó, I., and Patócs, A. (2015). Autophagy may contribute to the recovery of rat mesothelium following acute inflammation *in vivo*. *Cell Tissue Res.* 362, 127–137. doi:10.1007/s00441-015-2188-6

Balzer, M. S. (2020). Molecular pathways in peritoneal fibrosis. *Cell Signal* 75, 109778. doi:10.1016/j.cellsig.2020.109778

Baroni, G., Schuinski, A., de Moraes, T. P., Meyer, F., and Pecoits-Filho, R. (2012). Inflammation and the peritoneal membrane: Causes and impact on structure and function during peritoneal dialysis. *Mediat. Inflamm.*, 2012, 912595, doi:10.1155/2012/912595

Brown, M. C., Simpson, K., Kerssens, J. J., and Mactier, R. A. (2009). Encapsulating peritoneal sclerosis in the new millennium: A national cohort study. *Clin. J. Am. Soc. Nephrol.* 4, 1222–1229. doi:10.2215/CJN.01260209

Cabrera, S., Maciel, M., Herrera, I., Nava, T., Vergara, F., Gaxiola, M., et al. (2015). Essential role for the ATG4B protease and autophagy in bleomycin-induced pulmonary fibrosis. *Autophagy* 11, 670–684. doi:10.1080/15548627.2015.1034409

Ceri, M., Unverdi, S., Dogan, M., Unverdi, H., Karaca, G., Kocak, G., et al. (2012). Effect of sirolimus on the regression of peritoneal sclerosis in an experimental rat model. *Int. Urol. Nephrol.* 44, 977–982. doi:10.1007/s11255-012-0167-3

Chang, T. C., Hsu, M. F., and Wu, K. K. (2015). High glucose induces bone marrow-derived mesenchymal stem cell senescence by upregulating autophagy. *PLoS One* 10, e0126537. doi:10.1371/journal.pone.0126537

Chavada, R., Kok, J., van Hal, S., and Chen, S. C. (2011). Seeking clarity within cloudy effluents: Differentiating fungal from bacterial peritonitis in peritoneal dialysis patients. *PLoS One* 6, e28247. doi:10.1371/journal.pone.0028247

Choi, A. M., Ryter, S. W., and Levine, B. (2013). Autophagy in human health and disease. *N. Engl. J. Med.* 368, 1845–1846. doi:10.1056/NEJMc1303158

Dai, R., Zhang, L., Jin, H., Wang, D., Cheng, M., Sang, T., et al. (2022). Autophagy in renal fibrosis: Protection or promotion? *Front. Pharmacol.* 13, 963920. doi:10.3389/fphar.2022.963920

Davies, S. J., Bryan, J., Phillips, L., and Russell, G. I. (1996). Longitudinal changes in peritoneal kinetics: The effects of peritoneal dialysis and peritonitis. *Nephrol. Dial. Transpl.* 11, 498–506. doi:10.1093/oxfordjournals.ndt.a027318

De Vriese, A. S. (2005). The john F. Maher recipient lecture 2004: Rage in the peritoneum. *Perit. Dial. Int.* 25, 8–11. doi:10.1177/089686080502500102

De Vriese, A. S., Tilton, R. G., Mortier, S., and Lameire, N. H. (2006). Myofibroblast transdifferentiation of mesothelial cells is mediated by RAGE and contributes to peritoneal fibrosis in uraemia. *Nephrol. Dial. Transpl.* 21, 2549–2555. doi:10.1093/ndt/gfl271

DeBosch, B. J., Heitmeier, M. R., Mayer, A. L., Higgins, C. B., Crowley, J. R., Kraft, T. E., et al. (2016). Trehalose inhibits solute carrier 2A (SLC2A) proteins to induce autophagy and prevent hepatic steatosis. *Sci. Signal* 9, a21. doi:10.1126/scisignal.aac5472

Di Paolo, N., and Sacchi, G. (2000). Atlas of peritoneal histology. *Perit. Dial. Int.* 20 (3), S5–S96.

Doyle, A., Zhang, G., Abdel, F. E., Eissa, N. T., and Li, Y. P. (2011). Toll-like receptor 4 mediates lipopolysaccharide-induced muscle catabolism via coordinate activation of ubiquitin-proteasome and autophagy-lysosome pathways. *Faseb J.* 25, 99–110. doi:10.1096/fj.10-164152

Duman, S., Bozkurt, D., Sipahi, S., Sezak, M., Ozkan, S., Ertilav, M., et al. (2008). Effects of everolimus as an antiproliferative agent on regression of encapsulating peritoneal sclerosis in a rat model. *Adv. Perit. Dial.* 24, 104–110.

Fan, Y., Mao, R., and Yang, J. (2013). NF-κB and STAT3 signaling pathways collaboratively link inflammation to cancer. *Protein Cell* 4, 176–185. doi:10.1007/s13238-013-2084-3

Fielding, C. A., Jones, G. W., McLoughlin, R. M., McLeod, L., Hammond, V. J., Uceda, J., et al. (2014). Interleukin-6 signaling drives fibrosis in unresolved inflammation. *Immunity* 40, 40–50. doi:10.1016/j.immuni.2013.10.022

Garosi, G., Mancianti, N., Corciulo, R., La Milia, V., and Virga, G. (2013). Encapsulating peritoneal sclerosis. *J. Nephrol.* 26 (21), 177–187. doi:10.5301/JN.2013.11640

Ghadimi, M., Dashti-Khavidaki, S., and Khalili, H. (2016). mTOR inhibitors for management of encapsulating peritoneal sclerosis: a review of literatures. *Ren. Fail* 38, 1574–1580. doi:10.1080/0886022X.2016.1209026

Giacobino, J., Montelli, A. C., Barretti, P., Bruder-Nascimento, A., Caramori, J. T., Barbosa, L., et al. (2016). Fungal peritonitis in patients undergoing peritoneal dialysis (PD) in Brazil: Molecular identification, biofilm production and antifungal susceptibility of the agents. *Med. Mycol.* 54, 725–732. doi:10.1093/mmy/myw030

Gokal, R. (2002). Peritoneal dialysis in the 21st century: An analysis of current problems and future developments. *J. Am. Soc. Nephrol.* 13 (1), S104–S115. doi:10.1681/asn.v13suppl_1s104

Golper, T. A., Brier, M. E., Bunke, M., Schreiber, M. J., Bartlett, D. K., Hamilton, R. W., et al. (1996). Risk factors for peritonitis in long-term peritoneal dialysis: The network 9 peritonitis and catheter survival studies. Academic subcommittee of the steering committee of the network 9 peritonitis and catheter survival studies. *Am. J. Kidney Dis.* 28, 428–436. doi:10.1016/s0272-6386(96)90502-8

González-Mateo, G. T., Aguirre, A. R., Loureiro, J., Abensur, H., Sandoval, P., Sánchez-Tomero, J. A., et al. (2015). Rapamycin protects from type-I peritoneal membrane failure inhibiting the angiogenesis, lymphangiogenesis, and endo-MT. *Biomed. Res. Int.* 2015, 989560. doi:10.1155/2015/989560

Guo, H., Leung, J. C., Lam, M. F., Chan, L. Y., Tsang, A. W., Lan, H. Y., et al. (2007). Smad7 transgene attenuates peritoneal fibrosis in uremic rats treated with peritoneal dialysis. *J. Am. Soc. Nephrol.* 18, 2689–2703. doi:10.1681/ASN.2007010121

Gutierrez, M. G., Master, S. S., Singh, S. B., Taylor, G. A., Colombo, M. I., and Deretic, V. (2004). Autophagy is a defense mechanism inhibiting BCG and *Mycobacterium tuberculosis* survival in infected macrophages. *Cell* 119, 753–766. doi:10.1016/j.cell.2004.11.038

Hayat, A., Collins, J., and Saweirs, W. (2021). Study of early complications associated with peritoneal dialysis catheters: An analysis of the New Zealand peritoneal dialysis registry data. *Int. Urol. Nephrol.* 53, 1705–1711. doi:10.1007/s11255-021-02785-y

Helmke, A., Hüsing, A. M., Gaedcke, S., Brauns, N., Balzer, M. S., Reinhardt, M., et al. (2021). Peritoneal dialysate-range hypertonic glucose promotes T-cell IL-17 production that induces mesothelial inflammation. *Eur. J. Immunol.* 51, 354–367. doi:10.1002/eji.202048733

Hou, L. S., Zhang, Y. W., Li, H., Wang, W., Huan, M. L., Zhou, S. Y., et al. (2022). The regulatory role and mechanism of autophagy in energy metabolism-related hepatic fibrosis. *Pharmacol. Ther.* 234, 108117. doi:10.1016/j.pharmthera.2022.108117

Howell, M., Walker, R. C., and Howard, K. (2019). Cost effectiveness of dialysis modalities: A systematic review of economic evaluations. *Appl. Health Econ. Health Policy* 17, 315–330. doi:10.1007/s40258-018-00455-2

Hung, K. Y., Liu, S. Y., Yang, T. C., Liao, T. L., and Kao, S. H. (2014). High-dialysate-glucose-induced oxidative stress and mitochondrial-mediated apoptosis in human peritoneal mesothelial cells. *Oxid. Med. Cell Longev.*, 2014, 642793, doi:10.1155/2014/642793

Jia, M., Qiu, H., Lin, L., Zhang, S., Li, D., and Jin, D. (2022). Inhibition of PI3K/AKT/mTOR signalling pathway activates autophagy and suppresses peritoneal fibrosis in the process of peritoneal dialysis. *Front. Physiol.* 13, 778479. doi:10.3389/fphys.2022.778479

Kawakami, T., Gomez, I. G., Ren, S., Hudkins, K., Roach, A., Alpers, C. E., et al. (2015). Deficient autophagy results in mitochondrial dysfunction and FSGS. *J. Am. Soc. Nephrol.* 26, 1040–1052. doi:10.1681/ASN.2013111202

Kazancioglu, R., Kirikci, G., Albaz, M., Dolgun, R., and Ekiz, S. (2010). Fungal peritonitis among the peritoneal dialysis patients of four Turkish centres. *J. Ren. Care* 36, 186–190. doi:10.1111/j.1755-6686.2010.00193.x

Kitterer, D., Latus, J., Ulmer, C., Fritz, P., Biegger, D., Ott, G., et al. (2015). Activation of nuclear factor of activated T cells 5 in the peritoneal membrane of uremic patients. *Am. J. Physiol. Ren. Physiol.* 308, F1247–F1258. doi:10.1152/ajprenal.00617.2014

Klionsky, D. J., Petroni, G., Amaravadi, R. K., Baehrecke, E. H., Ballabio, A., Boya, P., et al. (2021). Autophagy in major human diseases. *Embo J.* 40, e108863. doi:10.15252/embj.2021108863

Kobayashi, T., Noguchi, T., Saito, K., Shirasaki, F., Kita, H., Nagata, M., et al. (2018). Eosinophilic inflammation in peritoneal fibrosis patients undergoing peritoneal dialysis. *Contrib. Nephrol.* 196, 1–4. doi:10.1159/000485689

Krediet, R. T., and Struijk, D. G. (2013). Peritoneal changes in patients on long-term peritoneal dialysis. *Nat. Rev. Nephrol.* 9, 419–429. doi:10.1038/nrneph.2013.99

Krediet, R. T. (2018). Ultrafiltration failure is a reflection of peritoneal alterations in patients treated with peritoneal dialysis. *Front. Physiol.* 9, 1815. doi:10.3389/fphys.2018.01815

Kubli, D. A., and Gustafsson, Å. B. (2012). Mitochondria and mitophagy: The yin and yang of cell death control. *Circ. Res.* 111, 1208–1221. doi:10.1161/CIRCRESAHA.112.265819

Lai, K. N., Lai, K. B., Lam, C. W., Chan, T. M., Li, F. K., and Leung, J. C. (2000). Changes of cytokine profiles during peritonitis in patients on continuous ambulatory peritoneal dialysis. *Am. J. Kidney Dis.* 35, 644–652. doi:10.1016/s0272-6386(00)70011-4

Lai, K. N., and Leung, J. C. (2010). Inflammation in peritoneal dialysis. *Nephron Clin. Pract.* 116, c11–c18. doi:10.1159/000314544

Lai, K. N., Tang, S. C., and Leung, J. C. (2007). Mediators of inflammation and fibrosis. *Perit. Dial. Int.* 27 (2), S65–S71. doi:10.1177/089686080702702s12

Lemasters, J. J. (2005). Selective mitochondrial autophagy, or mitophagy, as a targeted defense against oxidative stress, mitochondrial dysfunction, and aging. *Rejuvenation Res.* 8, 3–5. doi:10.1089/rej.2005.8.3

Leung, J. C., Chan, L. Y., Tang, S. C., Chu, K. M., and Lai, K. N. (2006). Leptin induces TGF-beta synthesis through functional leptin receptor expressed by human peritoneal mesothelial cell. *Kidney Int.* 69, 2078–2086. doi:10.1038/sj.ki.5000409

Leung, J. C., Lam, M. F., Tang, S. C., Chan, L. Y., Tam, K. Y., Yip, T. P., et al. (2009). Roles of neutrophil gelatinase-associated lipocalin in continuous ambulatory peritoneal dialysis-related peritonitis. *J. Clin. Immunol.* 29, 365–378. doi:10.1007/s10875-008-9271-7

Levallois, J., Nadeau-Fredette, A. C., Labbé, A. C., Laverdière, M., Ouimet, D., and Vallée, M. (2012). Ten-year experience with fungal peritonitis in peritoneal dialysis patients: Antifungal susceptibility patterns in a north-American center. *Int. J. Infect. Dis.* 16, e41–e43. doi:10.1016/j.ijid.2011.09.016

Li, D., Ding, Z., Du, K., Ye, X., and Cheng, S. (2021). Reactive oxygen species as a link between antioxidant pathways and autophagy. *Oxid. Med. Cell Longev.* 2021, 5583215. doi:10.1155/2021/5583215

Li, D., Lu, Z., Xu, Z., Ji, J., Zheng, Z., Lin, S., et al. (2016). Spironolactone promotes autophagy via inhibiting PI3K/AKT/mTOR signalling pathway and reduce adhesive capacity damage in podocytes under mechanical stress. *Biosci. Rep.* 36, e00355. doi:10.1042/BSR20160086

Li, P. K., Szeto, C. C., Piraino, B., de Arteaga, J., Fan, S., Figueiredo, A. E., et al. (2016). ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit. Dial. Int.* 36, 481–508. doi:10.3747/pdi.2016.00078

Li, R., Du, J. H., Yao, G. M., Yao, Y., and Zhang, J. (2019). Autophagy: A new mechanism for regulating VEGF and PEDF expression in retinal pigment epithelium cells. *Int. J. Ophthalmol.* 12, 557–562. doi:10.18240/ijo.2019.04.05

Li, S., Peng, F., Gong, W., Wu, J., Wang, Y., Xu, Z., et al. (2019). Dimethylaminomicheliolide ameliorates peritoneal fibrosis through the activation of autophagy. *J. Mol. Med. Berl.* 97, 659–674. doi:10.1007/s00109-019-01757-1

Li, S., Zhou, Y., Fan, J., Cao, S., Cao, T., Huang, F., et al. (2011). Heat shock protein 72 enhances autophagy as a protective mechanism in lipopolysaccharide-induced peritonitis in rats. *Am. J. Pathol.* 179, 2822–2834. doi:10.1016/j.ajpath.2011.08.013

Li, X., Zhang, W., Cao, Q., Wang, Z., Zhao, M., Xu, L., et al. (2020). Mitochondrial dysfunction in fibrotic diseases. *Cell Death Discov.* 6, 80. doi:10.1038/s41420-020-00316-9

Li, X. Y., Wu, J., Luo, D., Chen, W. X., Zhu, G. L., Zhang, Y. X., et al. (2017). Effect of high glucose-based peritoneal dialysis fluids on NLRP3-IL-1β in human peritoneal mesothelial cells. *Beijing Da Xue Xue Bao Yi Xue Ban.* 49, 954–960.

Liang, S., Wu, Y. S., Li, D. Y., Tang, J. X., and Liu, H. F. (2022). Autophagy and renal fibrosis. *Aging Dis.* 13, 712–731. doi:10.14336/AD.2021.1027

Ligeon, L. A., Temime-Smaali, N., and Lafont, F. (2011). Ubiquitylation and autophagy in the control of bacterial infections and related inflammatory responses. *Cell Microbiol.* 13, 1303–1311. doi:10.1111/j.1462-5822.2011.01628.x

Liu, Q., Zhang, Y., Mao, H., Chen, W., Luo, N., Zhou, Q., et al. (2012). A crosstalk between the Smad and JNK signaling in the TGF-β-induced epithelial-mesenchymal transition in rat peritoneal mesothelial cells. *PLoS One* 7, e32009. doi:10.1371/journal.pone.0032009

Lo, W. K., and Kawanishi, H. (2009). Encapsulating peritoneal sclerosis-medical and surgical treatment. *Perit. Dial. Int.* 29 (2), S211–S214. doi:10.1177/089686080902902s43

Loureiro, J., Aguilera, A., Selgas, R., Sandoval, P., Albar-Vizcaíno, P., Pérez-Lozano, M. L., et al. (2011). Blocking TGF-β1 protects the peritoneal membrane from dialysate-induced damage. *J. Am. Soc. Nephrol.* 22, 1682–1695. doi:10.1681/ASN.2010111197

Lu, Q., Wang, W. W., Zhang, M. Z., Ma, Z. X., Qiu, X. R., Shen, M., et al. (2019). ROS induces epithelial-mesenchymal transition via the TGF-β1/PI3K/Akt/mTOR pathway in diabetic nephropathy. *Exp. Ther. Med.* 17, 835–846. doi:10.3892/etm.2018.7014

Lu, X., Fan, Q., Xu, L., Li, L., Yue, Y., Xu, Y., et al. (2015). Ursolic acid attenuates diabetic mesangial cell injury through the up-regulation of autophagy via miRNA-21/PTEN/Akt/mTOR suppression. *PLoS One* 10, e0117400. doi:10.1371/journal.pone.0117400

Margetts, P. J., Bonniaud, P., Liu, L., Hoff, C. M., Holmes, C. J., West-Mays, J. A., et al. (2005). Transient overexpression of TGF-{beta}1 induces epithelial mesenchymal transition in the rodent peritoneum. *J. Am. Soc. Nephrol.* 16, 425–436. doi:10.1681/ASN.2004060436

Masola, V., Bonomini, M., Borrelli, S., Di Liberato, L., Vecchi, L., Onisto, M., et al. (2022). Fibrosis of peritoneal membrane as target of new therapies in peritoneal dialysis. *Int. J. Mol. Sci.* 23, 4831. doi:10.3390/ijms23094831

Matsuo, H., Tamura, M., Kabashima, N., Serino, R., Tokunaga, M., Shibata, T., et al. (2006). Prednisolone inhibits hyperosmolarity-induced expression of MCP-1 via NF-kappaB in peritoneal mesothelial cells. *Kidney Int.* 69, 736–746. doi:10.1038/sj.ki.5000131

Mayer, A. L., Higgins, C. B., Heitmeier, M. R., Kraft, T. E., Qian, X., Crowley, J. R., et al. (2016). SLC2A8 (GLUT8) is a mammalian trehalose transporter required for trehalose-induced autophagy. *Sci. Rep.* 6, 38586. doi:10.1038/srep38586

Mehrotra, R., Chiu, Y. W., Kalantar-Zadeh, K., Bargman, J., and Vonesh, E. (2011). Similar outcomes with hemodialysis and peritoneal dialysis in patients with end-stage renal disease. *Arch. Intern Med.* 171, 110–118. doi:10.1001/archinternmed.2010.352

Meng, D., Li, Z., Wang, G., Ling, L., Wu, Y., and Zhang, C. (2018). Carvedilol attenuates liver fibrosis by suppressing autophagy and promoting apoptosis in hepatic stellate cells. *Biomed. Pharmacother.* 108, 1617–1627. doi:10.1016/j.biopha.2018.10.005

Meng, N., Zhao, J., Su, L., Zhao, B., Zhang, Y., Zhang, S., et al. (2012). A butyrolactone derivative suppressed lipopolysaccharide-induced autophagic injury through inhibiting the autoregulatory loop of p8 and p53 in vascular endothelial cells. *Int. J. Biochem. Cell Biol.* 44, 311–319. doi:10.1016/j.biocel.2011.11.001

Miyake, T., Sakai, N., Tamai, A., Sato, K., Kamikawa, Y., Miyagawa, T., et al. (2020). Trehalose ameliorates peritoneal fibrosis by promoting Snail degradation and inhibiting mesothelial-to-mesenchymal transition in mesothelial cells. *Sci. Rep.* 10, 14292. doi:10.1038/s41598-020-71230-4

Morishita, H., and Mizushima, N. (2019). Diverse cellular roles of autophagy. *Annu. Rev. Cell Dev. Biol.* 35, 453–475. doi:10.1146/annurev-cellbio-100818-125300

Myers, M. J. (2004). Leptin receptor signaling and the regulation of mammalian physiology. *Recent Prog. Horm. Res.* 59, 287–304. doi:10.1210/rp.59.1.287

Nadeau-Fredette, A. C., and Bargman, J. M. (2015). Characteristics and outcomes of fungal peritonitis in a modern North American cohort. *Perit. Dial. Int.* 35, 78–84. doi:10.3747/pdi.2013.00179

Nakagawa, I., Amano, A., Mizushima, N., Yamamoto, A., Yamaguchi, H., Kamimoto, T., et al. (2004). Autophagy defends cells against invading group A Streptococcus. *Science* 306, 1037–1040. doi:10.1126/science.1103966

Namba, T., Takabatake, Y., Kimura, T., Takahashi, A., Yamamoto, T., Matsuda, J., et al. (2014). Autophagic clearance of mitochondria in the kidney copes with metabolic acidosis. *J. Am. Soc. Nephrol.* 25, 2254–2266. doi:10.1681/ASN.2013090986

Padwal, M., Cheng, G., Liu, L., Boivin, F., Gangji, A. S., Brimble, K. S., et al. (2018). WNT signaling is required for peritoneal membrane angiogenesis. *Am. J. Physiol. Ren. Physiol.* 314, F1036–F1045. doi:10.1152/ajprenal.00497.2017

Patel, P., Sekiguchi, Y., Oh, K. H., Patterson, S. E., Kolb, M. R., and Margetts, P. J. (2010). Smad3-dependent and -independent pathways are involved in peritoneal membrane injury. *Kidney Int.* 77, 319–328. doi:10.1038/ki.2009.436

Pepereke, S., Shah, A. D., and Brown, E. A. (2022). Encapsulating peritoneal sclerosis: Your questions answered. *Perit. Dial. Int.* 43, 119–127. doi:10.1177/08968608221125606

Peterson, P. K., Matzke, G., and Keane, W. F. (1987). Current concepts in the management of peritonitis in patients undergoing continuous ambulatory peritoneal dialysis. *Rev. Infect. Dis.* 9, 604–612. doi:10.1093/clinids/9.3.604

Ramil-Gómez, O., Rodríguez-Carmona, A., Fernández-Rodríguez, J. A., Pérez-Fontán, M., Ferreiro-Hermida, T., López-Pardo, M., et al. (2021). Mitochondrial dysfunction plays a relevant role in Pathophysiology of peritoneal membrane damage induced by peritoneal dialysis. *Antioxidants (Basel)* 10, 447. doi:10.3390/antiox10030447

Sakai, N., Nakamura, M., Lipson, K. E., Miyake, T., Kamikawa, Y., Sagara, A., et al. (2017). Inhibition of CTGF ameliorates peritoneal fibrosis through suppression of fibroblast and myofibroblast accumulation and angiogenesis. *Sci. Rep.* 7, 5392. doi:10.1038/s41598-017-05624-2

Schroder, K., and Tschopp, J. (2010). The inflammasomes. *Cell* 140, 821–832. doi:10.1016/j.cell.2010.01.040

Shi, Y., Hu, Y., Wang, Y., Ma, X., Tang, L., Tao, M., et al. (2021). Blockade of autophagy prevents the development and progression of peritoneal fibrosis. *Front. Pharmacol.* 12, 724141. doi:10.3389/fphar.2021.724141

Shin, H. S., Ko, J., Kim, D. A., Ryu, E. S., Ryu, H. M., Park, S. H., et al. (2017). Metformin ameliorates the phenotype transition of peritoneal mesothelial cells and peritoneal fibrosis via a modulation of oxidative stress. *Sci. Rep.* 7, 5690. doi:10.1038/s41598-017-05836-6

Sir, D., Tian, Y., Chen, W. L., Ann, D. K., Yen, T. S., and Ou, J. H. (2010). The early autophagic pathway is activated by Hepatitis B virus and required for viral DNA replication. *Proc. Natl. Acad. Sci. U. S. A.* 107, 4383–4388. doi:10.1073/pnas.0911373107

Smit, W., Schouten, N., van den Berg, N., Langedijk, M. J., Struijk, D. G., Krediet, R. T., et al. (2004). Analysis of the prevalence and causes of ultrafiltration failure during long-term peritoneal dialysis: A cross-sectional study. *Perit. Dial. Int.* 24, 562–570. doi:10.1177/089686080402400616

Stenvinkel, P., and Alvestrand, A. (2002). Inflammation in end-stage renal disease: Sources, consequences, and therapy. *Semin. Dial.* 15, 329–337. doi:10.1046/j.1525-139x.2002.00083.x

Strippoli, R., Moreno-Vicente, R., Battistelli, C., Cicchini, C., Noce, V., Amicone, L., et al. (2016). Molecular mechanisms underlying peritoneal EMT and fibrosis. *Stem Cells Int.*, 2016, 3543678, doi:10.1155/2016/3543678

Sun, M., Tan, L., and Hu, M. (2021). The role of autophagy in hepatic fibrosis. *Am. J. Transl. Res.* 13, 5747–5757.

Szeto, C. C., and Li, P. K. (2019). Peritoneal dialysis-associated peritonitis. *Clin. J. Am. Soc. Nephrol.* 14, 1100–1105. doi:10.2215/CJN.14631218

Thurston, T. L., Ryzhakov, G., Bloor, S., von Muhlinen, N., and Randow, F. (2009). The TBK1 adaptor and autophagy receptor NDP52 restricts the proliferation of ubiquitin-coated bacteria. *Nat. Immunol.* 10, 1215–1221. doi:10.1038/ni.1800

Tobudic, S., Forstner, C., Schranz, H., Poeppl, W., Vychytil, A., and Burgmann, H. (2013). Comparative *in vitro* fungicidal activity of echinocandins against Candida albicans in peritoneal dialysis fluids. *Mycoses* 56, 623–630. doi:10.1111/myc.12079

Wang, J., Feng, X., Zeng, Y., Fan, J., Wu, J., Li, Z., et al. (2013). Lipopolysaccharide (LPS)-induced autophagy is involved in the restriction of *Escherichia coli* in peritoneal mesothelial cells. *BMC Microbiol.* 13, 255. doi:10.1186/1471-2180-13-255

Wei, M., Li, Z., and Yang, Z. (2014). Crosstalk between protective autophagy and NF-κB signal in high glucose-induced podocytes. *Mol. Cell Biochem.* 394, 261–273. doi:10.1007/s11010-014-2102-7

Witowski, J., Wisniewska, J., Korybalska, K., Bender, T. O., Breborowicz, A., Gahl, G. M., et al. (2001). Prolonged exposure to glucose degradation products impairs viability and function of human peritoneal mesothelial cells. *J. Am. Soc. Nephrol.* 12, 2434–2441. doi:10.1681/ASN.V12112434

Wu, J., Li, X., Zhu, G., Zhang, Y., He, M., and Zhang, J. (2016). The role of Resveratrol-induced mitophagy/autophagy in peritoneal mesothelial cells inflammatory injury via NLRP3 inflammasome activation triggered by mitochondrial ROS. *Exp. Cell Res.* 341, 42–53. doi:10.1016/j.yexcr.2016.01.014

Wu, J., Xing, C., Zhang, L., Mao, H., Chen, X., Liang, M., et al. (2018). Autophagy promotes fibrosis and apoptosis in the peritoneum during long-term peritoneal dialysis. *J. Cell Mol. Med.* 22, 1190–1201. doi:10.1111/jcmm.13393

Wu, Y., Duan, X., Gao, Z., Yang, N., and Xue, F. (2022). AICAR attenuates postoperative abdominal adhesion formation by inhibiting oxidative stress and promoting mesothelial cell repair. *PLoS One* 17, e0272928. doi:10.1371/journal.pone.0272928

Wynn, T. A., and Vannella, K. M. (2016). Macrophages in tissue repair, regeneration, and fibrosis. *Immunity* 44, 450–462. doi:10.1016/j.immuni.2016.02.015

Xiao, J., Gong, Y., Chen, Y., Yu, D., Wang, X., Zhang, X., et al. (2017). IL-6 promotes epithelial-to-mesenchymal transition of human peritoneal mesothelial cells possibly through the JAK2/STAT3 signaling pathway. *Am. J. Physiol. Ren. Physiol.* 313, F310–F318. doi:10.1152/ajprenal.00428.2016

Xu, Y., Jagannath, C., Liu, X. D., Sharafkhaneh, A., Kolodziejska, K. E., and Eissa, N. T. (2007). Toll-like receptor 4 is a sensor for autophagy associated with innate immunity. *Immunity* 27, 135–144. doi:10.1016/j.immuni.2007.05.022

Xu, Z., Qiao, S., Qian, W., Zhu, Y., Yan, W., Shen, S., et al. (2022). Card9 protects fungal peritonitis through regulating Malt1-mediated activation of autophagy in macrophage. *Int. Immunopharmacol.* 110, 108941. doi:10.1016/j.intimp.2022.108941

Yáñez-Mó, M., Lara-Pezzi, E., Selgas, R., Ramírez-Huesca, M., Domínguez-Jiménez, C., Jiménez-Heffernan, J. A., et al. (2003). Peritoneal dialysis and epithelial-to-mesenchymal transition of mesothelial cells. *N. Engl. J. Med.* 348, 403–413. doi:10.1056/NEJMoa020809

Yang, F., Qu, Q., Zhao, C., Liu, X., Yang, P., Li, Z., et al. (2020). Paecilomyces cicadae-fermented Radix astragali activates podocyte autophagy by attenuating PI3K/AKT/mTOR pathways to protect against diabetic nephropathy in mice. *Biomed. Pharmacother.* 129, 110479. doi:10.1016/j.biopha.2020.110479

Yang, L., Fan, Y., Zhang, X., Liu, J., and Ma, J. (2017). Effect of 1,25(OH)2D3 on high glucose-induced autophagy inhibition in peritoneum. *Mol. Med. Rep.* 16, 7080–7085. doi:10.3892/mmr.2017.7408

Yang, L., Wu, L., Du, S., Hu, Y., Fan, Y., and Ma, J. (2016). 1,25(OH)2D3 inhibits high glucose-induced apoptosis and ROS production in human peritoneal mesothelial cells via the MAPK/P38 pathway. *Mol. Med. Rep.* 14, 839–844. doi:10.3892/mmr.2016.5323

Yang, X., Bao, M., Fang, Y., Yu, X., Ji, J., and Ding, X. (2021). STAT3/HIF-1α signaling activation mediates peritoneal fibrosis induced by high glucose. *J. Transl. Med.* 19, 283. doi:10.1186/s12967-021-02946-8

Yang, X., Yan, H., Jiang, N., Yu, Z., Yuan, J., Ni, Z., et al. (2020). IL-6 trans-signaling drives a STAT3-dependent pathway that leads to structural alterations of the peritoneal membrane. *Am. J. Physiol. Ren. Physiol.* 318, F338–F353. doi:10.1152/ajprenal.00319.2019

Yeates, K., Zhu, N., Vonesh, E., Trpeski, L., Blake, P., and Fenton, S. (2012). Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada. *Nephrol. Dial. Transpl.* 27, 3568–3575. doi:10.1093/ndt/gfr674

Yoshizawa, H., Morishita, Y., Watanabe, M., Ishibashi, K., Muto, S., Kusano, E., et al. (2015). TGF-β_1-siRNA delivery with nanoparticles inhibits peritoneal fibrosis. *Gene Ther.* 22, 333–340. doi:10.1038/gt.2014.116

Youle, R. J., and Narendra, D. P. (2011). Mechanisms of mitophagy. *Nat. Rev. Mol. Cell Biol.* 12, 9–14. doi:10.1038/nrm3028

Yung, S., and Chan, T. M. (2012). Pathophysiological changes to the peritoneal membrane during PD-related peritonitis: The role of mesothelial cells. *Mediat. Inflamm.*, 2012, 484167, doi:10.1155/2012/484167

Zareie, M., Tangelder, G. J., ter Wee, P. M., Hekking, L. H., van Lambalgen, A. A., Keuning, E. D., et al. (2005). Beneficial effects of aminoguanidine on peritoneal microcirculation and tissue remodelling in a rat model of PD. *Nephrol. Dial. Transpl.* 20, 2783–2792. doi:10.1093/ndt/gfi138

Zhang, X., Wang, J., Fan, Y., Yang, L., Wang, L., and Ma, J. (2012). Zinc supplementation attenuates high glucose-induced epithelial-to-mesenchymal transition of peritoneal mesothelial cells. *Biol. Trace Elem. Res.* 150, 229–235. doi:10.1007/s12011-012-9451-4

Zhang, Y., Feng, J., Wang, Q., Zhao, S., Xu, J., and Li, H. (2018). PPAR-γ agonist rosiglitazone ameliorates peritoneal deterioration in peritoneal dialysis rats with LPS-induced peritonitis through up-regulation of AQP-1 and ZO-1. *Biosci. Rep.* 38. doi:10.1042/BSR20180009

Zhang, Y., Sun, Q., Li, X., Ma, X., Li, Y., Jiao, Z., et al. (2018). Apigenin suppresses mouse peritoneal fibrosis by down-regulating miR34a expression. *Biomed. Pharmacother.* 106, 373–380. doi:10.1016/j.biopha.2018.06.138

Zhang, Y. F., Zou, X. L., Wu, J., Yu, X. Q., and Yang, X. (2015). Rosiglitazone, a peroxisome proliferator-activated receptor (PPAR)-γ agonist, attenuates inflammation via NF-κB inhibition in lipopolysaccharide-induced peritonitis. *Inflammation* 38, 2105–2115. doi:10.1007/s10753-015-0193-2

Zhao, X. C., Livingston, M. J., Liang, X. L., and Dong, Z. (2019). Cell apoptosis and autophagy in renal fibrosis. *Adv. Exp. Med. Biol.* 1165, 557–584. doi:10.1007/978-981-13-8871-2_28

Zhao, X. D., Qin, R. H., Yang, J. J., Xu, S. S., Tao, H., Ding, X. S., et al. (2018). DNMT3A controls miR-200b in cardiac fibroblast autophagy and cardiac fibrosis. *Inflamm. Res.* 67, 681–690. doi:10.1007/s00011-018-1159-2

Zhong, J., Gong, W., Chen, J., Qing, Y., Wu, S., Li, H., et al. (2018). Micheliolide alleviates hepatic steatosis in db/db mice by inhibiting inflammation and promoting autophagy via PPAR-γ-mediated NF-κB and AMPK/mTOR signaling. *Int. Immunopharmacol.* 59, 197–208. doi:10.1016/j.intimp.2018.03.036

Zhou, Q., Bajo, M. A., Del, P. G., Yu, X., and Selgas, R. (2016). Preventing peritoneal membrane fibrosis in peritoneal dialysis patients. *Kidney Int.* 90, 515–524. doi:10.1016/j.kint.2016.03.040

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 08 June 2023
DOI 10.3389/fmed.2023.1166024

OPEN ACCESS

EDITED BY
Guoshuang Xu,
Fourth Military Medical University, China

REVIEWED BY
Evangelia Dounousi,
University of Ioannina, Greece
Wei Fang,
Shanghai Jiao Tong University, China

*CORRESPONDENCE
Yusheng Yu
✉ yuyusheng0509@126.com

†These authors have contributed equally to this work

RECEIVED 14 February 2023
ACCEPTED 16 May 2023
PUBLISHED 08 June 2023

CITATION
Cheng S, Zhou T, Yu L, Zhang Z, Chen Y, Zhang M, Cui J, Yu W, Zhou J and Yu Y (2023) Comparison between the influence of roxadustat and recombinant human erythropoietin treatment on blood pressure and cardio-cerebrovascular complications in patients undergoing peritoneal dialysis. *Front. Med.* 10:1166024. doi: 10.3389/fmed.2023.1166024

Comparison between the influence of roxadustat and recombinant human erythropoietin treatment on blood pressure and cardio-cerebrovascular complications in patients undergoing peritoneal dialysis

Shuiqin Cheng†, Tingting Zhou†, Le Yu†, Zhihong Zhang, Yunmin Chen, Man Zhang, Jingjing Cui, Wenxin Yu, Jian Zhou and Yusheng Yu*

Department of Nephrology, National Clinical Research Center of Kidney Disease, Jinling Hosptial, Nanjing University School of Medicine, Nanjing, China

Introduction: Roxadustat treatment in PD patients is equivalent to ESAs in increasing hemoglobin (Hb). But blood pressure, cardiovascular parameters, cardio-cerebrovascular complications and prognosis in the two groups before and after treatment has not been sufficiently discussed.

Methods: Sixty PD patients who were treated with roxadustat for renal anemia in our PD center recruited from June 2019 to April 2020 as roxadustat group. PD patients treated with rHuEPO were enrolled at a 1:1 ratio as rHuEPO group using the method of propensity score matching. Hb, blood pressure, cardiovascular parameters, cardio-cerebrovascular complications and prognosis were compared between the two group. All patients were followed up for at least 24 months.

Results: There were no significant differences in baseline clinical data or laboratory values between roxadustat group and rHuEPO group. After 24 months of follow-up, there was no significant difference in Hb levels ($p>0.05$). There were no significant changes in blood pressure, or the incidence of nocturnal hypertension before and after treatment in roxadustat group ($p>0.05$), while blood pressure significantly increased in rHuEPO group after treatment ($p<0.05$). Compared with roxadustat group after follow-up, rHuEPO group had a higher incidence of hypertension, the levels of cardiovascular parameters were worse and cardio-cerebrovascular complications had a higher incidence ($p<0.05$). Cox regression analysis showed age, systolic blood pressure, fasting blood glucose, and rHuEPO use before baseline were risk factors for cardio-cerebrovascular complications in PD patients, while treatment with roxadustat was a protective factor for cardiovascular and cerebrovascular complications.

Conclusion: Compared with rHuEPO, roxadustat had less influence on blood pressure or cardiovascular parameters, and it was associated with a lower risk of cardio-cerebrovascular complications in patients undergoing PD. Roxadustat has a cardio-cerebrovascular protective advantage in PD patients with renal anemia.

KEYWORDS

roxadustat, recombinant human erythropoietin, peritoneal dialysis, blood pressure, cardio-cerebrovascular complications

Introduction

Treatment with erythropoiesis-stimulating agents (ESAs) is an important therapy in peritoneal dialysis (PD) patients with renal anemia (1). When high doses of ESAs were used to raise serum hemoglobin (Hb) and hematocrit to achieve target values, the risk of cardio-cerebrovascular events and death increased (2, 3). Roxadustat is a hypoxia-inducing factor prolyl hydroxylase inhibitor (HIF-PHI), hypoxia-inducing factor (HIF) is a transcription factor that acts as the body's primary oxygen partial pressure sensor, coordinating red blood cell production and Hb response. Roxadustat can be used for the treatment of renal anemia in patients with chronic kidney disease had good effectiveness and safety (4–6).

Recent studies (7, 8) have shown that roxadustat treatment in PD patients is equivalent to ESAs in increasing Hb. A previous study (9) found that compared with ESAs, roxadustat had no significant difference in blood pressure or cardiovascular effects in patients with renal anemia in chronic kidney disease (CKD); however, these comparisons were rarely reported in PD patients.

In this study, we retrospectively compared the effect of roxadustat and recombinant human erythropoietin (rHuEPO) on blood pressure, cardiovascular parameters and cardio-cerebrovascular complications in PD patients with renal anemia.

Material and method

Study design

This retrospective study analyzed renal anemia patients who underwent PD from June 2019 to April 2020 in the PD center of the National Clinical Research Center of Kidney Diseases in China. We enrolled 60 PD patients who were treated with roxadustat via oral administration for renal anemia as roxadustat group and 60 PD patients who were treated with rHuEPO via subcutaneous injection in a 1:1 ratio as rHuEPO group. The two groups were matched 1:1 by clinical data and biochemical data using the method of propensity score matching. Follow-up was finished in March 2022. All patients were followed up for at least 24 months.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) 18–80 years old, (2) PD patients with renal anemia, and (3) the treatment with roxadustat or rHuEPO was not interrupted during follow-up.

The exclusion criteria were as follows: (1) history of cardiovascular and cerebrovascular diseases, (2) abnormal liver function, (3) anemia due to hematological system diseases, tumors, rheumatoid diseases, gastrointestinal hemorrhage, and so on, (4) the treatment with roxadustat or rHuEPO was interrupted during follow-up, (5) incomplete clinical data.

Treatment strategy

The initial dose of roxadustat in PD patients weighing between 45 and 60 kg was 100 mg; in patients weighing ≥60 kg, the initial dose was 120 mg three times a week according to the instructions. The follow-up dose of roxadustat was adjusted to keep the latter target Hb level. rHuEPO was used according to the degree of anemia, age, initial dose and dose adjustment based on package insert guidelines. The Hb target is 110 ~ 120 g/dL, but no more than 130 g/dL. When transferrin saturation (TSAT) ≤20% or (and) ferritin ≤100 μg/L, oral iron therapy was the first choice. Iron status was evaluated 1 to 3 months later. The target values of TSAT and serum ferritin were 20 ~ 50% and 100 ~ 500 μg /L, respectively. If the values of TSAT and serum ferritin were not up to the target level, we could treat the patients with intravenous iron. Patients with serum ferritin ≥500 μg/L should not receive iron supplements. Hb levels were monitored at baseline, 2 weeks, 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months and 24 months; blood pressure and cardiovascular parameters were monitored at baseline and after follow-up, and we observed the occurrence and prognosis of cardiovascular and cerebrovascular complications after follow-up.

Measurements and variable definitions

Measurements: (1) Clinical data included age, sex, weight, height, duration of dialysis, blood pressure, diabetes, medication history, PD modalities, and urine volume, (2) Biochemical data and cardiovascular parameters included serum, dialysate and urine urea nitrogen, creatinine and glucose, serum albumin, Hb, total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), ferritin, serum iron, total iron-binding capacity, hypersensitive C-reactive protein (CRP), fasting blood glucose, N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin T (TnT), troponin I (TnI) and interventricular septal (IVS), left ventricular posterior wall thickness (LVPW), cardiothoracic ratio (CTR), and left ventricular ejection fraction (LVEF). Laboratory tests were performed at each follow-up visit, echocardiography was performed annually, (3) Cardio-cerebrovascular complications included angina pectoris, myocardial infarction and other coronary heart diseases, heart failure caused by various reasons, atrial fibrillation, atrioventricular block and other arrhythmias, stroke (cerebral infarction, cerebral hemorrhage) which were recorded by diagnosis codes, laboratory and image studies, and (4) The changes in the abovementioned parameters were recorded at baseline and after treatment.

Variable definitions: Renal anemia is defined as anemia caused by impaired production of EPO from the kidney and a hemoglobin level of <110 g/L. The control rate of Hb means the proportion of Hb controlled between 110 and 130 g/L. Mean arterial pressure (MAP) is defined as diastolic blood pressure + 1/3 (systolic blood pressure - diastolic blood pressure), systolic blood pressure and diastolic blood

TABLE 1 Baseline characteristics of PD patients in the two groups.

	Roxadustat (*n* =60)	rHuEPO (*n* =60)	*p*-value
Age (years)	46.6 ± 10.8	49.3 ± 11.2	0.172
Male, *n* (%)	29 (48.3)	29 (48.3)	1.000
Weight (kg)	58.2 ± 9.9	59.7 ± 10.8	0.411
Duration of dialysis (months)	6.5 (0–23.5)	9.0 (0–24.8)	0.386
MAP (mmHg)	108.1 ± 11.8	107.5 ± 11.7	0.757
Hypertension, *n* (%)	55 (91.6)	54 (90)	1.000
Diabetes, *n* (%)	6 (10)	7 (11.7)	1.000
rHuEPO use before, *n* (%)	27 (45)	29 (55.8)	0.855
Iron treatment, *n* (%)	50 (83.3)	52 (86.7)	0.799
Initial dialysis, *n* (%)	27 (45)	25 (41.7)	0.854
PD modalities, *n* (%)			
CAPD	5 (8.3)	3 (5)	0.717
DAPD	51 (85)	55 (91.7)	0.394
APD	4 (6.7)	2 (3.3)	0.678
KT/V	1.86 ± 0.5	1.97 ± 0.5	0.217
Ccr (L/1.73m^2)	68.6 ± 27.1	77.6 ± 29.5	0.447
Hb (g/L)	89.6 ± 13.7	90.2 ± 13.5	0.825
Total cholesterol (mmol/L)	4.5 ± 1.1	4.6 ± 1.1	0.517
Triglycerides (mmol/L)	1.7 ± 0.9	1.8 ± 1.0	0.901
HDL-C (mmol/L)	1.1 ± 0.3	1.2 ± 0.4	0.267
LDL-C (mmol/L)	2.5 ± 0.7	2.5 ± 0.8	0.830
Albumin (g/L)	37.6 ± 4.4	38.7 ± 4.6	0.189
Iron metabolism			
Ferritin ≥100 μg/L and TSAT ≥20%,*n* (%)	31 (51.7)	29 (48.3)	0.855
Ferritin <100 μg/L or TSAT <20%, *n* (%)	29 (48.3)	31 (51.7)	0.855
hs-CRP (mg/L)	1.1 (0.5–2.2)	1.1 (0.5–2.3)	0.780
Fasting blood glucose (mmol/L)	5.04 ± 0.67	5.14 ± 0.83	0.433

MAP, mean arterial pressure; CAPD, continuous ambulatory peritoneal dialysis; DAPD, daytime ambulatory peritoneal dialysis; APD, automated peritoneal dialysis; Kt/V, weekly urea clearance index; Ccr, weekly creatinine clearance; Hb, hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TSAT, transferrin saturation; hs-CRP, high-sensitivity C-reactive protein.

pressure were conducted by office, home or ambulatory blood pressure monitoring and we chose the mean value of blood pressure over multiple time points; nocturnal hypertension is defined as a blood pressure value of ≥120/70 mmHg at night (10) which was measured by home and ambulatory blood pressure monitoring; initial dialysis was defined as dialysis time within 3 months at the time of enrolment; TSAT was defined as serum iron/total iron-binding capacity×100%; CTR was defined as cardiac diameter/thoracic diameter in chest X-ray.

Statistical analysis

We used the propensity score matching method to improve the equilibrium between the two groups. Statistical analysis was performed using SPSS statistical software version 26.0 (SPSS Inc., Chicago, IL, United States). Descriptive parametric data consistent with a normal distribution are expressed as the mean ± standard deviation (SD), and nonparametric data are expressed as the median (interquartile range). We used Student's t-test and Mann–Whitney tests to compare continuous variables between the two groups. Categorical variables were expressed as percentages and compared using the χ2-test. The univariate Cox regression model was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) of each factor. GraphPad 8.0 software was used to draw the survival curve of cardio-cerebrovascular complications by Kaplan–Meier. The log-rank test was used to compare the survival curve between the two groups. $p < 0.05$ was considered to indicate statistical significance.

Results

Patient demographics and baseline characteristics

A total of 120 PD patients with renal anemia were included, i.e., 60 PD patients in roxadustat group and 60 PD patients in rHuEPO group. There were no significant differences in clinical and biochemical data at baseline between the two groups of PD patients ($p > 0.05$) (Table 1).

Hb levels

There was no significant difference in Hb between the two groups of PD patients at baseline, and both Hb levels increased significantly after treatment (Figure 1). There was no significant difference in Hb between the two groups at the 24-month follow-up (115.1 ± 5.5 vs. 114.8 ± 6.0, $p = 0.716$). The control rate of Hb in roxadustat group and rHuEPO group were 90 and 88.3%, respectively ($p > 0.05$).

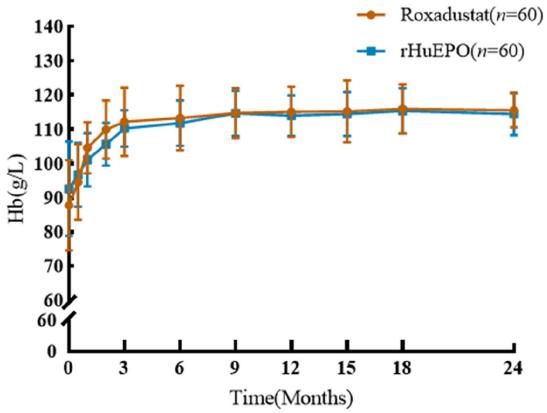


FIGURE 1
Comparison of Hb before and after treatment between the two groups.

Blood pressure

There were no significant differences in blood pressure between the two groups at baseline, and there were no significant changes in systolic blood pressure, diastolic blood pressure or nocturnal hypertension in roxadustat group before and after treatment ($p > 0.05$). After 24 months of follow-up, both systolic blood pressure and diastolic blood pressure in rHuEPO group were significantly higher than those at baseline, and the incidence of nocturnal hypertension increased ($p < 0.05$). However, after 24 months of follow-up, systolic and diastolic blood pressure and nocturnal hypertension increased in rHuEPO group compared with roxadustat group ($p < 0.05$) (Table 2).

Cardiovascular parameters and cardio-cerebrovascular complications

There were no significant differences in cardiovascular parameters before and after treatment in roxadustat group ($p > 0.05$). NT-proBNP, TnT, TnI and CTR increased and LVEF decreased in rHuEPO group compared with baseline ($p < 0.05$), but there was no significant change in IVS and LVPW ($p > 0.05$). Compared with roxadustat group, the levels of NT-proBNP, TnT, TnI and CTR in rHuEPO group increased, while LVEF decreased ($p < 0.05$). IVS and LVPW showed no significant difference ($p > 0.05$) (Table 2). Compared with baseline, rHuEPO group had more cardiovascular and cerebrovascular complications after treatment (26.7% vs. 0, $p < 0.05$). Cardiovascular and

TABLE 2 Comparison of blood pressure, cardiovascular parameters between the two groups of PD patients at baseline and after 24months of follow-up.

	Roxadustat (*n* =60)		rHuEPO (*n* =60)			
	Baseline variable	After 24 months of follow-up	Change from baseline	Baseline	After 24 months of follow-up	Change from baseline
Systolic blood pressure (mmHg)	131.3 ± 15.9	130.0 ± 12.5	−1.28 ± 13.4	131.1 ± 15.9	138.1 ± 14.0*#	7.02 ± 15.1#
Diastolic blood pressure (mmHg)	85.0 ± 10.2	83.1 ± 7.7	−1.93 ± 9.0	83.8 ± 10.1	89.8 ± 9.4*#	5.35 ± 10.8#
Nocturnal hypertension, *n* (%)	8 (13.3)	5 (8.3)	−3 (−5)	7 (11.7)	18 (30)*#	11 (18.3)#
Urine volume (mL)	1,100 (112–1457.5)	1,075 (157.5, 1437.5)	−50 (−100, 0)	1,100 (725–1337.5)	800 (450, 1087.5)*#	−200 (−487, −50)#
Weight (kg)	59.4 ± 9.9	57.8 ± 10.4	−0.4 ± 4.4	60.2 ± 10.8	59.7 ± 11.9	−0.0 ± 6.8
NT-proBNP (pmol/L)	170.2 (56.5, 475.8)	114.3 (34.4, 300.5)	−5.4 (−167.2, 158.5)	119.1 (60.1, 456.3)	424.4 (155.5, 1350.5)*#	95.3 (−17.2, 494.0)#
TnT (ng/mL)	0.019 (0.014, 0.034)	0.027 (0.021, 0.064)	0.007 (−0.004, 0.019)	0.021 (0.0125, 0.036)	0.066 (0.047, 0.0995)*#	0.048 (0.029, 0.072)#
TnI (ng/mL)	0.03 (0.02, 0.03)	0.0275 (0.015, 0.03)	0.005 (0,0.015)	0.035 (0.025, 0.04)	0.05 (0.0395, 0.06)*#	0.02 (0.01, 0.04)#
IVS (mm)	9.94 ± 1.52	10.03 ± 1.75	−0.09 ± 1.74	10.26 ± 1.92	10.52 ± 1.53	0.28 ± 1.82
LVPW (mm)	9.94 ± 1.23	10.06 ± 1.85	−0.38 ± 1.40	9.78 ± 1.43	10.1 ± 1.42	0.26 ± 1.94
LVEF (%)	62.8 ± 4.5	63.2 ± 4.8	0.9 ± 6.7	63.8 ± 6.1	60.9 ± 4.7*#	−3.3 ± 7.1#
Cardiothoracic ratio	0.48 ± 0.06	0.49 ± 0.04	−0.02 ± 0.05	0.48 ± 0.05	0.51 ± 0.07*	0.04 ± 0.06#

NT-proBNP, N-terminal pro-brain natriuretic peptide; TnT, troponin T; TnI, troponin I; IVS, interventricular septal; LVPW, left ventricular posterior wall thickness; LVEF, left ventricular ejection fraction.
Compared with baseline, *$p<0.05$; Compared with roxadustat group, #$p<0.05$.

TABLE 3 Comparison of cardio-cerebrovascular complications and prognosis of PD patients in the two groups during 24 months of follow-up.

Variable	HR	95% CI	*p*
Age (years)	1.045	1.006–1.086	0.022
Hb (g/L)	1.002	0.971–1.034	0.889
Systolic blood pressure (mmHg)	1.036	1.009–1.065	0.009
Diastolic blood pressure (mmHg)	1.033	0.989–1.079	0.139
Fasting blood glucose (mmol/L)	2.532	1.593–4.024	<0.001
rHuEPO use before	2.620	1.068–6.429	0.035
Roxadustat treatment	0.338	0.132–0.864	0.023
KT/V	0.619	0.233–1.641	0.335
Ccr (L/1.73 m²)	0.987	0.972–1.003	0.110
Total cholesterol (mmol/L)	1.151	0.775–1.709	0.485
LDL-C (mmol/L)	1.442	0.736–2.825	0.286
Blood albumin (g/L)	0.942	0.866–1.025	0.167
Hypersensitive CRP (mg/L)	0.950	0.834–1.081	0.436

HR, hazard ratio; CI, confidence interval; Hb, hemoglobin; Kt/V, weekly urea clearance index; Ccr, weekly creatinine clearance; LDL-C, low-density lipoprotein cholesterol; Hypersensitive CRP, hypersensitive C-reactive protein.

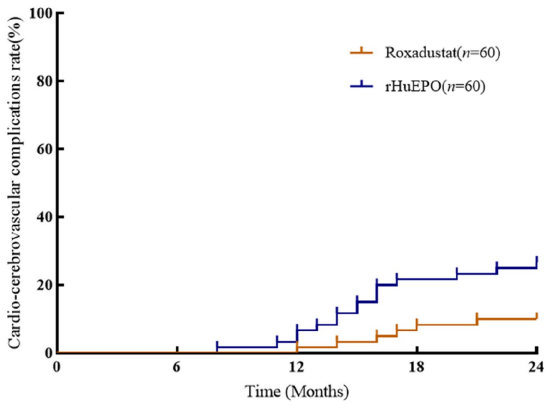


FIGURE 2
Comparison of incidence of cardio-cerebrovascular complications between the two groups. There was a significant difference among the two groups after 24 months of follow-up ($p<0.05$).

cerebrovascular complications increased in the rHuEPO group compared with those in roxadustat group after follow-up (26.7% vs. 10%, $p<0.05$) (Table 3, Figure 2).

Risk factors for cardio-cerebrovascular complications

Cox regression analysis showed that age, systolic blood pressure, fasting blood glucose, and rHuEPO use before baseline were risk factors for cardio-cerebrovascular complications in PD patients, while treatment with roxadustat was a protective factor for cardiovascular and cerebrovascular complications (Table 4).

Discussion

Renal anemia is a common complication in patients with CKD and is associated with increased cardiovascular events, hospitalization rates and mortality (11). Roxadustat is an oral HIF-PHI that can stimulate the production of endogenous erythropoietin (EPO) in the human body, and the process is very similar to the physiological regulation process of hypoxia at high altitude. HIF-PHI can increase the sensitivity of EPO receptors and promote iron absorption, which is more conducive to its clinical effect of improving renal anemia (12). Li et al. (13) showed that the effect of HIF-PHI in improving anemia was not affected by the inflammatory state and iron concentration in the human body. However, there have been few studies on the cardiovascular parameters and cardio-cerebrovascular complications of roxadustat. Therefore, this study aimed to observe cardiovascular parameters and cardio-cerebrovascular complications in PD patients to deepen the clinical understanding.

ESAs are direct vasoconstrictors that can raise blood pressure, and can also raise blood pressure by stimulating the production of endothelin, epinephrine, renin, and angiotensin. Furthermore, the effect of ESAs on blood viscosity is also a mechanism of hypertension (14); as a result, after using rHuEPO in clinical practice, PD patients are more likely to develop hypertension. In this study, compared with ESAs, roxadustat can correct anemia without increasing cardiovascular and cerebrovascular burden in PD patients. The lower blood pressure of roxadustat group has a protective effect on cardiovascular and cerebrovascular diseases. These results are related to the mechanism of HIF-PHI. Yu et al. (15) showed that HIF-PHI could reduce hypertension associated with high renin-angiotensin system activity or endothelial nitric oxide synthase (eNOS) deficiency in the angiotensin II (Ang II) hypertensive mouse model. Roxadustat downregulated the expression of angiotensin receptor 1, increased the expression of angiotensin receptor 2, eNOS and HIF1α protein levels, prevented Ang II-induced oxidative stress, eliminated hypertensive response, and prevented vascular thickening, myocardial hypertrophy and renal injury. HIF-PHI also regulated angiogenesis, glucose metabolism, cell proliferation and apoptosis in an animal model of nephropathy with metabolic syndrome. HIF-PHI increased renal glucose excretion, reduced fat weight, and corrected hypertension. The mechanism of HIF-PHI for lowering blood pressure could be that it induces the transcription of vasodilation-related genes (16). In this study, compared with rHuEPO group, the blood pressure of PD patients in roxadustat group was significantly lower, and the abovementioned mechanisms provide a certain theoretical basis for this result.

Signore et al. (16) showed that the level of NT-proBNP decreased, left ventricular end-diastolic pressure decreased, LVEF increased, cardiac systolic and diastolic function improved, cardiac blood flow and myocardial oxygenation increased, and myocardial hypertrophy, fibrosis, and remodeling decreased in renal anemia rats treated with HIF-PHI. Animal model analysis indicated that HIF-1 plays a key protective role in the pathophysiological mechanism of ischemic heart disease and pressure overload heart failure (17). HIF-1 is a

TABLE 4 Analysis of risk factors for cardiovascular and cerebrovascular complications in PD patients.

	Roxadustat (*n*=60)	rHuEPO (*n*=60)
Cardio-cerebrovascular complications, *n* (%)	6 (10)	16 (26.7)*
Coronary heart diseases, *n* (%)	1 (1.7)	5 (8.3)
Heart failure, *n* (%)	3 (5)	6 (10)
Arrhythmia, *n* (%)	0	1 (2)
Stroke, *n* (%)	2 (3.3)	4 (6.7)
Changed to HD or combined with HD due to cardio-cerebrovascular complication, *n* (%)	2 (3.3)	5 (8.3)
All-cause mortality, *n* (%)	0	1 (1.7)

HD, Hemodialysis; compared with roxadustat group, *$p<0.05$.

transcription factor that acts as a major regulator of oxygen homeostasis, it regulates angiogenesis and vascular remodeling, and utilizes oxygen by regulating glucose metabolism and redox homeostasis. In this study, PD patients treated with roxadustat had lower blood pressure and better cardiovascular parameters than those treated with rHuEPO, these results are considered to be related to the mechanism mentioned above.

Provenzano et al. (18) showed that roxadustat did not increase the risk of major adverse cardiovascular events (MACE, including cardiovascular death, myocardial infarction and stroke), MACE+ (MACE, unstable angina and congestive heart failure requiring hospitalization), or all-cause death compared with placebo in 4277 non-dialysis patients with CKD renal anemia. Recent randomized phase 3 trial study compared dialysis patients treated with roxadustat versus rHuEPO, there were no statistically significant differences in cardiovascular events and adverse events between the two groups (19). Barratt et al. (20) found that there were no significant differences in the risk of major adverse cardiovascular events (MACE, including cardiovascular death, myocardial infarction and stroke) and MACE+ (MACE, unstable angina and congestive heart failure requiring hospitalization) in non-dialysed CKD patients with renal anemia when the patients were treated with roxadustat compared with rHuEPO, but subgroup analysis found that roxadustat group had lower rates of hospitalization for congestive heart failure or unstable angina. Provenzano et al. (21) showed that roxadustat reduced the risk of MACE by 30% and MACE+ by 34% in initial dialysis patients compared with rHuEPO, therefore, in the study, roxadustat had a lower risk of MACE/MACE+ compared with rHuEPO in patients new to dialysis. Our study is the first time to compare blood pressure, the cardiovascular parameters and cardio-cerebrovascular complications treated with roxadustat versus rHuEPO only in PD patients. We had a continuous normative dynamic observation on cardio-cerebrovascular parameters and events. The highlight of this study is that roxadustat had a cardio-cerebrovascular protective effect on PD patients. The possible mechanism is that HIF and its family of proteins regulate an oxygen-dependent signalling cascade, perceive and regulate the hypoxia and ischemia of cardio-cerebrovascular vessels and play a protective role in regulation. In addition, HIF acts on endothelial cells, vascular smooth muscle cells and macrophages, and plays a key protective role in cardio-cerebrovascular atherosclerotic diseases through cell-specific responses (22, 23). Recently, Zhao et al. (24) found that roxadustat in routine treatment doses did not affect platelet production, activation or thrombosis and had significant cardiovascular and cerebrovascular protection advantages compared with ESAs. The cardiovascular protective effect of roxadustat could be observed in the above animal experiments and clinical investigations.

Acet et al. (25) showed that elevated blood glucose was an independent predictor of MACE, and Monami et al. (26) showed that the risk of MACE reduced and renal adverse events correspondingly reduced after blood glucose control. In this study, elevated fasting blood glucose was a risk factor for cardio-cerebrovascular complications in PD patients, suggesting that active control of blood glucose in PD patients is needed to reduce the incidence of cardio-cerebrovascular complications.

However, there are some limitations in this study. It is a retrospective study in a single center. And then the 2 years of follow-up time of cardio-cerebrovascular complications in this study was insufficient. Therefore, the results of this study need to be further validated with longer follow up in a multi-center prospective study.

Conclusion

In this study, compared with rHuEPO in PD patients, roxadustat has less impact on blood pressure and cardiovascular parameters, and the incidence of cardio-cerebrovascular complications is lower. Treatment with roxadustat in PD renal anemia patients offers cardio-cerebrovascular protection, especially in PD patients with cardiovascular complications or elevated cardiovascular parameters, which is worthy of in-depth clinical study and discussion. It is necessary to further increase the sample size and observation parameters to make the research results more objective and comprehensive.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Local Ethics Committee of Jinling Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

SC, TZ, and LY conceived the study, researched literatures and develop the protocol. YY and SC obtained ethical approval. LY and ZZ performed data analysis. SC, TZ, and LY wrote the first draft of the manuscript. YY approved the final version of this manuscript. All authors contributed to the article and approved the submitted version.

Funding

This study was financially supported by the Jiangsu Clinical Medical Center Project (Grant no. YYS2016001).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Perlman RL, Zhao J, Fuller DS, Bieber B, Li Y, Pisoni RL, et al. International Anemia prevalence and Management in Peritoneal Dialysis Patients. *Perit Dial Int*. (2019) 39:539–46. doi: 10.3747/pdi.2018.00249

2. Sakaguchi Y, Hamano T, Wada A, Masakane I. Types of erythropoietin-stimulating agents and mortality among patients undergoing hemodialysis. *J Am Soc Nephrol*. (2019) 30:1037–48. doi: 10.1681/ASN.2018101007

3. Pfeffer MA, Burdmann EA, Chen CY, Cooper ME, De Zeeuw D, Eckardt KU, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. (2009) 361:2019–32. doi: 10.1056/NEJMoa0907845

4. Provenzano R, Shutov E, Eremeeva L, Korneyeva S, Poole L, Saha G, et al. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. *Nephrol Dial Transplant*. (2021) 36:1717–30. doi: 10.1093/ndt/gfab051

5. Shutov E, Sulowicz W, Esposito C, Tataradze A, Andric B, Reusch M, et al. Roxadustat for the treatment of anemia in chronic kidney disease patients not on dialysis: a phase 3, randomized, double-blind, placebo-controlled study (ALPS). *Nephrol Dial Transplant*. (2021) 36:1629–39. doi: 10.1093/ndt/gfab057

6. Zheng Q, Yang H, Fu X, Huang Y, Wei R, Wang Y, et al. The efficacy and safety of roxadustat for anemia in patients with chronic kidney disease: a meta-analysis. *Nephrol Dial Transplant*. (2021) 36:1603–15. doi: 10.1093/ndt/gfaa110

7. Akizawa T, Otsuka T, Reusch M, Ueno M. Intermittent Oral dosing of Roxadustat in peritoneal Dialysis chronic kidney disease patients with Anemia: a randomized, phase 3, multicenter, Open-Label Study. *Ther Apher Dial*. (2020) 24:115–25. doi: 10.1111/1744-9987.12888

8. Hou YP, Mao XY, Wang C, Xu ZH, Bu ZH, Xu M, et al. Roxadustat treatment for anemia in peritoneal dialysis patients: a randomized controlled trial. *J Formos Med Assoc*. (2022) 121:529–38. doi: 10.1016/j.jfma.2021.06.004

9. Qie S, Jiao N, Duan K, Li J, Liu Y, Liu G. The efficacy and safety of roxadustat treatment for anemia in patients with kidney disease: a meta-analysis and systematic review. *Int Urol Nephrol*. (2021) 53:985–97. doi: 10.1007/s11255-020-02693-7

10. Unger T, Borghi C, Charchar F, Khan NA, Poulter NR, Prabhakaran D, et al. 2020 International Society of Hypertension Global Hypertension Practice Guidelines. *Hypertension*. (2020) 75:1334–57. doi: 10.1161/HYPERTENSIONAHA.120.15026

11. Locatelli F, Fishbane S, Block GA, Macdougall IC. Targeting hypoxia-inducible factors for the treatment of Anemia in chronic kidney disease patients. *Am J Nephrol*. (2017) 45:187–99. doi: 10.1159/000455166

12. Hou YP, Wang C, Mao XY, Zhang MZ, Li B. Roxadustat regulates iron metabolism in dialysis-dependent and non-dialysis-dependent chronic kidney disease patients: a meta-analysis. *J Formos Med Assoc*. (2022) 121:2288–99. doi: 10.1016/j.jfma.2022.06.008

13. Li ZL, Tu Y, Liu BC. Treatment of renal Anemia with Roxadustat: advantages and achievement. *Kidney Dis (Basel)*. (2020) 6:65–73. doi: 10.1159/000504850

14. Agarwal R. Mechanisms and mediators of hypertension induced by erythropoietin and related molecules. *Nephrol Dial Transplant*. (2018) 33:1690–8. doi: 10.1093/ndt/gfx324

15. Yu J, Wang S, Shi W, Zhou W, Niu Y, Huang S, et al. Roxadustat prevents Ang II hypertension by targeting angiotensin receptors and eNOS. *JCI. Insight*. (2021) 6:6. doi: 10.1172/jci.insight.133690

16. Signore PE, Guo G, Wei Z, Zhang W, Lin A, Del Balzo U. A small-molecule inhibitor of hypoxia-inducible factor prolyl hydroxylase improves obesity, nephropathy and cardiomyopathy in obese ZSF1 rats. *PLoS One*. (2021) 16:e0255022. doi: 10.1371/journal.pone.0255022

17. Semenza GL. Hypoxia-inducible factor 1 and cardiovascular disease. *Annu Rev Physiol*. (2014) 76:39–56. doi: 10.1146/annurev-physiol-021113-170322

18. Provenzano R, Szczech L, Leong R, Saikali KG, Zhong M, Lee TT, et al. Efficacy and cardiovascular safety of Roxadustat for treatment of Anemia in patients with non-Dialysis-dependent CKD: pooled results of three randomized clinical trials. *Clin J Am Soc Nephrol*. (2021) 16:1190–200. doi: 10.2215/CJN.16191020

19. Fishbane S, Pollock CA, El-Shahawy M, Escudero ET, Rastogi A, Van BP, et al. Roxadustat versus Epoetin Alfa for treating Anemia in patients with chronic kidney disease on Dialysis: results from the randomized phase 3 ROCKIES study. *J Am Soc Nephrol*. (2022) 33:850–66. doi: 10.1681/ASN.2020111638

20. Barratt J, Sulowicz W, Schomig M, Esposito C, Reusch M, Young J, et al. Efficacy and cardiovascular safety of Roxadustat in Dialysis-dependent chronic kidney disease: pooled analysis of four phase 3 studies. *Adv Ther*. (2021) 38:5345–60. doi: 10.1007/s12325-021-01903-7

21. Provenzano R, Fishbane S, Szczech L, Leong R, Saikali KG, Zhong M, et al. Pooled analysis of Roxadustat for Anemia in patients with kidney failure incident to Dialysis. *Kidney Int Rep*. (2021) 6:613–23. doi: 10.1016/j.ekir.2020.12.018

22. Sousa Fialho MDL, Abd Jamil AH, Stannard GA, Heather LC. Hypoxia-inducible factor 1 signalling, metabolism and its therapeutic potential in cardiovascular disease. *Biochim Biophys Acta Mol basis Dis*. (2019) 1865:831–43. doi: 10.1016/j.bbadis.2018.09.024

23. Jain T, Nikolopoulou EA, Xu Q, Qu A. Hypoxia inducible factor as a therapeutic target for atherosclerosis. *Pharmacol Ther*. (2018) 183:22–33. doi: 10.1016/j.pharmthera.2017.09.003

24. Zhao J, Xu Y, Xie J, Liu J, Zhang R, Yan X. Roxadustat does not affect platelet production, activation, and thrombosis formation. *Arterioscler Thromb Vasc Biol*. (2021) 41:2523–37. doi: 10.1161/ATVBAHA.121.316495

25. Acet H, Guzel T, Aslan B, Isik MA, Ertas F, Catalkaya S. Predictive value of C-reactive protein to albumin ratio in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. *Angiology*. (2021) 72:244–51. doi: 10.1177/0003319720963697

26. Monami M, Candido R, Pintaudi B, Targher G, Mannucci E, Of Theet al. Improvement of glycemic control in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. (2021) 31:2539–46. doi: 10.1016/j.numecd.2021.05.010

frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 27 July 2023
DOI 10.3389/fphys.2023.1172308

OPEN ACCESS

EDITED BY
Guoshuang Xu,
Fourth Military Medical University, China

REVIEWED BY
Isaac Teitelbaum,
University of Colorado Anschutz Medical Campus, United States
Jianhui Zhou,
Chinese PLA General Hospital, China

*CORRESPONDENCE
Qin Wang,
qinwang_1975@126.com

RECEIVED 23 February 2023
ACCEPTED 07 July 2023
PUBLISHED 27 July 2023

CITATION
Yu Z, Ding L, He Y, Huang J, Fang W, Gu L, Ni Z and Wang Q (2023), An observational study on the effect of seasonal variation on peritoneal dialysis patients.
Front. Physiol. 14:1172308.
doi: 10.3389/fphys.2023.1172308

An observational study on the effect of seasonal variation on peritoneal dialysis patients

Zanzhe Yu, Li Ding, Yanna He, Jiaying Huang, Wei Fang, Leyi Gu, Zhaohui Ni and Qin Wang*

Department of Nephrology, Molecular Cell Lab for Kidney Disease, Shanghai Peritoneal Dialysis Research Center, Renji Hospital, Uremia Diagnosis and Treatment Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Background: Seasonal variation has an impact on plants, wild animals, and also human beings. Data have shown seasonal variation has a significant impact on patients' fluid status, biochemistry results, and outcomes in hemodialysis populations. The relevant data on peritoneal dialysis is scant.

Methods: This was a cross sectional study. All patients followed up in our center had a peritoneal equilibration test and PD adequacy test every 6 months. All the peritoneal equilibration test and PD adequacy test data were collected during December 2019 to November 2020. The monthly delivery information of the whole center was collected from 2015 to 2019.

Results: There were 366 patients and 604 sets of peritoneal equilibration test and PD adequacy test results in the study. Plasma albumin and phosphate levels were higher in summer. The monthly average outdoor temperature was positively correlated with plasma albumin. There was no seasonal difference in peritoneal dialysis ultrafiltration or urine volume. The percentage of low glucose concentration (1.5%) usage was higher in summer and lower in winter.

Conclusion: Plasma albumin and phosphate levels were higher in summer in PD patients. Weaker glucose peritoneal dialysis dialysate was more widely used in summer. Understanding the seasonal variation of peritoneal dialysis is helpful in individualized treatment.

KEYWORDS

weather temperature, ultrafiltration, protein intake, fluid management, dialysate glucose concentration

Background

Seasonal variation has a wide impact on human beings. It is well known that the mortality rate varies between different seasons. The dominant cause of death is also different between seasons (Keatinge and Donaldson-The Eurowinter Group, 1997). Seasonal effects also vary between different geographical regions. The reasons for seasonal effects are complicated and likely to be a combination of a wide range of issues. Apart from temperature, humidity, and sunlight hours, seasons may also have an impact on food choice and the duration of physical activity (Shephard and Aoyagi, 2009).

For dialysis patients, there is the unique difficulty of maintaining fluid balance. The seasonal effects are likely to be more significant compared with the general population. Studies have shown significant seasonal variation in mortality rates, pre-dialysis systolic blood

pressure, intra-dialysis body weight gain, plasma albumin, and CRP levels in hemodialysis patients (Usvyat et al., 2012; Guinsburg et al., 2015). This phenomenon was first recognized in the early 21st century and further described in single-center, multi-center, and registry data. The seasonal effect on blood pressure is highly consistent among studies. Blood pressure is higher in winter (Sposito et al., 2000; Argiles et al., 2004; Broers et al., 2015). In the MONDO registry data, pre-dialysis blood pressure and intra-dialysis body weight gain were lower in summer, and plasma albumin and CRP levels were higher in winter (Guinsburg et al., 2015). The European data, which was also in the MONDO database, showed that sodium, hemoglobin, and CRP were higher in winter, plasma albumin was lower in autumn, and nPCR was lower in winter (Broers et al., 2015). The bioimpedance results showed that overhydration was more significant in summer compared with winter (Broers et al., 2015).

There is limited data on peritoneal dialysis patients regarding seasonal effects. A single-center study from Taiwan showed seasonal variations in peritoneal dialysis. Plasma sodium, potassium, and albumin were lower in summer, and ultrafiltration in PD was also lower in summer (Chen et al., 2010). The same team further noticed a seasonal variation in dialysate glucose concentration usage. Higher glucose concentration dialysate was less used in summer (Li et al., 2008). A single-center study from Beijing showed seasonal variations in blood pressure, but no change in body composition. The study did not show ultrafiltration, urine volume, or dialysate glucose usage (Cheng et al., 2006).

The current study meant to clarify the seasonal effects on peritoneal dialysis patients in Shanghai, a modern city with a typical maritime climate with four distinct seasons. We observed the seasonal variations of biochemical results, membrane function, ultrafiltration volume, and dialysate glucose usage.

Methods

Study design and patient population

All patients followed up in our center underwent a first PET test and dialysis adequacy test between 4 and 6 weeks after PD started and then every 6 months. Extra PET tests and dialysis adequacy tests were done if clinically relevant, e.g., unexpected reductions of ultrafiltration or clinical manifestations. All the patients who underwent PET tests and dialysis adequacy tests between December 2019 and November 2020 and who gave consent were enrolled in the study. Only the baseline and 6-month test data were analyzed. The biochemical results, membrane function, and dialysis adequacy data were recorded. In total, 366 patients underwent at least one PET test and 604 sets of data were included in the study.

Volume management policy of the center

The patients came to their outpatient clinic monthly. The patient's fluid status was evaluated through their blood pressure, body weight change, and edema status. Bioimpedance, BNP, and other relevant tests were conducted if needed. For patients with fluid overload, furosemide would be increased to 100 mg qd for patients with a urine volume of more than 200 mL per day, before increasing the glucose concentration in the dialysate prescription. For those with daily fluid removal of more than 800 mL per day (urine volume and dialysate ultrafiltration), fluid restriction education would be repeated and emphasized. Their prescribed dialysate regimes may have been change during the clinic visits and then the relevant dialysate shipment was arranged.

Data collection

The clinical data were collected from the clinical electronic records system. Historical temperature date was retrieved from www.weather.com.cn. The shipment information including dialysate glucose concentration was recorded. To show the seasonal variations of the cohort's dialysate glucose consumption, the monthly shipment records from 2015 to 2019 were analyzed in the study.

Statistical analysis

Numerical variables that followed normal distribution were described as mean ± SD. Numerical variables that did not follow normal distribution were described as median (interquartile range). The correlation between the monthly average temperature and other parameters were identified using Pearson's correlation. The difference between seasons were estimated using one-way ANOVA. IBM SPSS statistics 20 was the software used for the study.

Results

Seasonal variation and biochemical profiles

For analyzing purposes, March, April, and May were defined as spring; June, July, and August were defined as summer; September, October, and November were defined as autumn; and December, January, and February were defined as winter.

The seasonal variations of the biochemical profiles are shown in Table 1. Plasma albumin was higher in summer. Phosphate levels were also higher in summer. Hemoglobin levels were lower in spring compared with autumn. There was a positive correlation between the monthly average temperature and plasma albumin. The correlation between phosphate was nearly statistically significant ($r = 0.075$ $p = 0.066$). (Table 2).

There was no statistical correlation between the monthly average temperature and daily UF or urine volume (Table 3). As showed in Figures 1, 2, there was a significant seasonal variation in glucose usage. In summer, low glucose concentration dialysate (1.5%) was more widely used than in winter.

Discussion

Seasonal variation has a general impact on plants, animals, and human beings. It has been recognized for a long time. It is not clear how it affects certain populations, in which ways, and to what extent. The current study showed that low glucose concentration dialysate was used in summer. Plasma albumin and phosphate were higher in summer.

TABLE 1 Description of seasonal variations in biochemical profiles.

	Spring	Summer	Autumn	Winter	*p*
Albumin (g/L)	37.99 ± 4.33	39.26 ± 4.33	38.13 ± 4.34	37.57 ± 4.24	0.008**
Ca++ (mmol/L)	2.26 ± 0.22	2.25 ± 0.20	2.26 ± 0.21	2.24 ± 0.22	0.904
p (mmol/L)	1.67 ± 0.44	1.78 ± 0.48	1.60 ± 0.48	1.70 ± 0.47	0.010**
Hgb (g/L)	107.69 ± 18.94	111.63 ± 17.86	114.59 ± 17.95	111.50 ± 18.37	0.009**
Sodium (mmol/L)	140.16 ± 3.30	140.84 ± 2.67	140.63 ± 3.58	140.61 ± 3.08	0.259
hsCRP (mg/L)	2.2 (0.6,7.8)	2.0 (0.8,5.6)	2.2 (0.8,6.3)	2.7 (1.0,6.4)	0.19
4 h UF (mL)	320 (210,420)	330 (215,440)	300 (185,425)	325 (215,425)	0.377
Daily UF (mL)	498 (223,803)	530 (155,860)	528 (185,815)	373 (63,723)	0.263
Urine volume (mL)	285 (0,900)	300 (0,1000)	250 (0,900)	300 (0,1100)	0.52
D/Pcr4h	0.66 ± 0.10	0.67 ± 0.10	0.66 ± 0.09	0.65 ± 0.11	0.65

*$p < 0.01$, **$p < 0.01$.

TABLE 2 The correlation between monthly average temperature and biochemical profiles.

	Mean ± SD	Monthly mean maximum temperature		Monthly mean minimum temperature	
		r	*p*	*r*	*p*
Age (year)	57.05 ± 15.27	—	—	—	—
Male (%)	60.38	—	—	—	—
Alb (g/L)	38.26 ± 4.35	0.085*	0.039	0.086*	0.036
Ca++ (mmol/L)	2.56 ± 0.21	−0.002	0.955	−0.007	0.861
p (mmol/L)	1.69 ± 0.47	0.067	0.1	0.075	0.066
Hgb (g/L)	111.18 ± 18.45	0.014	0.742	0.021	0.608
Sodium (mmol/L)	140.54 ± 3.19	0.034	0.409	0.042	0.303
hsCRP (mg/L)	2.26 (0.77,6.42)	−0.052	0.207	−0.056	0.176

*$p < 0.01$, **$p < 0.01$. Lower glucose concentration dialysate in summer.

TABLE 3 The correlation between monthly average temperature and fluid removal.

		Monthly mean maximum temperature		Monthly mean minimum temperature	
		r	*p*	r	*p*
D/Pcr4h	0.66 ± 0.10	0.005	0.903	0.006	0.89
4 h UF (mL)	315 (200,428)	0.016	0.715	0.015	0.731
Daily UF (mL)	495 (158,815)	0.049	0.231	0.054	0.189
Urine volume (mL)	300 (0,1000)	0.045	0.273	0.042	0.309

Lower glucose concentration dialysate in summer

We found that lower glucose concentration dialysate was more frequently used in summer. This result is similar to the findings from the Taiwan cohort (Chen et al., 2010). The authors also found lower plasma sodium levels and less daily UF in summer. We did not find this change in our cohort. Extra sodium loss through sweat may be the reason for the low sodium levels in summer. Fluid loss from sweat is also a pathway for fluid removal in dialysis patients. We did not collect blood pressure data in the study. From the study in hemodialysis, blood pressure in summer was lower than in winter.

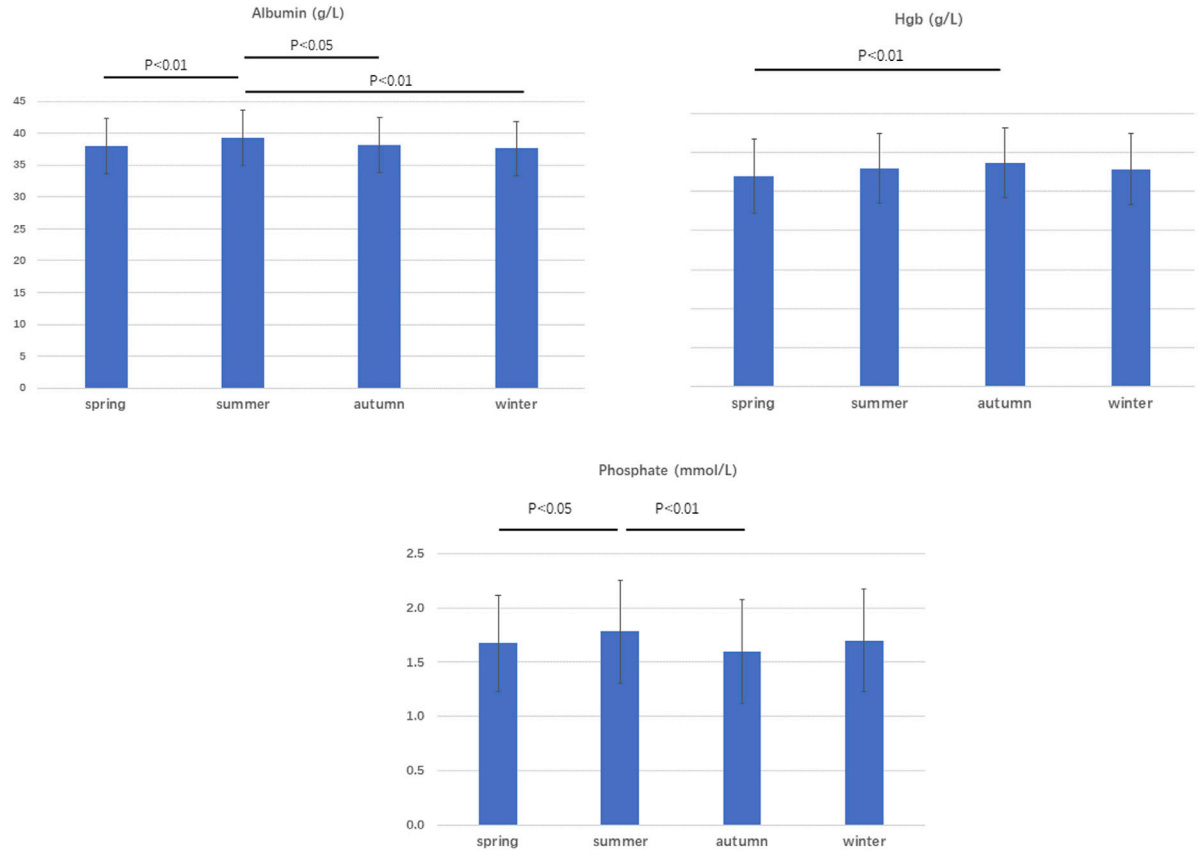


FIGURE 1
Plasma albumin, phosphate, and Hgb levels according to season.

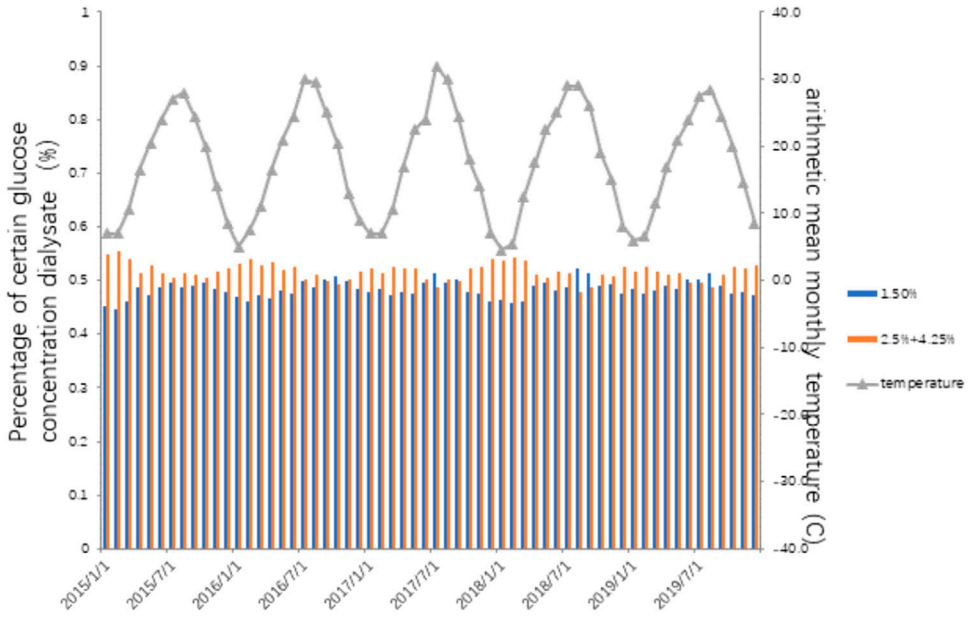


FIGURE 2
The relationship between monthly average temperature and dialysate glucose concentration.

Extra fluid and sodium loss from sweat may have a significant effect on ESRD patients.

Higher plasma albumin and phosphate in summer

The peak of albumin levels has appeared in different seasons in different studies. In the current study, plasma albumin was higher in summer. In the Taiwan cohort, plasma albumin was negatively correlated with outdoor temperature (Li et al., 2008). In the MONDO database, the European data showed plasma sodium, hemoglobin, and CRP were higher in winter. Plasma albumin was lower in autumn and higher in spring (Broers et al., 2015). In the MONDO registry system, plasma albumin was higher in winter and CRP was also higher in winter (Guinsburg et al., 2015). In the current study, CRP levels were lower in summer and there was a negative correlation between plasma albumin and CRP. The higher albumin level may be a result of less inflammation in summer.

On the other hand, plasma albumin also reflects nutritional status to some degree. Similar to the current study, no studies with a similar focus has detailed food intake data available. It is difficult to get direct evidence to show the relationship between plasma albumin and food intake in different seasons. We also found the phosphate levels were higher in summer. This may reflect a higher protein intake in summer. The seasonal effect on food intake is complicated. Major holidays may relate to high protein intake. Furthermore, the type of food available may be different in different seasons. Weather temperature may also have impact on appetite. In all, the seasonal effect may be different between cultures and geographical locations.

Improving patient management

Seasonal changes affect the human body in many ways. The reactions vary among different disease situations. Understanding the specific effects of seasonal changes on peritoneal dialysis patients, who have special difficulties in fluid balance, can help improve patient management and patient outcomes. In summer, considering the additional sweat loss of patients, relevant prescription changes can avoid volume deficiency and the related loss of residual renal function.

Relevance in clinical trials

Seasonal variations should also be considered when designing clinical trials and when interpreting study results. For clinical studies with long enrollment periods crossing different seasons, block randomization should be considered to avoid the impact of seasonal variation on the results (Lin et al., 2015). A balanced number of patients can be enrolled into different groups within short time periods. For clinical studies with observational periods across different seasons, the interpretation of specific variables should fully consider the impact of seasonal variation itself to avoid bias.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Shanghai Jiaotong University School of Medicine, Renji Hospital Ethics committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZY and LD contribute equally to the study. ZY and LD designed the study and wrote up the manuscript. YH and JH collected most of the data. WF, LG, and ZN helped in discussion and interpret the data. QW finalized the study design and the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Argiles, A., Lorho, R., Servel, M. F., Chong, G., Kerr, P. G., and Mourad, G. (2004). Seasonal modifications in blood pressure are mainly related to interdialytic body weight gain in dialysis patients. *Kidney Int.* 65, 1795–1801. doi:10.1111/j.1523-1755.2004.00569.x

Broers, N. J., Usvyat, L. A., Marcelli, D., Bayh, I., Scatizzi, L., Canaud, B., et al. (2015). Season affects body composition and estimation of fluid overload in haemodialysis patients: Variations in body composition; a survey from the European MONDO database. *Nephrol. Dial. Transpl.* 30, 676–681. doi:10.1093/ndt/gfu367

Chen, T. W., Li, S. Y., Chen, T. J., Chen, Y. C., Lai, C. L., Chen, J. Y., et al. (2010). The effect of weather on peritoneal dialysis (PD) prescription: Seasonal variation in PD dialysate utilization. *Perit. Dial. Int.* 30, 320–328. doi:10.3747/pdi.2009.00118

Cheng, L. T., Jiang, H. Y., Tang, L. J., and Wang, T. (2006). Seasonal variation in blood pressure of patients on continuous ambulatory peritoneal dialysis. *Blood Purif.* 24, 499–507. doi:10.1159/000096077

Keatinge, W. R., and Donaldson-The Eurowinter Group, G. C. (1997). Cold exposure and winter mortality from ischaemic heart disease, cerebrovascular disease, respiratory disease, and all causes in warm and cold regions of Europe. The Eurowinter Group. *Lancet* 349, 1341–1346.

Guinsburg, A. M., Usvyat, L. A., Etter, M., Xu, X., Thijssen, S., Marcelli, D., et al. (2015). Seasonal variations in mortality and clinical indicators in international hemodialysis populations from the MONDO registry. *BMC Nephrol.* 16, 139. doi:10.1186/s12882-015-0129-y

Li, S. Y., Chen, J. Y., Chuang, C. L., and Chen, T. W. (2008). Seasonal variations in serum sodium levels and other biochemical parameters among peritoneal dialysis patients. *Nephrol. Dial. Transpl.* 23, 687–692. doi:10.1093/ndt/gfm618

Lin, Y., Zhu, M., and Su, Z. (2015). The pursuit of balance: An overview of covariate-adaptive randomization techniques in clinical trials. *Contemp. Clin. Trials* 45, 21–25. doi:10.1016/j.cct.2015.07.011

Shephard, R. J., and Aoyagi, Y. (2009). Seasonal variations in physical activity and implications for human health. *Eur. J. Appl. Physiol.* 107, 251–271. doi:10.1007/s00421-009-1127-1

Sposito, M., Nieto, F. J., and Ventura, J. E. (2000). Seasonal variations of blood pressure and overhydration in patients on chronic hemodialysis. *Am. J. Kidney Dis.* 35, 812–818. doi:10.1016/s0272-6386(00)70249-6

Usvyat, L. A., Carter, M., Thijssen, S., Kooman, J. P., van der Sande, F. M., Zabetakis, P., et al. (2012). Seasonal variations in mortality, clinical, and laboratory parameters in hemodialysis patients: A 5-year cohort study. *Clin. J. Am. Soc. Nephrol.* 7, 108–115. doi:10.2215/CJN.03880411

frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 27 July 2023
DOI 10.3389/fphys.2023.1170537

OPEN ACCESS

EDITED BY
Guoshuang Xu,
Fourth Military Medical University, China

REVIEWED BY
Xinhui Liu,
Shenzhen Traditional Chinese Medicine Hospital, China
Liu Shiyi,
China Academy of Chinese Medical Sciences, China

*CORRESPONDENCE
Wen-Jing Zhao,
zhaowenjing@bjzhongyi.com
Wen-Quan Niu,
niuwenquan_shcn@163.com

†These authors share first authorship

RECEIVED 21 February 2023
ACCEPTED 07 July 2023
PUBLISHED 27 July 2023

CITATION
Li J-L, Cai Z, Zhao J, Zhu X-G, Li Q, Li Y-S, Liu M-C, Cui F-Q, Zhao W-J and Niu W-Q (2023), Association between anemia-related biomarkers and the adequacy of peritoneal dialysis in Chinese patients with chronic kidney disease.
Front. Physiol. 14:1170537.
doi: 10.3389/fphys.2023.1170537

Association between anemia-related biomarkers and the adequacy of peritoneal dialysis in Chinese patients with chronic kidney disease

Jia-Lin Li[1†], Zhen Cai[1†], Jing Zhao[1], Xiang-Gang Zhu[1], Qian Li[1], Yan-Shuang Li[1], Meng-Chao Liu[1], Fang-Qiang Cui[1], Wen-Jing Zhao[1*] and Wen-Quan Niu[2*]

[1]Department of Nephropathy, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing, China, [2]Center for Evidence-Based Medicine, Capital Institute of Pediatrics, Beijing, China

Objectives: The study aimed to examine the association of three anemia-related biomarkers with the adequacy of peritoneal dialysis (PD) in patients with chronic kidney disease (CKD).

Methods: This study included 127 PD patients. The total Kt/V urea (Kt/V) was calculated according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines. All patients were classified into two groups based on Kt/V, viz., adequate (Kt/V ≥1.7) and inadequate (Kt/V <1.7) groups. Effect sizes are expressed as odds ratios (ORs) and 95% confidence interval (CI).

Results: After adjusting for age, gender, hypertension, diabetes, and PD duration, 20 g/L increment in hemoglobin (Hgb) was observed to significantly reduce the risk of inadequate PD by 19% (OR; 95% CI; P: 0.81; 0.70 to 0.95; 0.009), 5 g/L increment in the mean corpuscular hemoglobin concentration (MCHC) by 7% (0.93; 0.88 to 0.98; 0.009), and 5% increment in transferrin saturation (TS) by 23% (0.77; 0.64 to 0.94; 0.012). The gender-specific nomogram model was constructed by incorporating three significant anemia-related biomarkers and convenient influencing factors, and the prediction accuracy was good (concordance index (C-index): 0.686 for men and 0.825 for women).

Conclusion: Our findings indicate that the deterioration of three anemia-related biomarkers (Hgb, MCHC, and TS) can precipitate the development of inadequate PD in Chinese patients with CKD.

KEYWORDS

chronic kidney disease, peritoneal dialysis, Kt/V urea, anemia, nomogram

Introduction

Chronic kidney disease (CKD) is a chronic disorder of public health importance affecting approximately 1/10 of adults worldwide (Yang et al., 2020a; Kovesdy, 2022). Echoing the high global burden of CKD, along comes kidney replacement therapy, which is expected to increase over the coming decade. Yet, due to the scarcity of organs for transplantation and healthcare cost of hemodialysis, as well as lack of hemodialysis centers, peritoneal dialysis

(PD), a form of home dialysis, is gaining popularity. Global statistics reveal an estimated 272,000 PD patients, accounting for 11% of dialysis patients (Li et al., 2017; Bartosova and Schmitt, 2018; Yang et al., 2020b; Himmelfarb et al., 2020; Thurlow et al., 2021). In China, the number of PD patients in 2017 was 86,264, which increases annually (Wilkie and Davies, 2018; Yang et al., 2021).

In patients with CKD, PD can meet the requirements of clearing uremic toxins and reaching an acid–base balance, as well as removing excess fluids (Chan et al., 2019). Dialysis adequacy should be monitored at regular intervals. It is widely acknowledged that the urea clearance index, Kt/V urea (Kt/V), is a key index of dialysis adequacy, and its minimum target value is recommended to be 1.7 according to the Kidney Disease Outcomes Quality Initiative (K/DOQI) and the International Society for Peritoneal Dialysis (ISPD). The calculation of Kt/V, which requires 24-h peritoneal dialysate and 24-h urine samples, is usually impractical in outpatients, which inspires us to seek other reliable and convenient biomarkers that can be used as predictors for the dialysis adequacy status.

It is widely recognized that renal anemia is a common complication of uremic patients, and patients with a lower Kt/V level require more erythropoietin to manage anemia. Several studies showed that patients with the total Kt/V level maintained below 1.70 as a lower level in hemoglobin indicated inadequate PD (Lo et al., 2003; Liu et al., 2022). In patients with persistently low hemoglobin levels, Li proposed that urea clearance should be optimized for a better range of Kt/V (Li et al., 2003). Other studies indicated that anemia-related biomarkers, such as the mean corpuscular hemoglobin concentration (MCHC) and transferrin saturation (TS), varied in CKD patients (Gafter-Gvili et al., 2019). As such, it is reasonable to speculate that renal anemia may serve as a promising harbinger of dialysis inadequacy. The medical literature has as of yet failed to reveal sufficient evidence to support this speculation.

To fill this gap in knowledge and produce more references for future studies, we aimed to examine whether anemia-related biomarkers, both individually and as a nomogram, can potentially predict the risk of inadequate PD in patients with CKD.

Methods

Study design

The conduct of this study was reviewed and approved by the ethics committees of the Beijing Hospital of Traditional Chinese Medicine, conforming to the principles of the Declaration of Helsinki. All participants provided their informed consent prior to their participation in the study.

Inclusion criteria

All study participants were Chinese adults who had PD catheter placement and regularly visited the Department of Nephrology at the Beijing Hospital of Traditional Chinese Medicine. This is a retrospective study conducted from September 2017 to October 2022. For consistency, the most recent PD adequacy assessment was recorded from the study participants.

Exclusion criteria

Initially, 142 patients were recruited in this study, and 15 of them were excluded due to the following reasons: 1) being under hemodialysis or after kidney transplantation; 2) recently experiencing significant changes in their weight; 3) having PD-related peritonitis occurrence in the last 3 months; 4) being diagnosed with diabetic ketoacidosis, acute cardiovascular events, or other severe disorders, including tumors; 5) having no consultation records for 3 months. Finally, 127 eligible patients with complete data were analyzed in this study.

Demographic information

In addition to the age and gender, the diagnoses of hypertension and diabetes mellitus were also performed at the time of enrollment. Hypertension was defined as having a systolic blood pressure value of ≥140 mmHg, diastolic blood pressure value of ≥90 mmHg, or the current use of antihypertensive agents (Writing Group of 2010 Chinese Guidelines for the Management of Hypertension, 2011). Diabetes mellitus was defined as having a fasting plasma glucose value of ≥7.0 mmol/L or taking hypoglycemic drugs or receiving parenteral insulin therapy (American Diabetes Association, 2013).

Clinical biomarkers

The collection of clinical biomarkers initiated from October 2022. Venous blood was taken in the fasting state. The total Kt/V value was calculated using the formula recommended in K/DOQI. Hemoglobin (Hgb) and the mean corpuscular hemoglobin concentration were measured using a hematology analyzer. Furthermore, the corresponding reference ranges used for Hgb were 115–150 g/L in women and 120–160 g/L in men. The MCHC was in a range of 316–354 g/L. Percentage of transferrin saturation was calculated by dividing serum iron by the total iron-binding capacity and multiplying the result by 100. TS ranged from 20% to 55%. Creatinine concentrations were determined by the enzymatic method, and urine microalbumin was determined by the immunoturbidimetric method. All assays were conducted at the Clinical Laboratory, Beijing Hospital of Traditional Chinese Medicine.

Based on the ISPD and K/DOQI guidelines, participants were classified into two groups according to total Kt/V, viz., adequate (Kt/V ≥1.7) and inadequate (Kt/V <1.7) groups.

Statistical analyses

Normally distributed variables are expressed as the mean (standard deviation), skewed variables as the median (interquartile range), and categorical variables as the count (percent). The χ^2 tests for categorical variables and Wilcoxon rank-sum tests for continuous variables were used to assess the differences in demographic data and clinical biomarkers between the two groups.

TABLE 1 Baseline characteristics of the study participants in the retrospective study.

Characteristic	Overall	Adequate group	Inadequate group	P
Sample size	127	76	51	
Male (n, %)	81 (63.8)	40 (52.6)	41 (80.4)**	0.001
Age (years)	58.26 (13.57)	59.68 (13.10)	56.14 (14.11)	0.122
Diabetes (n, %)	60 (47.2)	34 (44.7)	26 (51.0)	0.491
Hypertension (n, %)	92 (73.0)	52 (69.3)	40 (78.4)	0.261
PD duration (years)	2 [1, 3]	2 [1, 2]	2 [1, 3]	0.106
Kt/V	1.73 [1.57, 1.99]	1.96 [1.84, 2.17]	1.54 [1.44, 1.63]**	<0.001
Scr (μmol/L)	898.20 [727.10, 1,160.25]	829.15 [704.47, 1,006.23]	1,040.50 [806.00, 1,231.80]**	0.001
BUN (mmol/L)	18.77 [15.78, 22.06]	17.45 [14.52, 21.36]	19.56 [16.35, 22.48]*	0.036
Dialysate nitrogen	16.16 (4.94)	15.60 (4.61)	17.05 (5.45)	0.294
Hgb (g/L)	115.50 [108.00, 124.75]	115.50 [108.00, 126.00]	115.00 [104.75, 123.25]	0.545
HCT (%)	34.25 [32.02, 37.27]	34.20 [32.20, 37.62]	34.25 [31.77, 37.10]	0.186
MCV (fL)	90.2 [84.1, 95.2]	90.9 [83.3, 95.7]	89.8 [84.3, 95.6]	0.637
MCH (pg)	30.1 [28.2, 33.2]	29.0 [28.3, 33.4]	30.2 [28.0, 33.1]	0.138
MCHC (g/L)	334.12 (7.93)	334.41 (8.24)	333.69 (7.50)	0.620
TS (%)	26 [19, 32]	28 [22, 32]	22.00 [14, 29]**	0.006
Fer (μg/L)	277 [177, 380]	298.00 [211, 404]	234.00 [172, 360]	0.141

Abbreviations: Kt/V, total Kt/V urea; Scr, serum creatinine; BUN, blood urea nitrogen; Hgb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TS, transferrin saturation; Fer, ferritin. Data are expressed as the mean (standard deviation), median (interquartile range), number, or percentage, wherever appropriate.

To assess the prediction of anemia-related biomarkers with the risk of inadequate PD, logistic regression analysis was performed before and after adjusting for confounders. Gender, age, hypertension, diabetes mellitus, and PD duration were *a priori* balanced in logistic regression analyses. The gender differed significantly between the two groups (p = 0.001) in an unadjusted model. Hypertension control was reported as the preserve of the residual kidney function, which had an impact on the calculation of total Kt/V (Mathew et al., 2016). In many studies related to peritoneal dialysis, diabetes mellitus was considered as a factor that may have an influence on the results (Author Anonymous, 1996; Rocco M. et al., 2000; Wang et al., 2003). A younger age and diabetes were reported as significant risk factors for hyperphosphatemia in PD patients (Imtiaz et al., 2017), indicative of inadequate PD. PD, as a form of home dialysis, has a requirement of proficient operation and patience during daily dialysis. As for PD duration, it is reported that the function of the peritoneal membrane and the residual renal function may change rapidly in the first 2 years (Davies et al., 2001), which is the reason why the PD duration was taken into consideration. The effect-size estimate is denoted using odds ratios (ORs) and 95% confidence interval (95% CI).

The calibration capability was assessed using the −2 log likelihood ratio test, the Akaike information criterion (AIC), and the Bayesian information criterion (BIC) to inspect how closely the prediction probability for the addition of significant anemia-related biomarkers reflected the actual observed risk and the global fit of the modified risk model. In addition, decision curve analysis reflects the net benefit of adding anemia-related biomarkers. In this curve, the *X*-axis denotes thresholds for the risk of inadequate PD, and the *Y*-axis denotes net benefits on different thresholds. Furthermore, the area under the receiver operating characteristics curve (AUROC) was also calculated for each model.

The nomogram model was constructed using the "RMS" package in the R programming environment (version 3.5.2), and the predictive accuracy was reflected by the concordance index (C-index). Statistical power was calculated by using power and sample size calculations (PS) software version 3.0.7. Unless otherwise stated, STATA software version 16 (StataCorp, College Station, TX, USA) was used for data cleaning and statistical analyses. Without prior notice, the statistical significance was set at a probability of less than 5%.

Results

Baseline characteristics

Table 1 presents the baseline characteristics of the study participants in this study. Of 127 patients involved, 76 were in the adequate group (as controls) and 51 were in the inadequate group (as cases). The gender differed significantly between the two groups (p = 0.001). Distributions of age and PD duration, as well as percentages of hypertension and diabetes, were comparable. As for anemia-related biomarkers, only TS was significantly higher in cases than that in controls (p = 0.006).

TABLE 2 Risk prediction of three anemia-related biomarkers for inadequate peritoneal dialysis.

Significant risk factor	Odds ratio; 95% confidence interval; P	
	Before adjustment	After adjustment
Hgb (per 20 g/L increment)	0.92, 0.86 to 0.98, 0.014	0.81, 0.70 to 0.95, 0.009
MCHC (per +5 g/L increment)	0.97, 0.96 to 0.99, 0.019	0.93, 0.88 to 0.98, 0.009
TS (per +5% increment)	0.91, 0.83 to 0.99, 0.042	0.77, 0.64 to 0.94, 0.012

Abbreviations: Hgb, hemoglobin; MCHC, mean corpuscular hemoglobin concentration; TS, transferrin saturation; OR, odds ratio; 95% CI, 95% confidence interval.

TABLE 3 Prediction accuracy gained by adding three anemia-related biomarkers to the basic model for inadequate peritoneal dialysis.

Calibration and discrimination statistics	Basic model	Full model
AIC	164.1	82.3
BIC	175.5	97.9
LR test (χ^2)	14.08	
LR test (P)	0.003	
AUROC (95% CI)	0.819 (0.719; 0.919)	0.719 (0.594; 0.844)
ROC (P)	0.085	

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; LR, likelihood ratio. The basic model included age, gender, diabetes mellitus, hypertension, and duration of peritoneal dialysis.

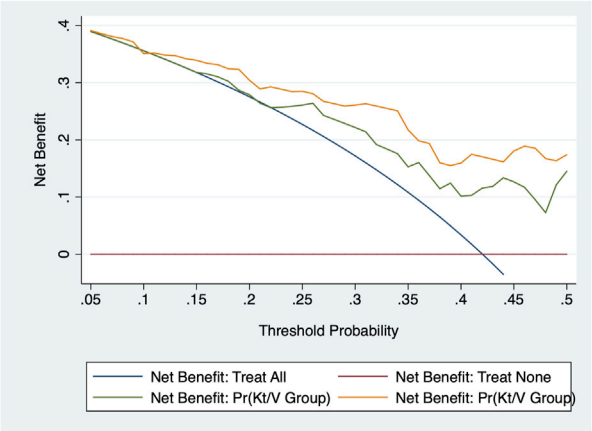


FIGURE 1
Decision curve analysis of adding three anemia-related biomarkers to the basic model in the prediction of the adequacy of peritoneal dialysis.

Predicting inadequate PD

Table 2 shows the risk prediction of anemia-related biomarkers under study for inadequate PD. After balancing age, gender, hypertension, diabetes mellitus, and PD duration, 20 g/L increment in Hgb was observed to significantly reduce the risk of inadequate PD by 19% (0.81; 0.70 to 0.95; 0.009), 5 g/L increment in the MCHC by 7% (0.93; 0.88 to 0.98; 0.009), and 5% increment in TS by 23% (0.77; 0.64 to 0.94; 0.012). In view of the statistical significance, power estimation revealed that the aforementioned association was convincing, with the power being over 80%.

Prediction accuracy assessment

Table 3 shows the prediction accuracy driven by adding anemia-related biomarkers to the basic model (including age, gender, diabetes mellitus, hypertension, and PD duration). As for calibration, a reduction in both the AIC and BIC statistics was greater than 10 after adding biomarkers to the basic model. In addition, the likelihood ratio test revealed the significance to be at a level of 3%, which was further confirmed by decision curve analysis (Figure 1) and the AUROC.

Nomogram model

To facilitate clinical application, a nomogram model was constructed upon being stratified by gender, as illustrated in Figure 2. The prediction model was constructed on the basis of age, diabetes mellitus, hypertension, and PD duration, as well as three significant anemia-related biomarkers. This model was featured by a decent accuracy, as reflected by both the C-index (0.686 for men and 0.825 for women) and calibration curves after bootstrapping 1,000 repetitions (Supplementary Figure S1).

For example, assuming a woman aged 60 years old with diabetes mellitus and hypertension, PD for 3 years, Hgb of 90 g/L, MCHC of 315 g/L, TS of 15%, and her total points being 350, then the probability of experiencing inadequate PD was estimated to be nearly 90%.

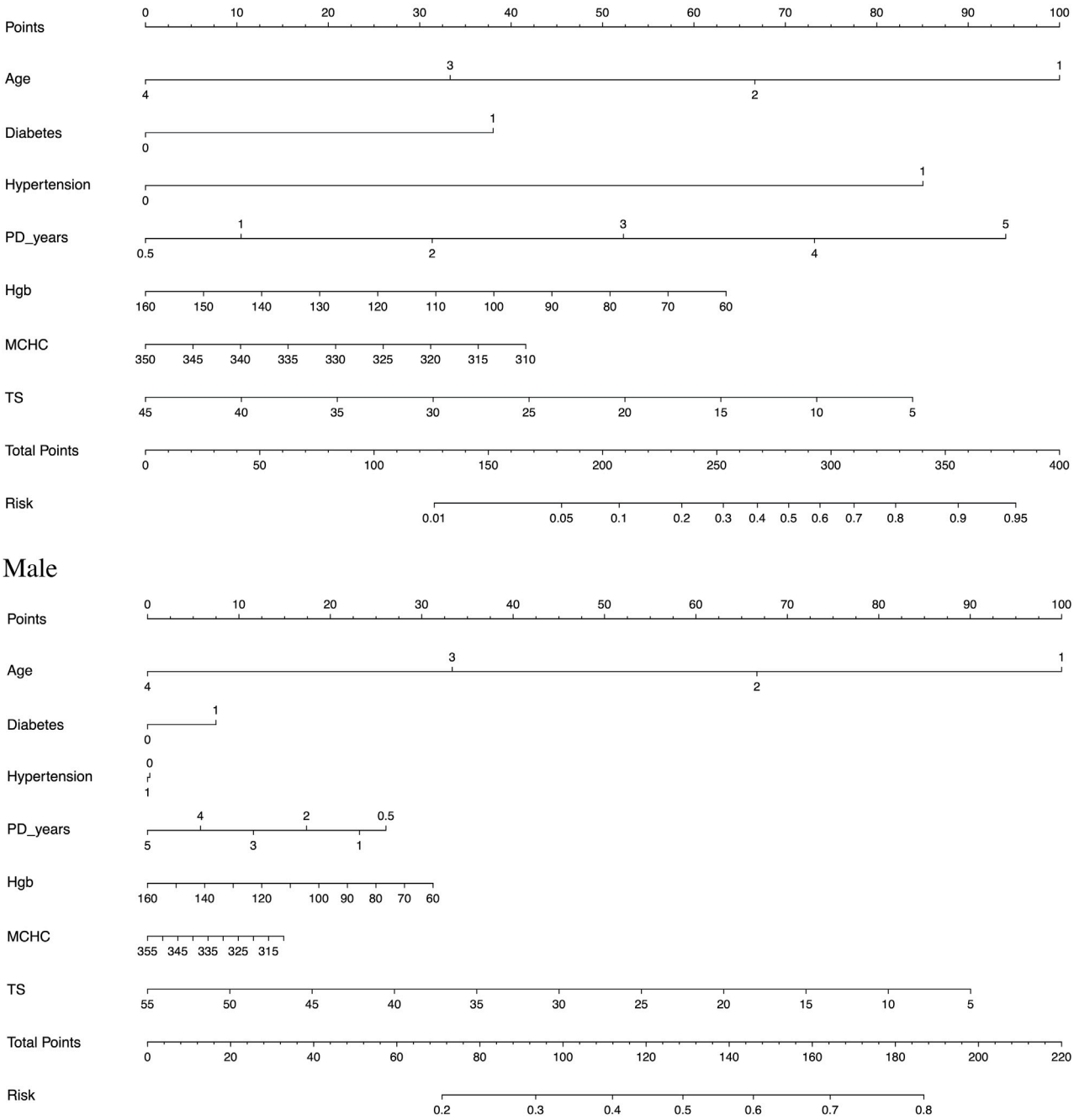


FIGURE 2
Nomogram prediction models constructed and stratified by gender on the basis of age (age is described as 1–4, with under 30 years old as 1, 31–50 as 2, 51–70 as 3, and 71–90 as 4), diabetes mellitus, hypertension, and PD duration, as well as three significant anemia-related biomarkers (hemoglobin (Hgb), mean corpuscular hemoglobin concentration (MCHC), and transferrin saturation (TS)), respectively.

Discussion

The aim of this retrospective study was to examine the prediction of anemia-related biomarkers for inadequate PD in patients with CKD. Our key findings are that the deterioration of three anemia-related biomarkers (Hgb, MCHC, and TS) can precipitate the development of inadequate PD in Chinese patients with CKD. To the best of our knowledge, this is, thus far, the first report that has evaluated the prediction of anemia-related biomarkers for inadequate PD among Chinese adults.

Some studies have examined the association between anemia and PD adequacy, whereas the results of these studies are inconsistent and inconclusive. For instance, a randomized

prospective cohort in Hong Kong showed that patients with their total Kt/V maintained below 1.70 had lower levels of Hgb and more severe anemia (Lo et al., 2003). A significant correlation between anemia-related biomarkers and the total Kt/V was demonstrated in a study in Czech Republic, which made a conclusion that the relationship between anemia and blood purification is best expressed using the Kt/V index in PD patients (Opatrny et al., 1999). In addition, data from the Healthcare Financing Administration (HCFA) ESRD Core Indicators Project indicated that people in PD with lower Kt/V tend to have significantly lower mean hematocrit values, with a greater proportion of patients having a hematocrit level of less than 28% (Rocco M. V. et al., 2000). A retrospective cohort study in China demonstrated that PD patients with dialysis inadequacy had lower Hgb levels (Li et al., 2003). However, a study from Canada reported that Kt/V provided by PD did not seem important in the improvement of anemia (Ossareh et al., 2003). The reasons behind these conflicting findings are manifold. The first reason might be due to the differences in study populations. Mounting evidence suggests that inter-individual differences in anemia parameters have been linked in part to genetic polymorphisms in dialysis patients (Girndt et al., 2006; Kopp and Winkler, 2018). The second reason might be related to unaccounted residual confounding, which might yield a possible selection bias. The third reason is that the contribution of any individual biomarkers to reflect the level of Kt/V and the adequacy of PD is likely to be small, considering the complex nature of PD (Li and Szeto, 2003; Ryckelynck et al., 2012).

The important finding of this study is that TS differed significantly between patients in the adequate and inadequate groups, which is rarely reported in the medical literature. This finding is biologically plausible. TS can reflect a soluble transferrin receptor, which is a biomarker of erythropoiesis and is often impaired in dialysis patients (Gafter-Gvili et al., 2019). There is also evidence that TS can reflect the levels of anemia in PD patients and can further indicate the inadequacy of dialysis (Yavuz et al., 2004; Chung et al., 2012; Belo et al., 2019). Moreover, further regression analyses revealed that an increase in Hgb, MCHC, and TS levels was independently and significantly associated with the reduced risk of inadequate PD in patients with CKD. In light of the cross-sectional nature of this study, our findings support the candidacy of anemia-related biomarkers in the development of inadequate PD among patients with CKD.

Because of the complicated profiles of inadequate PD in patients with CKD, the contribution of individual biomarkers may be small or dependent on the presence of other biomarkers. The majority of studies in this field focused on single biomarkers, while disregarding other relevant biomarkers and overlooking their joint contribution. In this study, we not only assessed the association of anemia-related biomarkers with inadequate PD individually but also jointly in the form of a nomogram. In view of the marked gender differences in the incidence of inadequate PD among patients with CKD, we separately constructed nomogram models for anemia-related biomarkers and the risk of substandard Kt/V by gender, and both models were featured through decent prediction accuracy. For practical reasons, these nomogram models can be routinely applied in clinical practice to facilitate clinical decision-making and the personalized management of PD.

Several possible limitations should be acknowledged for this study. First, the cross-sectional data on this study preclude further comments on the cause–effect relationship between anemia-related biomarkers and Kt/V, and all study participants were recruited from one center, requiring further external validation. Second, some unmeasured characteristics of study subjects, such as dietary habits, might confound the association of anemia-related biomarkers with PD (Finkelstein et al., 2011). Third, all study participants were enrolled from a single center, which might yield a possibility of population stratification and limit the extrapolation of our conclusions. We agree that future studies that examined the implication of anemia-related biomarkers in inadequate PD are encouraged.

In spite of these limitations, our findings indicate the deterioration of three anemia-related biomarkers (Hgb, MCHC, and TS) can precipitate the development of inadequate PD in Chinese patients with CKD. Importantly, we have constructed a nomogram model based on anemia-related biomarkers for predicting inadequate PD, which can help provide evidence for medical decision-making and arguments for future research work on anemia as candidate monitors. Meanwhile, we hope that further investigations on the molecular mechanisms linking anemia-related biomarkers and PD inadequacy are warranted.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the ethics committees of the Beijing Hospital of Traditional Chinese Medicine. The patients/participants provided their written informed consent to participate in this study.

Author contributions

W-JZ and W-QN planned and designed the study, and directed its implementation. W-JZ and W-QN drafted the protocol. X-GZ and M-CL obtained statutory and ethics approvals. Y-SL and QL contributed to data acquisition. J-LL and F-QC conducted statistical analyses. JZ and ZC carried out the data preparation and quality control. J-LL, ZC, and W-QN wrote the manuscript. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Capital Health Development Scientific Research Project (grant no. 2020-3-2235) and the Beijing Municipal Administration of Hospitals Incubating Program (grant no. PZ2021022).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors, and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2023.1170537/full#supplementary-material

References

American Diabetes Association (2013). Diagnosis and classification of diabetes mellitus. *Diabetes Care* 36 (1), S67–S74. doi:10.2337/dc13-S067

Author Anonymous (1996). Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. Canada-USA (CANUSA) peritoneal dialysis study group. *J. Am. Soc. Nephrol.* 7 (2), 198–207. doi:10.1681/ASN.V72198

Bartosova, M., and Schmitt, C. P. (2018). Biocompatible peritoneal dialysis: The target is still way off. *Front. Physiol.* 9, 1853. doi:10.3389/fphys.2018.01853

Belo, L., Rocha, S., Valente, M. J., Coimbra, S., Catarino, C., Bronze-da-Rocha, E., et al. (2019). Hepcidin and diabetes are independently related with soluble transferrin receptor levels in chronic dialysis patients. *Ren. Fail* 41 (1), 662–672. doi:10.1080/0886022X.2019.1635893

Chan, C. T., Blankestijn, P. J., Dember, L. M., Gallieni, M., Harris, D. C. H., Lok, C. E., et al. (2019). Dialysis initiation, modality choice, access, and prescription: Conclusions from a kidney disease: Improving global outcomes (KDIGO) controversies conference. *Kidney Int.* 96 (1), 37–47. doi:10.1016/j.kint.2019.01.017

Chung, M., Moorthy, D., Hadar, N., Salvi, P., Iovin, R. C., and Lau, J. (2012). *Biomarkers for assessing and managing iron deficiency anemia in late-stage chronic kidney disease*. Rockville (MD): Agency for Healthcare Research and Quality.

Davies, S. J., Phillips, L., Naish, P. F., and Russell, G. I. (2001). Peritoneal glucose exposure and changes in membrane solute transport with time on peritoneal dialysis. *J. Am. Soc. Nephrol.* 12 (5), 1046–1051. doi:10.1681/ASN.V1251046

Finkelstein, F. O., Juergensen, P., Wang, S., Santacroce, S., Levine, M., Kotanko, P., et al. (2011). Hemoglobin and plasma vitamin C levels in patients on peritoneal dialysis. *Perit. Dial. Int.* 31 (1), 74–79. doi:10.3747/pdi.2009.00154

Gafter-Gvili, A., Schechter, A., and Rozen-Zvi, B. (2019). Iron deficiency anemia in chronic kidney disease. *Acta Haematol.* 142 (1), 44–50. doi:10.1159/000496492

Girndt, M., Heine, G. H., Kohler, H., and DialGene, C. (2006). Gene polymorphism association studies in dialysis: Anemia and host immunity. *Semin. Dial.* 19 (3), 227–231. doi:10.1111/j.1525-139X.2006.00159.x

Himmelfarb, J., Vanholder, R., Mehrotra, R., and Tonelli, M. (2020). The current and future landscape of dialysis. *Nat. Rev. Nephrol.* 16 (10), 573–585. doi:10.1038/s41581-020-0315-4

Imtiaz, R., Hawken, S., McCormick, B. B., Leung, S., Hiremath, S., and Zimmerman, D. L. (2017). Diabetes mellitus and younger age are risk factors for hyperphosphatemia in peritoneal dialysis patients. *Nutrients* 9 (2), 152. doi:10.3390/nu9020152

Kopp, J. B., and Winkler, C. A. (2018). Genetics, genomics, and precision medicine in end-stage kidney disease. *Semin. Nephrol.* 38 (4), 317–324. doi:10.1016/j.semnephrol.2018.05.002

Kovesdy, C. P. (2022). Epidemiology of chronic kidney disease: An update 2022. *Kidney Int. Suppl.* 12 (1), 7–11. doi:10.1016/j.kisu.2021.11.003

Li, P. K., and Szeto, C. C. (2003). Peritoneal dialysis adequacy in Asia--is higher better? *Perit. Dial. Int.* 23 (2), S65–S68. doi:10.1177/089686080302302s14

Li, S., Foley, R. N., Gilbertson, D. T., Liu, J., and Collins, A. J. (2003). Clinical factors associated with achieving K/DOQI hemoglobin targets in hemodialysis patients. *Int. Urol. Nephrol.* 35 (3), 399–405. doi:10.1023/b:urol.0000022951.17591.0b

Li, P. K., Chow, K. M., Van de Luijtgaarden, M. W., Johnson, D. W., Jager, K. J., Mehrotra, R., et al. (2017). Changes in the worldwide epidemiology of peritoneal dialysis. *Nat. Rev. Nephrol.* 13 (2), 90–103. doi:10.1038/nrneph.2016.181

Liu, S., Zhang, L., Ma, S., Xiao, J., Liu, D., Ding, R., et al. (2022). Kt/V reach rate is associated with clinical outcome in incident peritoneal dialysis patients. *Ren. Fail* 44 (1), 482–489. doi:10.1080/0886022X.2022.2048854

Liu, L. S., and Writing Group of 2010 Chinese Guidelines for the Management of Hypertension (2011). 2010 Chinese guidelines for the management of hypertension. *Zhonghua Xin Xue Guan Bing Za Zhi* 39 (7), 579–615.

Lo, W. K., Ho, Y. W., Li, C. S., Wong, K. S., Chan, T. M., Yu, A. W., et al. (2003). Effect of Kt/V on survival and clinical outcome in CAPD patients in a randomized prospective study. *Kidney Int.* 64 (2), 649–656. doi:10.1046/j.1523-1755.2003.00098.x

Mathew, A. T., Fishbane, S., Obi, Y., and Kalantar-Zadeh, K. (2016). Preservation of residual kidney function in hemodialysis patients: Reviving an old concept. *Kidney Int.* 90 (2), 262–271. doi:10.1016/j.kint.2016.02.037

NKF KDOQI guidelines (2006). Clinical practice guidelines and clinical practice recommendations. Clinical practice guidelines for peritoneal dialysis adequacy. Available at: http://kidneyfoundation.cachefly.net/professionals/KDOQI/guideline_upHD_PD_VA/pd_rec2.htm. (Last accessed on April 30, 2019).

Opatrny, K., Jr., Opatrna, S., Sefrna, F., and Wirth, J. (1999). The anemia in continuous ambulatory peritoneal dialysis patients is related to Kt/V index. *Artif. Organs* 23 (1), 65–69. doi:10.1046/j.1525-1594.1999.06221.x

Ossareh, S., Roozbeh, J., Krishnan, M., Liakopoulos, V., Bargman, J. M., and Oreopoulos, D. G. (2003). Fatigue in chronic peritoneal dialysis patients. *Int. Urol. Nephrol.* 35 (4), 535–541. doi:10.1023/b:urol.0000025610.67447.b9

Rocco, M., Soucie, J. M., Pastan, S., and McClellan, W. M. (2000a). Peritoneal dialysis adequacy and risk of death. *Kidney Int.* 58 (1), 446–457. doi:10.1046/j.1523-1755.2000.00184.x

Rocco, M. V., Frankenfield, D. L., Frederick, P. R., Pugh, J., McClellan, W. M., and Owen, W. F. (2000b). Intermediate outcomes by race and ethnicity in peritoneal dialysis patients: Results from the 1997 ESRD Core Indicators Project. *Perit. Dial. Int.* 20 (3), 328–335. doi:10.1177/089686080002000310

Ryckelynck, J. P., Ficheux, M., Castrale, C., Henri, P., and Lobbedez, T. (2012). Adequacy in peritoneal dialysis. *Contrib. Nephrol.* 178, 195–199. doi:10.1159/000337852

Thurlow, J. S., Joshi, M., Yan, G., Norris, K. C., Agodoa, L. Y., Yuan, C. M., et al. (2021). Global epidemiology of end-stage kidney disease and disparities in kidney replacement therapy. *Am. J. Nephrol.* 52 (2), 98–107. doi:10.1159/000514550

Wang, A. Y., Sanderson, J., Sea, M. M., Wang, M., Lam, C. W., Li, P. K., et al. (2003). Important factors other than dialysis adequacy associated with inadequate dietary protein and energy intakes in patients receiving maintenance peritoneal dialysis. *Am. J. Clin. Nutr.* 77 (4), 834–841. doi:10.1093/ajcn/77.4.834

Wilkie, M., and Davies, S. (2018). Insights on peritoneal dialysis in China. *Perit. Dial. Int.* 38 (Suppl. 2), S16–S18. doi:10.3747/pdi.2018.00224

Yang, C., Gao, B., Zhao, X., Su, Z., Sun, X., Wang, H. Y., et al. (2020a). Executive summary for China kidney disease network (CK-net) 2016 annual data report. *Kidney Int.* 98 (6), 1419–1423. doi:10.1016/j.kint.2020.09.003

Yang, C., Wang, H., Zhao, X., Matsushita, K., Coresh, J., Zhang, L., et al. (2020b). CKD in China: Evolving spectrum and public health implications. *Am. J. Kidney Dis.* 76 (2), 258–264. doi:10.1053/j.ajkd.2019.05.032

Yang, C., Yang, Z., Wang, J., Wang, H. Y., Su, Z., Chen, R., et al. (2021). Estimation of prevalence of kidney disease treated with dialysis in China: A study of insurance claims data. *Am. J. Kidney Dis.* 77 (6), 889–897.e1. doi:10.1053/j.ajkd.2020.11.021

Yavuz, A., Akbas, S. H., Tuncer, M., Kolagasi, O., Cetinkaya, R., Gurkan, A., et al. (2004). Influence of inflammation on the relation between markers of iron deficiency in renal replacement therapy. *Transpl. Proc.* 36 (1), 41–43. doi:10.1016/j.transproceed.2003.11.054

frontiers | Frontiers in Physiology

TYPE Review
PUBLISHED 25 September 2023
DOI 10.3389/fphys.2023.1220450

OPEN ACCESS

EDITED BY
Paola Pontrelli,
University of Bari Aldo Moro, Italy

REVIEWED BY
Jianhui Zhou,
Chinese PLA General Hospital, China
Liu Shiyi,
China Academy of Chinese Medical Sciences, China

*CORRESPONDENCE
Jianping Liu,
ndefy14105@ncu.edu.cn

RECEIVED 10 May 2023
ACCEPTED 13 September 2023
PUBLISHED 25 September 2023

CITATION
Li J, Liu Y and Liu J (2023), A review of research progress on mechanisms of peritoneal fibrosis related to peritoneal dialysis.
Front. Physiol. 14:1220450.
doi: 10.3389/fphys.2023.1220450

A review of research progress on mechanisms of peritoneal fibrosis related to peritoneal dialysis

Jin'e Li[1,2], Yinghong Liu[3] and Jianping Liu[1]*

[1]Department of Endocrinology and Metabolism, The Second Affiliated Hospital of Nanchang University, Nanchang, China, [2]Jiangxi Medical College, Nanchang University, Nanchang, China, [3]Department of Nephrology, Second Xiangya Hospital, Central South University, Changsha, China

Peritoneal dialysis (PD) is an effective alternative treatment for patients with end-stage renal disease (ESRD) and is increasingly being adopted and promoted worldwide. However, as the duration of peritoneal dialysis extends, it can expose problems with dialysis inadequacy and ultrafiltration failure. The exact mechanism and aetiology of ultrafiltration failure have been of great concern, with triggers such as biological incompatibility of peritoneal dialysis solutions, uraemia toxins, and recurrent intraperitoneal inflammation initiating multiple pathways that regulate the release of various cytokines, promote the transcription of fibrosis-related genes, and deposit extracellular matrix. As a result, peritoneal fibrosis occurs. Exploring the pathogenic factors and molecular mechanisms can help us prevent peritoneal fibrosis and prolong the duration of Peritoneal dialysis.

KEYWORDS

peritoneal dialysis, peritoneal fibrosis, EMT, TGF-β1, mechanism

1 Introduction

The peritoneum is made up of a single layer of mesoderm-derived mesothelial cells and a thin layer of connective tissue consisting of a dense subepithelial band. The dense band, composed mainly of collagen fibre bundles, along with some lymphocyte tubes, fibroblasts, mast cells, macrophages, and capillaries, plays a crucial role in maintaining the function and structure of the peritoneum (Bajo et al., 2017). The peritoneal natural semipermeable membrane is responsible for ultrafiltration and solute diffusion during dialysis by converting solutes and water and removing metabolites while maintaining water and electrolyte balance.

Peritoneal dialysis is a cost-effective method of dialysis (Li et al., 2017) that is gaining international attention. However, various nonphysiological factors in the dialysate, such as hyperosmolarity, hyperglycaemia, low pH, glucose degradation products (GDPs), and advanced glycosylation end products (AGEs), can lead to chronic stimulation and damage of the peritoneum in PD patients, causing peritoneal sclerosis. Peritoneal fibrosis has always been a hot topic of research. Here, we provide an overview of how factors such as inflammation, oxidative stress, glucose metabolism, and hypoxia mediate peritoneal fibrosis through cytokine generation and molecular pathway activation.

2 EMT induced by TGF-β

Epithelial-mesenchymal transition (EMT) is a complex biological process characterized by the gradual loss of epithelial-specific markers, such as E-cadherin and zonula occludens-1, and the acquisition of a fibroblast phenotype expressing fibroblast-specific protein 1 (FSP1)

and α-smooth muscle actin (α-SMA). This process is accompanied by changes in cellular behaviour and the production of extracellular matrix (ECM) (Kalluri and Neilson, 2003).

The exact mechanisms underlying the EMT of peritoneal mesothelial cells remain unclear, but they are thought to involve the interaction of cytokines, inflammatory factors, and transcription regulators. Evidence suggests that Smad and non-Smad signalling pathways induced by TGF-β1 play a dominant role in the EMT of peritoneal fibrosis (Lho et al., 2021). In the early phase of fibrosis, glucose, GDPs, and advanced glycosylation end products (AGEs) can upregulate type I and type II TGF-β receptors in mesothelial cells (Suryantoro et al., 2023) by activating protein kinase C-α (PKC-α) (Wang et al., 2016). TGF-β1 signalling activates the phosphorylation of Smad2 and Smad3 via type I TGF-β receptors, and Smad2/Smad3 are transported to the nucleus, where they directly bind to DNA and regulate the transcription of target genes, including Snail, collagen, α-SMA, fibronectin, CTGF, β-catenin, plasminogen activator inhibitor-1 (PAI-1), and matrix metalloproteinase-2 (MMP2), promoting fibrosis (Derynck and Zhang, 2003; Hirahara et al., 2009; Xiao et al., 2010; Lei et al., 2012; Zhang et al., 2022a; Huang et al., 2022; Masola et al., 2022) (Figure 1). Smad1/5/8 proteins activated by ALKs in response to BMP (bone morphogenetic proteins) one to four or other ligands are also transported to the nucleus to regulate the transcription of target genes (Balzer, 2020). In addition to the Smad-dependent signalling pathway, there are also various non-Smad signalling pathways involved in the process of fibrosis, such as PI3K/Akt, c-Jun N-terminal kinases (JNK), Wnt/β-catenin, and ERK/NF-κB (Liu et al., 2012; Jang et al., 2013; Zhang et al., 2013; Lamouille et al., 2014).

Numerous studies have reported various initiating factors in epithelial-mesenchymal transition (EMT). For instance, caveolin-1 has been proposed to play a critical role in EMT associated with peritoneal fibrosis in patients with Parkinson's disease (Strippoli et al., 2015). Furthermore, overexpression of insulin-like growth factor 1 receptor (IGF-1R) has been linked to the promotion of EMT in human peritoneal mesothelial cells (Xia et al., 2022). These findings have expanded our understanding of potential strategies for preventing and treating EMT.

3 Inflammation

Inflammation is a frequent underlying cause of peritoneal fibrosis in patients with PD. While it can be directly induced by pathogenic microorganisms, peritoneal inflammation may also result from the accumulation of uraemia toxins, mechanical stress on blood vessel walls, ageing, and complications of diabetes (Cueto-Manzano et al., 2007). In PD patients, an increase in the number of peritoneal macrophages suggests chronic peritoneal inflammation, even in the absence of acute peritonitis.

The inflammatory response is a complex process involving multiple molecular mechanisms, inflammatory mediators, and signalling pathways. The peritoneum can be damaged by various factors, activating macrophages and neutrophils that mediate NF-κB signalling pathways via Toll-like receptors (TLRs) and release numerous inflammatory cytokines, such as IL-6, IL-1β, IL-8, and TNF-α, leading to peritoneal fibrosis (Kato et al., 2004). TLRs can also activate the downstream molecules of JNK, p38MAPKs, and ERK1/2 through the MyD88 signalling pathway, promoting the expression of proinflammatory cytokines. In addition, the NLRP3 inflammasome, a cellular complex composed of proteins, can activate the cysteine-dependent aspartate-directed proteolytic enzyme and induce the production of IL-1 and IL-18, resulting in inflammatory responses (Hautem et al., 2017) (Figure 1). IL-6 plays a crucial role in regulating inflammation and can be secreted by macrophages, monocytes, and human peritoneal mesothelial cells. Exposure to dialysate and IL-1β can trigger the release of IL-6, which has been reported to increase proportionally with the glucose concentration in the dialysate (Milan Manani et al., 2016; Yang et al., 2020). IL-6, along with soluble IL-6 receptors, can facilitate the synthesis and secretion of MCP-1, MCP-3, and IL-8, as well as adhesion molecules and angiogenesis factors (Salgado et al., 2002; Bellón et al., 2011). IL-17, mainly produced by Th17 cells and γδ T cells, was detected in peritoneal biopsies of PD patients but not healthy subjects (Rodrigues-Díez et al., 2014). IL-17 can promote the production of ELR + CXC chemokines in mesothelial cells, such as CXCL1 and CXCL8. Furthermore, it is believed that IL-17 might directly stimulate mesothelial cells to produce VEGF via an unidentified mechanism (Witowski et al., 2018).

In addition, recent studies have begun to focus on the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway (Decout et al., 2021; Zhang et al., 2022b). Inflammation leads to damage to mitochondrial DNA (mtDNA), which can be released into the cytoplasm under cellular stress and recognized by various DNA sensing mechanisms, including TLR-9, cytoplasmic cGAS-STING signalling, and inflammasome activation, which can result in the development of fibrosis, as well as pathological angiogenesis and endothelial-to-mesenchymal transition (Wang et al., 2022a; Wang et al., 2022b). In the future, there may be more research on peritoneal fibrosis related to peritoneal dialysis that focuses on the cGAS-STING pathway.

4 Regulation of epigenetic genes

The role of epigenetic modifications in fibrosis has garnered increasing recognition. Epigenetic regulation mainly includes DNA methylation, histone modification, and noncoding RNA regulation. It is widely believed that DNA methylation of cytosine-phosphate-guanine (CpG) dinucleotide sites near the gene promoter leads to target gene silencing. In 2017, Kim et al. found that DNMT1 (DNA methyltransferase 1) inhibits RASAL1 protein expression by promoting hypermethylation of RASAL1 (Ras GTPase activating-like protein 1), which in turn upregulates the expression of TGF-β1 and accelerates peritoneal thickening *in vivo* in experiments with encapsulating peritoneal sclerosis rats (Kim et al., 2014). Histone methylation has also been implicated in PF, as Maeda et al. demonstrated that the expression of H3K9 histone methyltransferase and H3K4 methyltransferase can exacerbate the thickening of the submesothelial compact zone (Maeda et al., 2017). Recent studies have also linked high expression of EZH2 (Zeste homologue enhancer 2) with peritoneal fibrosis, possibly through the activation of profibrotic signalling pathways (Wang et al., 2020; Shi et al., 2022).

Furthermore, there is a growing body of evidence indicating that different types of noncoding RNAs, including microRNAs (miRNAs) and long-chain noncoding RNAs (lncRNAs), are involved in the transcription of genes that regulate peritoneal fibrosis (Liu et al., 2019) (Figure 1). Studies have suggested that certain miRNAs, such as miR-129–5p and miRNA-302c, have a protective effect on the peritoneum during dialysis, while others, such as miRNA-30b, miRNA-23, and miRNA-21, can exacerbate peritoneal fibrosis (Xiao et al., 2015; Morishita et al., 2016a; Hirai et al., 2017; Lopez-Anton et al., 2017; Yanai et al., 2018; Zhang et al., 2019). The functions of miRNAs are diverse and complex, primarily involving the regulation of gene expression through interactions with DNA, RNA, proteins, or their combinatorial interactions involved in transcriptional and posttranscriptional regulation (Guo et al., 2020). Some researchers also believe that lncRNAs, such as BC049991 and AK080622, may participate in peritoneal fibrosis by influencing heat shock protein 72 (HSP72) (Bergmann and Spector, 2014). Additionally, lncRNA AV310809 promotes TGF-β1 by activating the Wnt2/β-catenin signalling pathway, which induces EMT in human peritoneal mesothelial cells (Bergmann and Spector, 2014). While circular RNAs (circRNAs) have been implicated in organ fibrosis, such as cardiac fibrosis, liver fibrosis, and pulmonary fibrosis (Li et al., 2019; Yousefi and Soltani, 2021), relatively little is known about their involvement in peritoneal fibrosis. It is possible that circRNAs may be involved in peritoneal fibrosis by inducing EMT, but further research is needed to determine the specific principles and molecular mechanisms.

5 Autophagy and apoptosis

Autophagy is a double-edged sword. On the one hand, it can be activated by cells to prevent organelle damage caused by reactive oxygen species (ROS) under certain external stimuli. However, it may also induce epithelial apoptosis or EMT. Studies have shown that autophagy initiation can prevent peritoneal tissue damage by blocking NLRP3/IL-1β-mediated inflammasome activation (Wu et al., 2016) (Figure 1).

Normally, autophagy activation and inhibition are in balance, and excessive activation or inhibition can lead to oxidative stress, inflammatory damage, and even fibrosis. In fact, it has been reported that rapamycin, an autophagy inducer, stimulates mTOR signalling in peritoneal mesodermal cells activated by hyperglycaemia, reducing EMT and improving peritoneal fibrosis (Wu et al., 2018). Conversely, high glucose peritoneal dialysate has been shown to induce autophagy and fibrosis in human peritoneal mesothelial cells (Wu et al., 2018). This may be involved in EMT, the proinflammatory response, and angiogenesis by regulating the TGF-β/Smad3, EGFR/ERK1/2, STAT3/NF-κB, and β-catenin axes (Shi et al., 2021), suggesting that autophagy plays a role in peritoneal fibrosis.

Autophagy is reported to contribute to apoptosis as type II programmed cell death via autodigestive cellular progression or extracellular stimulation (Ghavami et al., 2015; Zou et al., 2016). Some researchers have reported that high-glucose peritoneal dialysate induces Beclin 1-dependent autophagy in human peritoneal mesoepithelial cells (HPMCs) and that autophagy inhibition reduces EMT, fibrosis and apoptosis in HPMCs (Wu et al., 2018). It has also been suggested that promoting mitochondrial synthesis and inhibiting apoptosis can improve peritoneal fibrosis (Li et al., 2022).

6 Pseudohypoxia and angiogenesis

Angiogenesis is considered to be a significant factor in peritoneal ultrafiltration failure (Schilte et al., 2009). Neovascularization increases the effective surface area for solute exchange and decreases osmotic pressure driven by glucose from the peritoneal dialysate, resulting in a decrease in ultrafiltration volume. Neovascularization is often associated with hypoxia in physiological or pathological states (Lei et al., 2012). Peritoneal mesenchymal cells overmetabolize glucose, leading to pseudohypoxia with increased NADH-NAD+ (oxidized-reduced nicotinamide dinucleotide ratio) in the cytosol (Krediet and Parikova, 2022) (Figure 1). This ratio promotes the expression of hypoxia-inducible factor-1 (HIF-1), which is one of the most important regulators in the hypoxia response. HIF-1 can regulate the transcription of various genes, mediate the occurrence of EMT, and thus participate in peritoneal fibrosis. YANG et al. have suggested that the activation of the HIF-1α/STAT3 signaling pathway is the main contributor to EMT of mesenchymal cells induced by high glucose, and that knockdown of HIF-1α could alleviate the EMT and fibrosis process (Yang et al., 2021). Yoshiyuki et al. found that hypoxia can promote the expression of HIF-1α, Snail-1, VEGF, and MMP-2 in rat mesenchymal cells, which induces EMT, and that HIF-1α inhibitors can diminish fibrosis by suppressing the expression of these factors (Morishita et al., 2016b). VEGF is a key player in peritoneal angiogenesis, and studies have shown that peritoneal dialysis solution with glucose is related to the growth of VEGF (Zweers et al., 2001). GDPs in PD solution can induce the formation of AGEs, and the AGE (RAGE) receptor plays a profibrotic role by mediating the activation of VEGF to induce capillary angiogenesis and promoting TGF-β-induced EMT (De Vriese et al., 2006; Boulanger et al., 2007). Angiogenesis is regulated by cell growth factors such as VEGF and basic fibroblast growth factor (bFGF), as well as statins such as angiostatin and endostatin (ES) (Kakuta et al., 2005; Tanabe et al., 2007; Nakao et al., 2010).

Apart from VEGF, several other factors contribute to peritoneal neovascularization. Aquaporin-1 (AQP 1), which is responsible for fluid transport, plays a vital role in angiogenesis and endothelial cell migration (Saadoun et al., 2005). Angiotensin 2 (Ang-2) is an angiogenic factor that has been found to be involved in peritoneal neovascularization in rats with EPS (Io et al., 2004). Prostaglandin E2 and MCP-1 enhance epithelial cell migration and induce the transcription of angiogenin-related genes, contributing to angiogenesis (Ito et al., 2000; Xiao et al., 2010). Moreover, peritoneal smooth muscle cells are activated after infection and induce the formation of new blood vessels by producing proangiogenic factors such as TGF-β, fibroblast growth factor, VEGF, tumour necrosis factor-α, and IL-8 (Aroeira et al., 2005). Inflammatory factors such as IL-1β and IL-6 may also participate in neovascularization by stimulating endothelial progenitor cell proliferation and inducing VEGF synthesis (Rosell et al., 2009; Catar et al., 2017).

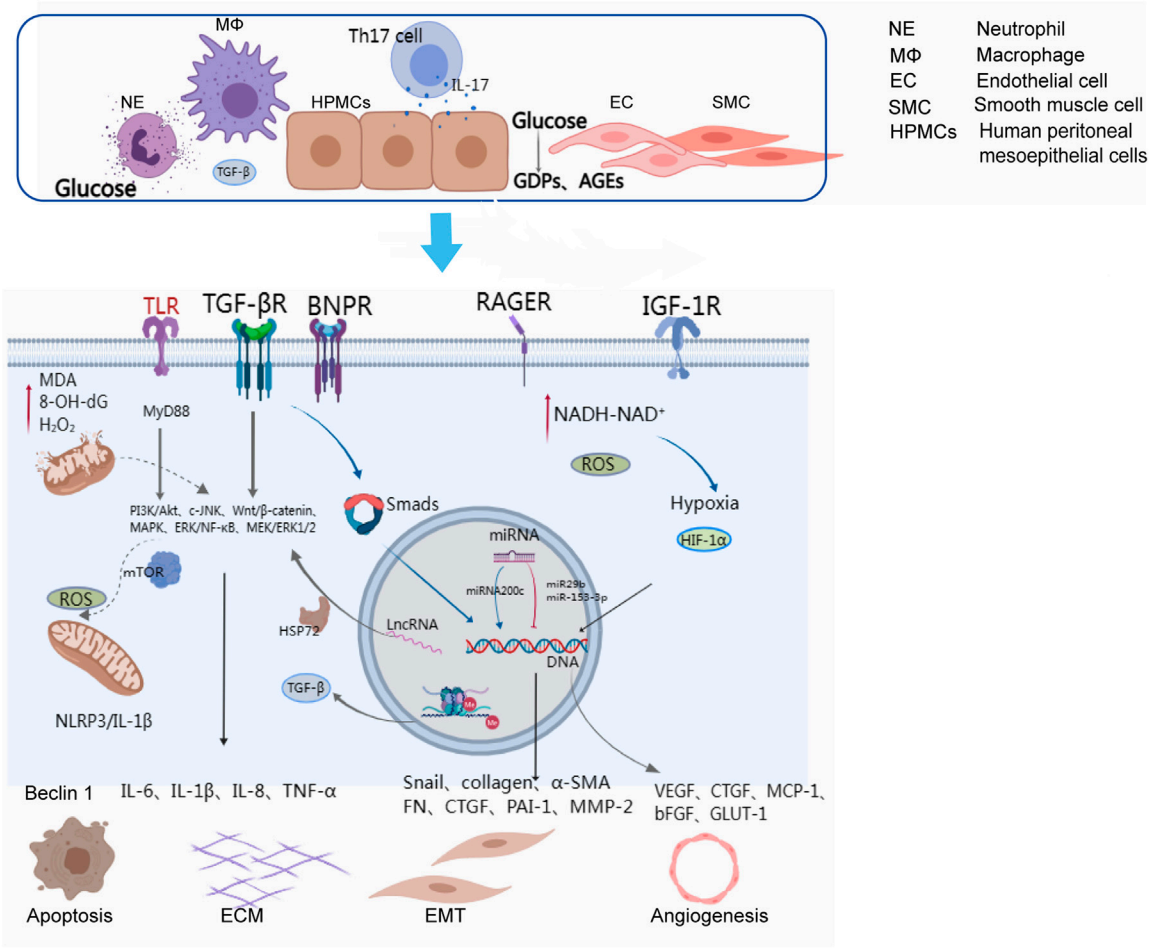


FIGURE 1
Cells and activated molecular pathways involved in peritoneal ultrafiltration failure.

7 Oxidative stress and glucose metabolism

Oxidative stress is a common occurrence in patients with chronic kidney disease (CKD) and its severity increases with the progression of the disease (Dounousi et al., 2006). In patients undergoing peritoneal dialysis, oxidative stress is mainly attributed to the bioincompatibility components of the peritoneal dialysis fluid, such as high glucose concentration, acidic pH, high osmolarity (Liakopoulos et al., 2017) and uraemic toxins (Castoldi et al., 2010). The accumulation of glucose degradation products (GDPs) in the peritoneum triggers the formation of excessive advanced glycation end products (AGEs), reactive oxygen species (ROS), and advanced oxidized protein products (AOPPs). The main pathway of ROS formation is through increased glucose oxidative metabolism triggered by GDPs and AGEs. The accumulation of AGEs in the peritoneal dialysis fluid promotes the expression and accumulation of specific multiligand transmembrane receptors, known as RAGE, in the peritoneum (Figure 1). These receptors induce morphological modifications of intracellular proteins, which alter the structure of the extracellular matrix (ECM) composition and the receptors expressed on the peritoneal cell membrane. Finally, ROS are produced when AGEs and AGE-modified proteins closely integrate with RAGE. Furthermore, ROS mediate the activation of proinflammatory factors, cytokines, transcription factors and growth factors, contributing to downstream aberrant gene transcription and apoptosis (Roumeliotis et al., 2020).

Si et al. found that PD fluid indeed induces metabolic reprogramming in the mouse peritoneum through conducting gene expression profiling and metabolomics analyses. Specifically, this reprogramming is characterized by a state of hyperglycolysis (Si et al., 2019). Correcting the metabolic state in mesothelial cells may be a therapeutic approach to treating peritoneal fibrosis (Si et al., 2019; Fu et al., 2022). GLUTs and SGLTs are involved in glucose transport and energy metabolism (Onishi et al., 2015; Han et al., 2022). The presence of high glucose levels in peritoneal dialysis fluid can potentially stimulate the expression of GLUT1 and SGLT1, leading to enhanced glucose absorption and a reduction of the osmotic gradient for ultrafiltration (Schröppel et al., 1998; Hong et al., 2016). Unfortunately, this process can ultimately contribute to the development of peritoneal fibrosis. With the continuous emergence of new hypoglycaemic drugs, some have found that SGLT-2 inhibitors reduce the absorption of glucose in peritoneal dialysate by inhibiting the activity of SGLT-2 (Zhou et al., 2019).

They also significantly reduce the concentration of TGF-β, peritoneal thickening and fibrosis, and microvascular density, thus improving ultrafiltration (Balzer et al., 2020; Shentu et al., 2021). However, considering that the primary target of SGLT inhibitors in oral formulations is the renal tubules, it may be necessary to create more dosage forms, such as those that can be administered by intraperitoneal injection or added to peritoneal dialysis fluid, to improve peritoneal fibrosis.

8 Conclusion

In general, there are many factors involved in the development of peritoneal fibrosis in patients with abdominal dialysis, and the molecular signalling pathways involved are also complex, with interactions and influences on each other. Several factors are recognized for their importance in the development of peritoneal fibrosis in patients with PD. The most important is the use of traditional biocompatible peritoneal dialysis, which contains high glucose concentrations and glucose degradation products. Growth factor TGF-β1 is transformed by inducing many profibrotic events, including epithelium-mesenchymal transformation, fibroblast proliferation, and extracellular matrix deposition, playing a central role in peritoneal fibrosis. A solution containing high glucose stimulates the synthesis of TGF-β1 by activating protein kinase C in peritoneal cells and induces TGF-β type I and type II receptors, which induce various fibrosis-related signalling molecular transport pathways, including Smad-dependent and Smad-independent signalling pathways. Increasing studies on epigenetic regulation, hypoxic stimulation, and neovascularization are beginning to confirm their involvement. Peritonitis promotes peritoneal fibrosis through inflammatory factors such as IL-1β and IL-6, exacerbating the chronic induction of TGF-β1 synthesis (Kang et al., 1999), and promoting fibrosis events. Among the many factors involved in peritoneal fibrosis, EMT, the inflammatory response, autophagy, epigenetic regulation, and neovascularization are the dominant factors in fibrosis, of which TGF-β1 plays an important role in the activation of various signalling pathways, the induction of inflammatory factors, and the hypoxia stress response. Correspondingly, many scholars increasingly emphasize the proposed peritoneal mesothelial cell markers that reflect the inflammatory state of the peritoneum and the degree of fibrosis, and the application of clinical evaluation of peritoneal ultrafiltration function is an important part of the evaluation of the treatment effect. Carbohydrate antigen CA125, CTGF, suppression of tumorigenicity 2, MMP-2, and microRNAs (Mizutani et al., 2010; Ge et al., 2012; Barreto et al., 2013; Krediet and Struijk, 2013; Kim et al., 2019) are some of the biomarkers that have been proposed thus far, and the specificity and sensitivity of their diagnosis still need to be confirmed by more studies. Based on the above-related precipitating factors in the final treatment, the proposed peritoneal fibrosis treatments mainly include the use of biocompatible dialysate, tyrosine kinase inhibitors, inflammatory factor blockers, renin-angiotensin system inhibitors, and immunosuppressants, but most of these are still being studied in animal experiments or early clinical studies and are not widely used in clinical practice. In the future, more research is needed to further supplement the research targets and specific and detailed molecular mechanisms related to peritoneal fibrosis, and more clinical therapeutic drug intervention experiments will make greater contributions to delaying peritoneal fibrosis and providing more effective abdominal dialysis therapy for patients with PD.

Author contributions

JL crafted and authored the manuscript, while YL contributed valuable ideas, and JPL meticulously revised and thoroughly reviewed the document. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the National Natural Science Foundation of China (Grant Nos. 82160162, and 81760150) and the Key Project of Jiangxi Provincial Natural Science Foundation (Grant No. 20202ACBL206008).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

Aroeira, L. S., Aguilera, A., Selgas, R., Ramírez-Huesca, M., Pérez-Lozano, M. L., Cirugeda, A., et al. (2005). Mesenchymal conversion of mesothelial cells as a mechanism responsible for high solute transport rate in peritoneal dialysis: role of vascular endothelial growth factor. *Am. J. kidney Dis.* 46, 938–948. the official journal of the National Kidney Foundation. doi:10.1053/j.ajkd.2005.08.011

Bajo, M. A., Del Peso, G., and Teitelbaum, I. (2017). Peritoneal membrane preservation. *Seminars Nephrol.* 37, 77–92. doi:10.1016/j.semnephrol.2016.10.009

Balzer, M. S., Rong, S., Nordlohne, J., Zemtsovski, J. D., Schmidt, S., Stapel, B., et al. (2020). SGLT2 inhibition by intraperitoneal dapagliflozin mitigates peritoneal fibrosis and ultrafiltration failure in a mouse model of chronic peritoneal exposure to high-glucose dialysate. *Biomolecules* 10, 1573. doi:10.3390/biom10111573

Balzer, M. S. (2020). Molecular pathways in peritoneal fibrosis. *Cell. Signal.* 75, 109778. doi:10.1016/j.cellsig.2020.109778

Barreto, D. L., Coester, A. M., Struijk, D. G., and Krediet, R. T. (2013). Can effluent matrix metalloproteinase 2 and plasminogen activator inhibitor 1 be used as biomarkers of peritoneal membrane alterations in peritoneal dialysis patients? *Perit. Dial. Int.* 33, 529–537. journal of the International Society for Peritoneal Dialysis. doi:10.3747/pdi.2012.01063

Bellón, T., Martínez, V., Lucendo, B., del Peso, G., Castro, M. J., Aroeira, L. S., et al. (2011). Alternative activation of macrophages in human peritoneum: implications for peritoneal fibrosis. *Nephrol. Dial. Transplant.* 26, 2995–3005. official publication of the European Dialysis and Transplant Association - European Renal Association. doi:10.1093/ndt/gfq771

Bergmann, J. H., and Spector, D. L. (2014). Long non-coding RNAs: modulators of nuclear structure and function. *Curr. Opin. Cell. Biol.* 26, 10–18. doi:10.1016/j.ceb.2013.08.005

Boulanger, E., Grossin, N., Wautier, M. P., Taamma, R., and Wautier, J. L. (2007). Mesothelial RAGE activation by AGEs enhances VEGF release and potentiates capillary tube formation. *Kidney Int.* 71, 126–133. doi:10.1038/sj.ki.5002016

Castoldi, G., Antolini, L., Bombardi, C., Perego, L., Mariani, P., Viganò, M. R., et al. (2010). Oxidative stress biomarkers and chromogranin A in uremic patients: effects of dialytic treatment. *Clin. Biochem.* 43, 1387–1392. doi:10.1016/j.clinbiochem.2010.08.028

Catar, R., Witowski, J., Zhu, N., Lücht, C., Derrac Soria, A., Uceda Fernandez, J., et al. (2017). IL-6 trans-signaling links inflammation with angiogenesis in the peritoneal membrane. *J. Am. Soc. Nephrol.* 28, 1188–1199. doi:10.1681/ASN.2015101169

Cueto-Manzano, A. M., González-Espinoza, L., Martin del Campo, F., Fortes, P. C., and Pecoits-Filho, R. (2007). Inflammation in peritoneal dialysis: A Latin-American perspective. *Perit. Dial. Int.* 27, 347–352. journal of the International Society for Peritoneal Dialysis. doi:10.1177/089686080702700326

De Vriese, A. S., Tilton, R. G., Mortier, S., and Lameire, N. H. (2006). Myofibroblast transdifferentiation of mesothelial cells is mediated by RAGE and contributes to peritoneal fibrosis in uraemia. *Nephrol. Dial. Transplant.* 21, 2549–2555. official publication of the European Dialysis and Transplant Association - European Renal Association. doi:10.1093/ndt/gfl271

Decout, A., Katz, J. D., Venkatraman, S., and Ablasser, A. (2021). The cGAS-STING pathway as a therapeutic target in inflammatory diseases. *Nat. Rev. Immunol.* 21, 548–569. doi:10.1038/s41577-021-00524-z

Derynck, R., and Zhang, Y. E. (2003). Smad-dependent and Smad-independent pathways in TGF-beta family signalling. *Nature* 425, 577–584. doi:10.1038/nature02006

Dounousi, E., Papavasiliou, E., Makedou, A., Ioannou, K., Katopodis, K. P., Tselepis, A., et al. (2006). Oxidative stress is progressively enhanced with advancing stages of CKD. *Am. J. kidney Dis.* 48, 752–760. the official journal of the National Kidney Foundation. doi:10.1053/j.ajkd.2006.08.015

Fu, J., Li, N., He, M., Huang, D., and Zhang, P. (2022). STAT3 signaling mediates peritoneal fibrosis by activating hyperglycolysis. *Am. J. Transl. Res.* 14, 7552–7565.

Ge, Y., Xiao, L., Chen, X., Peng, Y., Sun, L., and Liu, F. (2012). MicroRNAs in peritoneal dialysis effluent are promising biomarkers for peritoneal fibrosis in peritoneal dialysis patients. *Med. hypotheses* 78, 155–156. doi:10.1016/j.mehy.2011.10.015

Ghavami, S., Cunnington, R. H., Gupta, S., Yeganeh, B., Filomeno, K. L., Freed, D. H., et al. (2015). Autophagy is a regulator of TGF-β1-induced fibrogenesis in primary human atrial myofibroblasts. *Cell. death Dis.* 6, e1696. doi:10.1038/cddis.2015.36

Guo, Y., Wang, L., Gou, R., Tang, L., and Liu, P. (2020). Noncoding RNAs in peritoneal fibrosis: background, mechanism, and therapeutic approach. *Biomed. Pharmacother. = Biomedecine Pharmacother.* 129, 110385. doi:10.1016/j.biopha.2020.110385

Han, L., Qu, Q., Aydin, D., Panova, O., Robertson, M. J., Xu, Y., et al. (2022). Structure and mechanism of the SGLT family of glucose transporters. *Nature* 601, 274–279. doi:10.1038/s41586-021-04211-w

Hautem, N., Morelle, J., Sow, A., Corbet, C., Feron, O., Goffin, E., et al. (2017). The NLRP3 inflammasome has a critical role in peritoneal dialysis-related peritonitis. *J. Am. Soc. Nephrol.* 28, 2038–2052. doi:10.1681/ASN.2016070729

Hirahara, I., Ishibashi, Y., Kaname, S., Kusano, E., and Fujita, T. (2009). Methylglyoxal induces peritoneal thickening by mesenchymal-like mesothelial cells in rats. *Nephrol. Dial. Transplant.* 24, 437–447. official publication of the European Dialysis and Transplant Association - European Renal Association. doi:10.1093/ndt/gfn495

Hirai, K., Yoshizawa, H., Imai, T., Igarashi, Y., Hirahara, I., Ookawara, S., et al. (2017). Detection of microRNA expression in peritoneal membrane of rats using quantitative real-time PCR. *J. Vis. Exp.*, 55505. doi:10.3791/55505

Hong, M., Nie, Z., Chen, Z., Yu, X., and Bao, B. (2016). High glucose dialysate enhances peritoneal fibrosis through upregulating glucose transporters GLUT1 and SGLT1. *Zhejiang da xue xue bao. Yi xue ban = J. Zhejiang Univ. Med. Sci.* 45, 598–606. doi:10.3785/j.issn.1008-9292.2016.11.07

Huang, Q., Xiao, R., Lu, J., Zhang, Y., Xu, L., Gao, J., et al. (2022). Endoglin aggravates peritoneal fibrosis by regulating the activation of TGF-β/ALK/Smads signaling. *Front. Pharmacol.* 13, 973182. doi:10.3389/fphar.2022.973182

Io, H., Hamada, C., Ro, Y., Ito, Y., Hirahara, I., and Tomino, Y. (2004). Morphologic changes of peritoneum and expression of VEGF in encapsulated peritoneal sclerosis rat models. *Kidney Int.* 65, 1927–1936. doi:10.1111/j.1523-1755.2004.00599.x

Ito, T., Yorioka, N., Yamamoto, M., Kataoka, K., and Yamakido, M. (2000). Effect of glucose on intercellular junctions of cultured human peritoneal mesothelial cells. *J. Am. Soc. Nephrol.* 11, 1969–1979. doi:10.1681/ASN.V11111969

Jang, Y. H., Shin, H. S., Sun Choi, H., Ryu, E. S., Jin Kim, M., Ki Min, S., et al. (2013). Effects of dexamethasone on the TGF-β1-induced epithelial-to-mesenchymal transition in human peritoneal mesothelial cells. *Laboratory investigation; a J. Tech. methods pathology* 93, 194–206. doi:10.1038/labinvest.2012.166

Kakuta, T., Tanaka, R., Satoh, Y., Izuhara, Y., Inagi, R., Nangaku, M., et al. (2005). Pyridoxamine improves functional, structural, and biochemical alterations of peritoneal membranes in uremic peritoneal dialysis rats. *Kidney Int.* 68, 1326–1336. doi:10.1111/j.1523-1755.2005.00531.x

Kalluri, R., and Neilson, E. G. (2003). Epithelial-mesenchymal transition and its implications for fibrosis. *J. Clin. investigation* 112, 1776–1784. doi:10.1172/JCI20530

Kang, D. H., Hong, Y. S., Lim, H. J., Choi, J. H., Han, D. S., and Yoon, K. I. (1999). High glucose solution and spent dialysate stimulate the synthesis of transforming growth factor-β_1 of human peritoneal mesothelial cells: effect of cytokine costimulation. *Perit. Dial. Int.* 19, 221–230. journal of the International Society for Peritoneal Dialysis. doi:10.1177/089686089901900307

Kato, S., Yuzawa, Y., Tsuboi, N., Maruyama, S., Morita, Y., Matsuguchi, T., et al. (2004). Endotoxin-induced chemokine expression in murine peritoneal mesothelial cells: the role of toll-like receptor 4. *J. Am. Soc. Nephrol.* 15, 1289–1299.

Kim, K. H., Ryu, H. M., Oh, S. H., Oh, E. J., Ahn, J. S., Lee, J. H., et al. (2014). Effect of DNA demethylation in experimental encapsulating peritoneal sclerosis. *Ther. Apher. dialysis* 18, 628–636. official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. doi:10.1111/1744-9987.12186

Kim, Y. C., Kim, K. H., Lee, S., Jo, J. W., Park, J. Y., Park, M. S., et al. (2019). ST2 blockade mitigates peritoneal fibrosis induced by TGF-β and high glucose. *J. Cell. Mol. Med.* 23, 6872–6884. doi:10.1111/jcmm.14571

Krediet, R. T., and Parikova, A. (2022). Relative contributions of pseudohypoxia and inflammation to peritoneal alterations with long-term peritoneal dialysis patients. *Clin. J. Am. Soc. Nephrol. CJASN* 17, 1259–1266. doi:10.2215/CJN.15371121

Krediet, R. T., and Struijk, D. G. (2013). Peritoneal changes in patients on long-term peritoneal dialysis. *Nat. Rev. Nephrol.* 9, 419–429. doi:10.1038/nrneph.2013.99

Lamouille, S., Xu, J., and Derynck, R. (2014). Molecular mechanisms of epithelial-mesenchymal transition. *Nat. Rev. Mol. Cell. Biol.* 15, 178–196. doi:10.1038/nrm3758

Lei, P., Jiang, Z., Zhu, H., Li, X., Su, N., and Yu, X. (2012). Poly(ADP-ribose) polymerase-1 in high glucose-induced epithelial-mesenchymal transition during peritoneal fibrosis. *Int. J. Mol. Med.* 29, 472–478. doi:10.3892/ijmm.2011.859

Lho, Y., Do, J. Y., Heo, J. Y., Kim, A. Y., Kim, S. W., and Kang, S. H. (2021). Effects of TGF-β1 receptor inhibitor GW788388 on the epithelial to mesenchymal transition of peritoneal mesothelial cells. *Int. J. Mol. Sci.* 22, 4739. doi:10.3390/ijms22094739

Li, P. K., Chow, K. M., Van de Luijtgaarden, M. W., Johnson, D. W., Jager, K. J., Mehrotra, R., et al. (2017). Changes in the worldwide epidemiology of peritoneal dialysis. *Nat. Rev. Nephrol.* 13, 90–103. doi:10.1038/nrneph.2016.181

Li, C., Wang, Z., Zhang, J., Zhao, X., Xu, P., Liu, X., et al. (2019). Crosstalk of mRNA, miRNA, lncRNA, and circRNA and their regulatory pattern in pulmonary fibrosis. *Mol. Ther. Nucleic acids* 18, 204–218. doi:10.1016/j.omtn.2019.08.018

Li, Z. H., Xu, R., Shi, J., Yu, M. S., Zhong, Y., He, W. M., et al. (2022). Astragalus total saponins ameliorate peritoneal fibrosis by promoting mitochondrial synthesis and inhibiting apoptosis. *Am. J. Chin. Med.* 50, 261–274. doi:10.1142/S0192415X22500094

Liakopoulos, V., Roumeliotis, S., Gorny, X., Eleftheriadis, T., and Mertens, P. R. (2017). Oxidative stress in patients undergoing peritoneal dialysis: A current review of the literature. *Oxidative Med. Cell. Longev.* 2017, 3494867. doi:10.1155/2017/3494867

Liu, Q., Zhang, Y., Mao, H., Chen, W., Luo, N., Zhou, Q., et al. (2012). A crosstalk between the Smad and JNK signaling in the TGF-β-induced epithelial-mesenchymal transition in rat peritoneal mesothelial cells. *PloS one* 7, e32009. doi:10.1371/journal.pone.0032009

Liu, W., Feng, R., Li, X., Li, D., and Zhai, W. (2019). TGF-β- and lipopolysaccharide-induced upregulation of circular RNA PWWP2A promotes hepatic fibrosis via sponging miR-203 and miR-223. *Aging* 11, 9569–9580. doi:10.18632/aging.102405

Lopez-Anton, M., Lambie, M., Lopez-Cabrera, M., Schmitt, C. P., Ruiz-Carpio, V., Bartosova, M., et al. (2017). miR-21 promotes fibrogenesis in peritoneal dialysis. *Am. J. pathology* 187, 1537–1550. doi:10.1016/j.ajpath.2017.03.007

Maeda, K., Doi, S., Nakashima, A., Nagai, T., Irifuku, T., Ueno, T., et al. (2017). Inhibition of H3K9 methyltransferase G9a ameliorates methylglyoxal-induced peritoneal fibrosis. *PloS one* 12, e0173706. doi:10.1371/journal.pone.0173706

Masola, V., Bonomini, M., Borrelli, S., Di Liberato, L., Vecchi, L., Onisto, M., et al. (2022). Fibrosis of peritoneal membrane as target of new therapies in peritoneal dialysis. *Int. J. Mol. Sci.* 23, 4831. doi:10.3390/ijms23094831

Milan Manani, S., Virzì, G. M., Clementi, A., Brocca, A., de Cal, M., Tantillo, I., et al. (2016). Pro-inflammatory cytokines: A possible relationship with dialytic adequacy and serum albumin in peritoneal dialysis patients. *Clin. kidney J.* 9, 153–157. doi:10.1093/ckj/sfv137

Mizutani, M., Ito, Y., Mizuno, M., Nishimura, H., Suzuki, Y., Hattori, R., et al. (2010). Connective tissue growth factor (CTGF/CCN2) is increased in peritoneal dialysis

patients with high peritoneal solute transport rate. *Am. J. physiology. Ren. physiology* 298, F721–F733. doi:10.1152/ajprenal.00368.2009

Morishita, Y., Yoshizawa, H., Watanabe, M., Imai, R., Imai, T., Hirahara, I., et al. (2016a). MicroRNA expression profiling in peritoneal fibrosis. *Transl. Res. J. laboratory Clin. Med.* 169, 47–66. doi:10.1016/j.trsl.2015.10.009

Morishita, Y., Ookawara, S., Hirahara, I., Muto, S., and Nagata, D. (2016b). HIF-1α mediates Hypoxia-induced epithelial-mesenchymal transition in peritoneal mesothelial cells. *Ren. Fail.* 38, 282–289. doi:10.3109/0886022X.2015.1127741

Nakao, A., Nakao, K., Takatori, Y., Kojo, S., Inoue, J., Akagi, S., et al. (2010). Effects of icodextrin peritoneal dialysis solution on the peritoneal membrane in the STZ-induced diabetic rat model with partial nephrectomy. *Nephrol. Dial. Transplant.* 25, 1479–1488. official publication of the European Dialysis and Transplant Association - European Renal Association. doi:10.1093/ndt/gfp479

Onishi, A., Akimoto, T., Urabe, M., Hirahara, I., Muto, S., Ozawa, K., et al. (2015). Attenuation of methylglyoxal-induced peritoneal fibrosis: immunomodulation by interleukin-10. *a J. Tech. methods pathology* 95, 1353–1362. doi:10.1038/labinvest.2015.110

Rodrigues-Díez, R., Aroeira, L. S., Orejudo, M., Bajo, M. A., Heffernan, J. J., Rodrigues-Díez, R. R., et al. (2014). IL-17A is a novel player in dialysis-induced peritoneal damage. *Kidney Int.* 86, 303–315. doi:10.1038/ki.2014.33

Rosell, A., Arai, K., Lok, J., He, T., Guo, S., Navarro, M., et al. (2009). Interleukin-1beta augments angiogenic responses of murine endothelial progenitor cells *in vitro*. *J. Cereb. blood flow metabolism* 29, 933–943. official journal of the International Society of Cerebral Blood Flow and Metabolism. doi:10.1038/jcbfm.2009.17

Roumeliotis, S., Dounousi, E., Salmas, M., Eleftheriadis, T., and Liakopoulos, V. (2020). Unfavorable effects of peritoneal dialysis solutions on the peritoneal membrane: the role of oxidative stress. *Biomolecules* 10, 768. doi:10.3390/biom10050768

Saadoun, S., Papadopoulos, M. C., Hara-Chikuma, M., and Verkman, A. S. (2005). Impairment of angiogenesis and cell migration by targeted aquaporin-1 gene disruption. *Nature* 434, 786–792. doi:10.1038/nature03460

Salgado, R., Benoy, I., Weytjens, R., Van Bockstaele, D., Van Marck, E., Huget, P., et al. (2002). Arterio-venous gradients of IL-6, plasma and serum VEGF and D-dimers in human cancer. *Br. J. cancer* 87, 1437–1444. doi:10.1038/sj.bjc.6600655

Schilte, M. N., Celie, J. W., Wee, P. M., Beelen, R. H., and van den Born, J. (2009). Factors contributing to peritoneal tissue remodeling in peritoneal dialysis. *Perit. Dial. Int.* 29, 605–617. journal of the International Society for Peritoneal Dialysis. doi:10.1177/089686080902900604

Schröppel, B., Fischereder, M., Wiese, P., Segerer, S., Huber, S., Kretzler, M., et al. (1998). Expression of glucose transporters in human peritoneal mesothelial cells. *Kidney Int.* 53, 1278–1287. doi:10.1046/j.1523-1755.1998.00899.x

Shentu, Y., Li, Y., Xie, S., Jiang, H., Sun, S., Lin, R., et al. (2021). Empagliflozin, a sodium glucose cotransporter-2 inhibitor, ameliorates peritoneal fibrosis via suppressing TGF-β/Smad signaling. *Int. Immunopharmacol.* 93, 107374. doi:10.1016/j.intimp.2021.107374

Shi, Y., Hu, Y., Wang, Y., Ma, X., Tang, L., Tao, M., et al. (2021). Blockade of autophagy prevents the development and progression of peritoneal fibrosis. *Front. Pharmacol.* 12, 724141. doi:10.3389/fphar.2021.724141

Shi, Y., Li, J., Chen, H., Hu, Y., Tang, L., Wang, Y., et al. (2022). Inhibition of EZH2 suppresses peritoneal angiogenesis by targeting a VEGFR2/ERK1/2/HIF-1α-dependent signaling pathway. *J. pathology* 258, 164–178. doi:10.1002/path.5987

Si, M., Wang, Q., Li, Y., Lin, H., Luo, D., Zhao, W., et al. (2019). Inhibition of hyperglycolysis in mesothelial cells prevents peritoneal fibrosis. *Sci. Transl. Med.* 11, eaav5341. doi:10.1126/scitranslmed.aav5341

Strippoli, R., Loureiro, J., Moreno, V., Benedicto, I., Lozano, M. L., Barreiro, O., et al. (2015). Caveolin-1 deficiency induces a MEK-ERK1/2-Snail-1-dependent epithelial-mesenchymal transition and fibrosis during peritoneal dialysis. *EMBO Mol. Med.* 7, 102–123. doi:10.15252/emmm.201404127

Suryantoro, S. D., Thaha, M., Sutanto, H., and Firdausa, S. (2023). Current insights into cellular determinants of peritoneal fibrosis in peritoneal dialysis: A narrative review. *J. Clin. Med.* 12, 4401. doi:10.3390/jcm12134401

Tanabe, K., Maeshima, Y., Ichinose, K., Kitayama, H., Takazawa, Y., Hirokoshi, K., et al. (2007). Endostatin peptide, an inhibitor of angiogenesis, prevents the progression of peritoneal sclerosis in a mouse experimental model. *Kidney Int.* 71, 227–238. doi:10.1038/sj.ki.5002040

Wang, L., Balzer, M. S., Rong, S., Menne, J., von Vietinghoff, S., Dong, L., et al. (2016). Protein kinase C α inhibition prevents peritoneal damage in a mouse model of chronic peritoneal exposure to high-glucose dialysate. *Kidney Int.* 89, 1253–1267. doi:10.1016/j.kint.2016.01.025

Wang, Q., Xu, L., Zhang, X., Liu, D., and Wang, R. (2020). GSK343, an inhibitor of EZH2, mitigates fibrosis and inflammation mediated by HIF-1α in human peritoneal mesothelial cells treated with high glucose. *Eur. J. Pharmacol.* 880, 173076. doi:10.1016/j.ejphar.2020.173076

Wang, Q., Bu, Q., Liu, M., Zhang, R., Gu, J., Li, L., et al. (2022a). XBP1-mediated activation of the STING signalling pathway in macrophages contributes to liver fibrosis progression. *JHEP Rep. innovation hepatology* 4, 100555. doi:10.1016/j.jhepr.2022.100555

Wang, L., Zhang, Y., Ren, Y., Yang, X., Ben, H., Zhao, F., et al. (2022b). Pharmacological targeting of cGAS/STING-YAP axis suppresses pathological angiogenesis and ameliorates organ fibrosis. *Eur. J. Pharmacol.* 932, 175241. doi:10.1016/j.ejphar.2022.175241

Witowski, J., Kamhieh-Milz, J., Kawka, E., Catar, R., and Jörres, A. (2018). IL-17 in peritoneal dialysis-associated inflammation and angiogenesis: conclusions and perspectives. *Front. physiology* 9, 1694. doi:10.3389/fphys.2018.01694

Wu, J., Li, X., Zhu, G., Zhang, Y., He, M., and Zhang, J. (2016). The role of Resveratrol-induced mitophagy/autophagy in peritoneal mesothelial cells inflammatory injury via NLRP3 inflammasome activation triggered by mitochondrial ROS. *Exp. Cell. Res.* 341, 42–53. doi:10.1016/j.yexcr.2016.01.014

Wu, J., Xing, C., Zhang, L., Mao, H., Chen, X., Liang, M., et al. (2018). Autophagy promotes fibrosis and apoptosis in the peritoneum during long-term peritoneal dialysis. *J. Cell. Mol. Med.* 22, 1190–1201. doi:10.1111/jcmm.13393

Xia, Y., Wan, C., Zhang, Q., Wang, H., Feng, Y., and Jiang, C. (2022). Role of IGF-1R in epithelial-mesenchymal transdifferentiation of human peritoneal mesothelial cells. *Clin. Exp. Nephrol.* 26, 630–639. doi:10.1007/s10157-022-02209-w

Xiao, L., Sun, L., Liu, F. Y., Peng, Y. M., and Duan, S. B. (2010). Connective tissue growth factor knockdown attenuated matrix protein production and vascular endothelial growth factor expression induced by transforming growth factor-beta1 in cultured human peritoneal mesothelial cells. *Ther. Apher. dialysis* 14, 27–34. official peer-reviewed journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy. doi:10.1111/j.1744-9987.2009.00701.x

Xiao, L., Zhou, X., Liu, F., Hu, C., Zhu, X., Luo, Y., et al. (2015). MicroRNA-129-5p modulates epithelial-to-mesenchymal transition by targeting SIP1 and SOX4 during peritoneal dialysis. *Laboratory investigation; a J. Tech. methods pathology* 95, 817–832. doi:10.1038/labinvest.2015.57

Yanai, K., Ishii, H., Aomatsu, A., Ishibashi, K., and Morishita, Y. (2018). MicroRNAs in peritoneal fibrosis: A systematic review. *Discov. Med.* 26, 271–280.

Yang, X., Yan, H., Jiang, N., Yu, Z., Yuan, J., Ni, Z., et al. (2020). IL-6 trans-signaling drives a STAT3-dependent pathway that leads to structural alterations of the peritoneal membrane. *Am. J. physiology. Ren. physiology* 318, F338–f353. doi:10.1152/ajprenal.00319.2019

Yang, X., Bao, M., Fang, Y., Yu, X., Ji, J., and Ding, X. (2021). STAT3/HIF-1α signaling activation mediates peritoneal fibrosis induced by high glucose. *J. Transl. Med.* 19, 283. doi:10.1186/s12967-021-02946-8

Yousefi, F., and Soltani, B. M. (2021). Circular RNAs as potential theranostics in the cardiac fibrosis. *Heart Fail. Rev.* 26, 195–203. doi:10.1007/s10741-019-09908-9

Zhang, F., Liu, H., Liu, F., Peng, Y., Chen, M., Liu, Y., et al. (2013). New insights into the pathogenesis and treatment of peritoneal fibrosis: A potential role of wnt/β-catenin induced epithelial to mesenchymal transition and stem cells for therapy. *Med. hypotheses* 81, 97–100. doi:10.1016/j.mehy.2013.03.036

Zhang, X. W., Wang, L., and Ding, H. (2019). Long noncoding RNA AK089579 inhibits epithelial-to-mesenchymal transition of peritoneal mesothelial cells by competitively binding to microRNA-296-3p via DOK2 in peritoneal fibrosis. *FASEB J.* 33, 5112–5125. official publication of the Federation of American Societies for Experimental Biology. doi:10.1096/fj.201801111RR

Zhang, Y., Feng, W., Peng, X., Zhu, L., Wang, Z., Shen, H., et al. (2022a). Parthenolide alleviates peritoneal fibrosis by inhibiting inflammation via the NF-κB/TGF-β/Smad signaling axis. *Laboratory investigation; a J. Tech. methods pathology* 102, 1346–1354. doi:10.1038/s41374-022-00834-3

Zhang, D., Liu, Y., Zhu, Y., Zhang, Q., Guan, H., Liu, S., et al. (2022b). A non-canonical cGAS-STING-PERK pathway facilitates the translational program critical for senescence and organ fibrosis. *Nat. Cell. Biol.* 24, 766–782. doi:10.1038/s41556-022-00894-z

Zhou, Y., Fan, J., Zheng, C., Yin, P., Wu, H., Li, X., et al. (2019). SGLT-2 inhibitors reduce glucose absorption from peritoneal dialysis solution by suppressing the activity of SGLT-2. *Biomed. Pharmacother. = Biomedecine Pharmacother.* 109, 1327–1338. doi:10.1016/j.biopha.2018.10.106

Zou, M., Wang, F., Gao, R., Wu, J., Ou, Y., Chen, X., et al. (2016). Autophagy inhibition of hsa-miR-19a-3p/19b-3p by targeting TGF-β R II during TGF-β1-induced fibrogenesis in human cardiac fibroblasts. *Sci. Rep.* 6, 24747. doi:10.1038/srep24747

Zweers, M. M., Struijk, D. G., Smit, W., and Krediet, R. T. (2001). Vascular endothelial growth factor in peritoneal dialysis: A longitudinal follow-up. *J. laboratory Clin. Med.* 137, 125–132. doi:10.1067/mlc.2001.112235

frontiers | Frontiers in Medicine

TYPE Original Research
PUBLISHED 23 November 2023
DOI 10.3389/fmed.2023.1297296

OPEN ACCESS

EDITED BY
Lijie He,
Fourth Military Medical University, China

REVIEWED BY
M. Jahangir Alam,
University of Houston, United States
Haruhito Yoshimine,
Kagoshima University, Japan

*CORRESPONDENCE
Ying Ma
ying.ma228@163.com

RECEIVED 19 September 2023
ACCEPTED 24 October 2023
PUBLISHED 23 November 2023

CITATION
Yu X, Li Z, Yang X, Wang X, Nan D, Lu W, Lv J and Ma Y (2023) *Microbacterium spp*. peritonitis in patients undergoing peritoneal dialysis: a single-center experience and literature review. *Front. Med.* 10:1297296.
doi: 10.3389/fmed.2023.1297296

Microbacterium spp. peritonitis in patients undergoing peritoneal dialysis: a single-center experience and literature review

Xiao Yu[1,2], Zhao Li[1], Xinbo Yang[2], Xiaopei Wang[1], Di Nan[2], Wanhong Lu[1], Jing Lv[1] and Ying Ma[1]*

[1]Department of Nephrology, Kidney Hospital, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, China, [2]Department of Nephrology, The Second Affiliated Hospital of Shaanxi University of Traditional Chinese Medicine, Xianyang, China

Introduction: Peritoneal dialysis-related peritonitis (PDRP) caused by *Microbacterium spp*. is very rare, with only 9 cases reported to date. In this study, we report the treatment experiences of 7 patients at our peritoneal dialysis center.

Methods: We retrospectively collected clinical characteristics and antibiotic management of all 7 episodes of PDRP caused by *Microbacterium spp*. in 7 patients from at our center over 4 years, and reviewed the documented *Microbacterium spp*. PDRP in the literature.

Results: Empiric antibiotic therapy was initiated as soon as possible, and consisted of intraperitoneal (IP) gentamicin in combination with vancomycin. After up to 5 days, gentamicin was changed to meropenem if the treatment was not effective. The intended course of antibiotic treatment was 21-day. Totally, 6 episodes were cured (85.7%), which was higher than reported.

Conclusion: The 21-day antibiotic therapy program by combining vancomycin and meropenem may benefit the management of *Microbacterium spp*. PDRP.

KEYWORDS

***Microbacterium spp.*, peritoneal dialysis (PD), peritonitis, vancomycin, meropenem**

Introduction

Peritoneal dialysis (PD)-related peritonitis (PDRP) is a significant complication in patients undergoing PD, leading to hospitalization, catheter loss, technique failure, conversion to hemodialysis, and death (1). *Microbacterium spp.* is a genus of aerobic Gram-positive bacteria present in the environment, characterized by rod-shaped Gram-positive bacilli that are non-sporulating, acid-resistant, aerobic, and weakly anaerobic, primarily undergoing respiratory metabolism with occasional weak fermentation. Their nutritional requirements are complex. PDRP caused by *Microbacterium spp.* is rare, with only nine cases reported to date. In this study, we summarized the treatment experiences of the seven *Microbacterium* species episodes at our center and reviewed previously reported cases, trying to explore potential approaches that may benefit the cure rate of *Microbacterium spp.* peritonitis.

Materials and methods

We reviewed the records of PDRP cases identified as *Microbacterium spp.* infections at the center of the First Affiliated Hospital of Xi'an Jiaotong University from January 2019 to April 2023. Clinical and demographic data included age, gender, and ESRD cause. For the *Microbacterium spp.* peritonitis episodes, we also collected precise data on *Microbacterium* species and potential risk factors, such as catheter-related infection, body mass index (BMI), and personal exposure including keeping domestic pets, weeding or growing crops, and Charlson Comorbidity Index [CCI, the CCI index assigns 1 point for the history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease (transient ischemic attack or cerebrovascular accident with minor or no residua), dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, and diabetes without end-organ damage; 2 points for hemiplegia, moderate-to-severe renal disease, diabetes with end-organ damage, tumor without metastases, leukemia, lymphoma, and myeloma; 3 points for moderate-to-severe liver disease; and 6 points for metastatic solid tumor or acquired immunodeficiency syndrome. For every decade over 40 years of age, 1 point is added to the score] (1). Additionally, PD duration, residual glomerular filtration rate (rGFR), catheter-related infections, clinical features of peritonitis, and both blood and dialysate examination results, including blood cell counts, serum albumin, serum potassium, C-reactive protein (CRP), procalcitonin (PCT), effluent white blood cell count, and microbiologic causes, were retrospectively collected.

Peritonitis was diagnosed according to the peritonitis definition in the 2022 International Society for Peritoneal Dialysis (ISPD) guidelines. *Microbacterium spp.* peritonitis was enrolled based on dialysate culture. To increase the yield of peritoneal effluent culture, we directly inoculated the effluent into rapid blood culture bottle kits (aerobic and anaerobic, BacT/Alert, bioMérieux, Inc., Basingstoke, UK). Our center has not provided drug sensitivity results due to limited technical experience. According to the ISPD guidelines, we initiated empiric antibiotic therapy as soon as possible. All patients enrolled in the outpatient service received intermittent IP gentamicin at a dose of 0.6 mg/kg/d, up to a maximum of 40 mg in one PD exchange, in combination with IP vancomycin (administered at a dose of 15 mg/kg of body weight rounded to the nearest 500 mg to the longest dwell bag for at least 6 h). Vancomycin was used in accordance with the vancomycin-monitoring protocol previously reported (2). After 5 days of empiric treatment, antibiotic therapy was adjusted according to the treatment effect. We defined a dialysis effluent white cell count of $<100/\mu l$ and a neutrophil percentage of $<50\%$ as treatment-effective. Gentamicin was changed to meropenem (1 g/day by IP injection) if the empirical treatment was not effective. Prophylactic antifungal therapy (fluconazole, 0.2 g/day) was administered 7 days after combination antibiotic treatment (Figure 1).

We performed a literature search on PubMed, Wiley, Nature, the National Center for Biotechnology Information, and the China National Knowledge Infrastructure using the search terms "*Microbacterium*" and "peritoneal dialysis-related peritonitis." We collected the general information of the reported patients infected by *Microbacterium spp.*, such as sex, age at onset, and clinical features. In addition, we summarized the characteristics of all patients, clinical history, characteristics of antibiotic sensitivities, antibiotic treatment regimen, duration of treatment, and treatment outcome according to the ISPD guideline recommendation (3). Additionally, the exit site is cleansed using sterile saline solution every day or every 2 days, and mupirocin cream is applied to the catheter exit site and an exit site dressing cover is used to prevent catheter-related infection (4).

Follow-up was conducted until 31 July 2023, and outcomes for all episodes were identified and classified as medical cure, refractory, recurrence, and relapsing as recommended by the ISPD guideline (3). In refractory peritonitis cases, catheter removal is indicated to preserve the peritoneum for future PD and prevent morbidity and mortality. However, we propose that if the PD effluent white cell count is decreasing toward normal, it may be appropriate to observe the antibiotic effect for longer than 5 days instead of mandating PD catheter removal by day 5. The final decision on whether to remove the catheters depends on the clinical severity and the options available to the patients. In cases where the patient's clinical condition is not deteriorating and they prefer to continue with PD, we aim to minimize premature or unnecessary PD catheter removal.

Results

According to the ISPD recommendations, seven patients were diagnosed with PDRP (3), and Table 1 shows their demographic and clinical characteristics. The average age was 47.4 ± 18.7 years, and all were men. Chronic glomerulonephritis is the leading cause of end-stage renal disease. Their median PD duration was 51 months. All the patients in our study were on continuous ambulatory peritoneal dialysis (CAPD) using a glucose-based acidic lactate PD solution. Total KT/V urea was 1.97 ± 0.52/week. The common manifestations of the peritonitis were abdominal pain and cloudy dialysis effluent. There was no concomitant catheter-related infection. Because all patients were on dialysis, the minimum CCI is 2. The CCI in Case 3 is as high as 12.

The antibiotic management and clinical outcomes of *Microbacterium spp.* peritonitis at our PD center are presented in Table 2. At our center, we achieved medical cure in six patients (Cases 1, 2, 4, 5, 6, and 7), while one patient (Case 3) experienced relapsing. Throughout the treatment, we continued CAPD. After 3 months of follow-up, Cases 3 and 4 received PD catheter removal due to relapsing and repeat peritonitis, respectively.

Totally, nine cases of PDRP caused by *Microbacterium spp.* were reported previously, comprising three cases of *M. paraoxydans*, two cases of *M. oxydans*, two cases of *M. arborescens*, one case of *M. resistens*, and one case of *M. aurum*. Table 3 shows general information about the reported patients infected by *Microbacterium spp.* Among the episodes, five episodes (Cases B, C, E, G, and H) experienced medical cure, while four episodes (Cases A, D, F, and I) failed, involving three catheter removals and one refractory peritonitis. Antimicrobial susceptibility testing (AST) revealed 21 antibiotics used in the treatment of these 9 patients.

All nine patients underwent AST, and antibiotic therapy was modified until the culture results were known. In the AST,

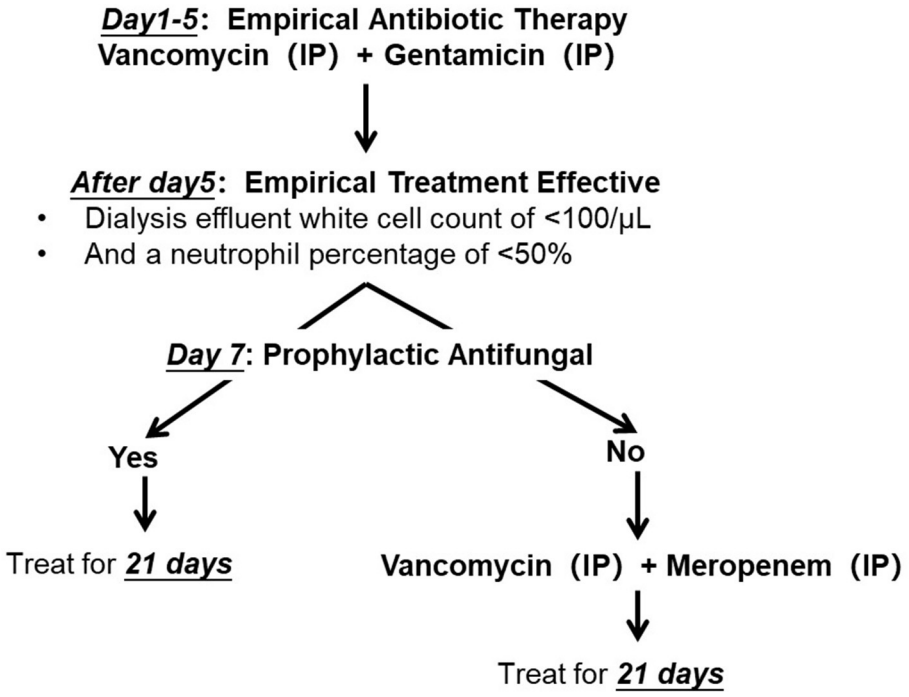


FIGURE 1
Antibiotic protocol of *Microbacterium spp*. peritoneal dialysis related peritonitis. IP, intraperitoneal administration.

six patients exhibited sensitivity to ampicillin, five patients to trimethoprim/sulfamethoxazole, four patients to penicillin, four patients to gentamicin, four patients to erythromycin, three patients to vancomycin, and three patients to ceftriaxone. However, a few reports mentioned antibiotic resistance, among which three showed resistances to vancomycin, two to ceftazidime, one to cefazolin, one to penicillin, one to aztreonam, one to colistin, and one to netilmicin (Figure 2).

As for the administration of vancomycin in the reported cases, six patients (Cases A, B, D, E, F, and G) received IP vancomycin, and it was employed as an empiric antibiotic in five patients (Cases A, B, D, E, and F); patient A showed susceptibility to vancomycin (minimum inhibitory concentration [MIC] determined by the E-test was 8 mg/L) and improved with IP aztreonam 2 g and vancomycin 1 g in 2 L of dialysate. After 4 days with amoxicillin/clavulanic acid (875 mg twice a day orally), the patient was discharged. However, the patient experienced relapsing on day 8. Patient B was susceptible to vancomycin (MIC determined by the E-test was unknown). Treatment was initiated with IP gentamicin (20 mg/24 h) and vancomycin (2 g/72 h), and vancomycin was continued for 3 weeks while the patient experienced a repeat episode. Patient D was empirically treated with IP vancomycin (12 g/3 d), ceftazidime (1 g/d), and amikacin (2 mg/kg/d). Because of the resistance to vancomycin shown by AST, it was adjusted to IP ampicillin (250 mg, thrice daily) plus IP gentamicin (45 mg/d). After 3 days, gentamicin was discontinued, and the patient was discharged with a prescription of IP ampicillin (250 mg, thrice daily) to be taken for 1 more week. However, the patient experienced a relapse on day 8. Patient E was susceptible to vancomycin. Empirical therapy involved oral ciprofloxacin (MIC 1.0 mg/L) and IP vancomycin. Aerobic culture revealed the growth of two types of organisms (*Acinetobacter spp.* and *Microbacterium aurum*). Oral ciprofloxacin was continued for 3 weeks, but the patient experienced a repeat episode after 4 months. For patient F, empirical therapy with IP vancomycin was initiated, but AST did not contain vancomycin. The aerobic culture grew three types of organisms (*Coagulase-negative staphylococci*, *Streptococcus mitis,* and *Corynebacterium amycolatum*). He underwent PD catheter removal due to refractory and recurrent peritonitis. Patient G was treated empirically with IP cefazolin (15 mg/kg/day) and ceftazidime (1 g/day) for the first 11 days. On day 12, the antibiotics were changed to IP administration of vancomycin (2 g loading, followed by 1 g every 5 days; the MIC determined by the E-test was 2 μg/ml) and oral administration of clarithromycin (500 mg every 12 h). After 2 weeks of antibiotic administration, the patient was cured.

Three patients were treated without vancomycin, among whom patients C and H were vancomycin-resistant. In detail, the treatment for patient C was changed to intravenous erythromycin (MIC $\leq$ 0.12 mg/L, 14 days) and oral sulfamethoxazole/trimethoprim (MIC $\leq$ 0.5 mg/L, 21 days) after AST, and PD was interrupted (hemodialysis with a dual-lumen catheter as vascular access was performed seven times in total). The patient was cured after 3 weeks of antibiotic administration. Patient H received empirical therapy with IP cefazolin (1 gram every 24 h) and ceftazidime (1.5 grams every 24 h) for 2 weeks. However, patient H experienced a repeat episode after 2 months. Furthermore, due to an AST without vancomycin, the treatment of patient I was changed to IP cefepime (CPM, 14 days), and she relapsed after 1 week.

TABLE 1 Characteristics of six patients with *Microbacterium spp*. peritoneal dialysis-related peritonitis at our center.

Case	1	2	3	4	5	6	7
Gender	Male	Male	Male	Male	Male	Male	Male
Age	28	65	65	29	71	35	39
BMI (kg/m^2)	27.7	18.9	17	26	23.4	22.5	26.7
Primary disease	HTN	DM	DM	HTN	CGN	CGN	CGN
WBC ($\times 10^9$/L)	8.8	6.68	2.85	13.82	9.2	4.22	8.47
NEU (%)	75.1	77.5	79.8	82.4	79.5	72.2	86.2
CRP (mg/L)	18.9	200.5	9.31	8.23	43.8	23.4	48.3
PCT (ng/mL)	0.168	6.76	2.13	0.388	0.401	0.406	0.205
HGB (g/L)	103	101	116	106	138	105	94
ALB (g/L)	29.7	20.3	29.7	36.7	27.8	31.8	28.1
BUN (mmol/L)	15.85	14.75	19.14	20.55	20.54	20.81	17.61
CRE (umol/L)	654	951	491	826	784	538	901
rGFR (ml/min/1.73m^2)	8	6	7	6	6	13	5.7
Chol (mmol/L)	5.06	3.29	4.2	4.54	3.74	3.0	3.26
TG (mmol/L)	1.45	1.27	1.11	2.06	1.7	0.54	3.22
Serum potassium (mmol/L)	4.06	3.14	3.29	3.78	3.35	3.75	3.22
Serum calcium (mmol/L)	2.26	1.86	1.89	2.42	2.3	2.15	2.04
Serum phosphorus (mmol/L)	1.79	1.19	1.44	1.9	1.49	1.25	1.29
CCI	2	8	12	2	5	2	2
PD duration (months)	19	180	61	24	51	17	60
tKT/V urea	2.96	N/A	1.59	2.14	1.66	1.69	1.8
PD exchange volume (L/day)	8	9[a]	8	8	8	10	10
PD ultrafiltration volume (ml/day)	450	N/A	430	400	520	670	540
Main symptoms	AP, CPDE	AP, CPDE	AP, CPDE	AP, CPDE	AP, CPDE	AP, CPDE	AP, CPDE
Catheter-related infection (either exit-site or tunnel)	No	No	No	No	No	No	No

[a]This patient received 8 L and 10 L alternately, thus the average PD exchange volume was 9 L/day, with no available PD adequacy test in the last 2 months. HTN, Hypertension; DM, Diabetes mellitus; CGN, Chronic glomerulonephritis; WBC, White blood cell; NEU, Neutrophils; CRP, C-reactive protein; PCT, Procalcitonin; HGB, Hemoglobin; ALB, Albumin; BUN, Urea nitrogen; CRE, Creatinine; CCI, Charlson Comorbidity Index [The CCI index assigns 1 point for history of myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease (transient ischemic attack or cerebrovascular accident with minor or no residua), dementia, chronic pulmonary disease, connective tissue disorder, peptic ulcer disease, mild liver disease, and diabetes without end-organ damage; 2 points are assigned for hemiplegia, moderate to severe renal disease, diabetes with end-organ damage, tumor without metastases, leukemia, lymphoma, and myeloma; 3 points are assigned for moderate or severe liver disease; and 6 points are assigned for metastatic solid tumor or acquired immunodeficiency syndrome (AIDS). For every decade over 40 years of age, 1 point is added to the score.]; AP, abdominal pain; CPDE, cloudy PD effluent; F, fever; N/A, not available.

Discussion

This report was a single-center experience and literature review of PDRP caused by *Microbacterium spp*., comprising seven cases from our center and nine cases from the literature. Clinical features, therapeutic management, and clinical outcomes were collected. In our center, the clinical cure rate was 85.7% (6/7), while in the literature review, it was 55.6% (5/9).

Our six patients (Cases 1, 2, 4, 5, 6, and 7) were cured, and the cure rate was 85.7%, which was higher than reported (55.6%). Importantly, the six cured patients did not experience refractory peritonitis, all-cause hospitalization, technique failure, or death during a follow-up period of 3 months. Only one patient (Case 3) experienced relapsing. In the literature review, although five patients (Cases B, C, E, G, and H) were cured, Cases B and H experienced a repeat episode within 3 months, and patient E experienced a repeat episode after 4 months.

The focus of the literature reviews was on the results of AST and antibiotic management, which revealed that the sensitivity rate of *Microbacterium spp*. to vancomycin was 50%, although the sample size was small. Vancomycin was still used despite treatment failure in some cases, and the serum vancomycin levels were not mentioned. Although the ISPD guideline showed controversy in the relationship between serum vancomycin levels and peritonitis outcomes, we previously discovered that serum vancomycin levels correlate with short-term adverse outcomes of PD-associated peritonitis, and the diagnostic threshold value of day 5 serum vancomycin levels for short-term adverse outcomes was

TABLE 2 Antibiotic management and clinical outcomes of the *Microbacterium spp.* peritonitis at our PD center.

Case	Species	Culture (days)	PD effluent routine test (day 0)		Empirical antibiotics	PD effluent routine test (day 5)		Day-5 serum vancomycin level (mg/L)	Adjusted antibiotics	PD effluent routine test (day 10)		PD effluent routine test (day 14)		Antibiotic treatment duration (days)	Outcome
			WBC ($\times 10^6$/L)	PMN (%)		WBC ($\times 10^6$/L)	PMN (%)			WBC ($\times 10^6$/L)	PMN (%)	WBC ($\times 10^6$/L)	PMN (%)		
1	*M. arborescens*	1.29	942	64.2	IP GM+ VAN	105	65	8.8	IP MEM+VAN	105	25	84	17	21	Medical cure
2	*M. arborescens*	1.08	582	93	IP GM+ VAN	105	39	11.4	IP MEM+VAN	26	39	14	14	21	Medical cure
3	*M. paraoxydans*	1.29	547	94	IP GM+ VAN	315	95	8.9	IP MEM+VAN	62	90	81	21	21	Relapsing (PD catheter removal for cure)
4	*M. arborescens*	1.23	315	93	IP GM+ VAN	278	95	9.5	IP MEM+VAN	36	82	38	29	21	Repeat (PD catheter Removal for cure)
5	*M. arborescens*	3.75	1,454	79	IP GM+ VAN	124	70	16.4	IP MEM+VAN	52	15	11	18	21	Medical cure
6	*M. spp*	2.6	463	65	IP GM+ VAN	681	86	15.1	IP MEM+VAN	44	94	35	3.1	21	Medical cure
7	*M. aurantiacum*	2.12	737	88.6	IP GM+ VAN	259	63.7	10.2	IP MEM+VAN	107	31.8	58	26	21	Medical cure

M, Microbacterium; PD, peritoneal dialysis; IP, intraperitoneal; GM, gentamicin; CZ, cefazolin; CAZ, ceftazidime; MSS, mezlocillin sodium/sulbactam; MEM, meropenem; VAN, vancomycin; ONZ, ornidazole. Medical cure, Complete resolution of peritonitis together with NONE of the following complications: relapse/recurrent peritonitis, catheter removal, transfer to hemodialysis for 30 days or death; Refractory, Peritonitis episode with persistently cloudy bags or persistent dialysis effluent leukocyte count $>100 \times 10^9$/L after 5 days of appropriate antibiotic therapy; Recurrent, Peritonitis episode that occurs within 4 weeks of completion of therapy of a prior episode but with a different organism; Relapsing, Peritonitis episode that occurs within 4 weeks of completion of therapy of a prior episode with the same organism or one sterile (culture negative) episode (i.e., specific organism).

10.3389/fmed.2023.1297296

TABLE 3 Outlines of patients with peritoneal dialysis-related peritonitis identified in the literature.

Case	References	Age (years)/sex	Duration of PD (years)	Species	PD effluent routine test		Antibiotic treatment initial treatment	After drug sensitivity testing	Antibiotic treatment (days)	Outcome
					WBC ($\times 10^6$/L)	PMN (%)				
A	Wybo et al. (5)	48/Female	1.8	*M. oxydans*	N/A	N/A	IP ATM+VAN (4 days)	Po AM/CA (8 days)	8	Relapsing (day 8)
B	Adams et al. (6)	57/Female	8	*M. arborescens*	N/A	N/A	IP GEN+VAN	IP GEN + VAN (21 days)	21	Repeat (month1), IP GEN+VAN (6 days), until the PD catheter removal.
C	Miyamoto et al. (7)	60/Male	2.3	*M. paraoxydans*	826	74	IP CZ+CAZ (7 days)	IP ERY (14 d), Po SXT (21 days)	21	Medical cure
D	Gallois et al. (8)	71/Male	1.1	*M. resistens*	678	83	IP VAN+CAZ+AMI	IP AMP (7 days) + GEN (3 days)	7	Relapsing (day 6, IP AMP(47 days) + GEN (5 days), until the PD catheter removal)
E	Yusuf et al. (9)	80/Male	NK	*M. aurum*	1070	55	Po CIP+IP VAN (7 days)	Po CIP (21 days)	21	Repeat (month 4), PD catheter removal for cure
F	Yusuf et al. (9)	48/Female	NK	*M. oxydans*	767	64	IPATM+VAN (3 days)	Po AM/CA+ IP VAN (7 days)	10	Refractory and Recurrent (PD catheter removal for cure)
G	Choi et al. (10)	54/Female	1	*M. paraoxydans*	2900	84	IP CZ+CAZ (11 days)	IP VAN, Po CLI (14 days)	14	Medical cure
H	Lam et al. (11)	74/Male	1.4	*M. paraoxydans*	815	78	IP CZ+CAZ (14 days)	No change	14	Repeat (month 2), PD catheter removal for cure.
I	Girişgen et al. (12)	16/Female	3	*M. arborescens*	N/A	N/A	IP CZ+CAZ	IP CPM (14 days)		Relapsing (day 7), PD catheter removal for cure.

N/A, not available; Po, peros; ATM, aztreonam; VAN, vancomycin; AM/CA, amoxicillin/clavulanate; GEN, gentamicin; CZ, cefazolin; CAZ, ceftazidime; CIP, ciprofloxacin SXT, trimethoprim/sulfamethoxazole; ERY, erythromycin; AMP, ampicillin; CLI, clarithromycin; CPM, cefepime; AMI, amikacin.

10.3389/fmed.2023.1297296

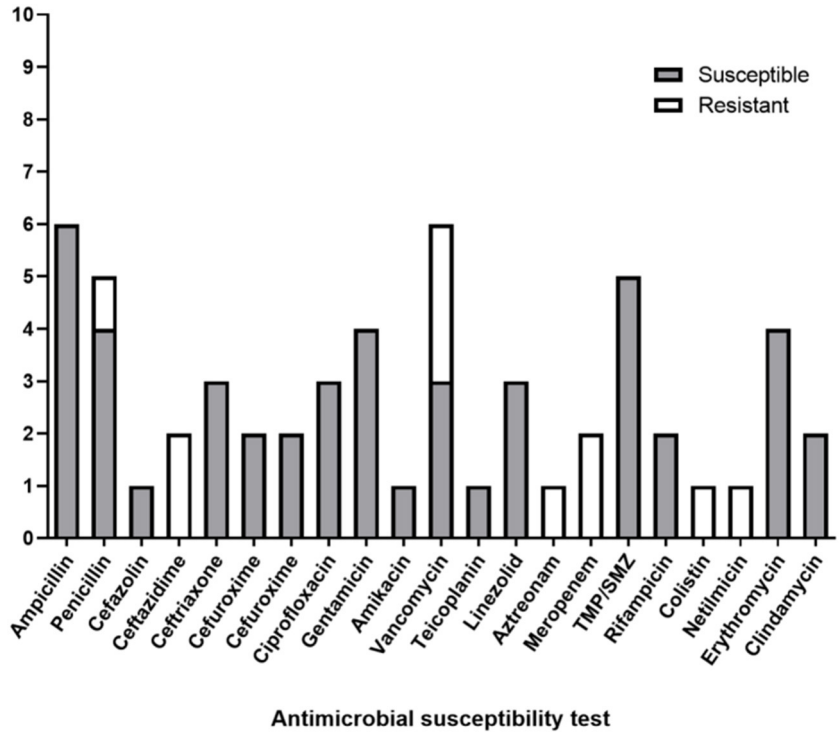


FIGURE 2
The characteristics of antibiotic sensitivities in literature reviews.

10.1 mg/L^2. In this study, the mean serum vancomycin level on day 5 was 11.5 ± 3.1 mg/L in medica-cured cases, which was suboptimal in the relapsing case.

The combination of vancomycin and meropenem as adjusted antibiotic therapy may benefit our cure rate. A review of 50 human specimens (species obtained from blood cultures, wounds, normally sterile anatomical sites, sterile materials, urine, and miscellaneous materials) revealed that *Microbacterium spp.* are susceptible to vancomycin (98% of the isolates were susceptible) (13). This provides the theoretical basis for the continued use of vancomycin to treat *Microbacterium spp.* PDRP. Moreover, meropenem exhibits an ultra-broad spectrum of antibacterial activity, encompassing Gram-positive and Gram-negative aerobes and anaerobes, including numerous strains resistant to other antibacterials (14). Furthermore, in the review of 50 human specimens, all 50 isolates were susceptible to meropenem.

The 21-day antibiotic course may be another potential beneficial measure to improve the cure rate in our center. As for the previously reported cured cases, patients B, C, and E received 21 days of antibiotic treatment, while for patients G and H, the course of antibiotic treatment was 14 days. The 2016 ISPD guideline recommended a 21-day course of effective antibiotic treatment for corynebacterial peritonitis. Considering *Microbacterium spp.* as a genus of coryneform bacteria originally proposed by Orla-Jensen in 1919 (15), we proposed a 21-day treatment duration for our seven patients. Since the 2022 ISPD peritonitis guideline suggested that *Corynebacterium* peritonitis should be treated with effective antibiotics for 2 weeks, a shorter treatment duration in *Microbacterium spp.* peritonitis deserves future observation accordingly.

The high positive rate of *Microbacterium spp.* in our center may be attributed to the improvement of our culture technology. We employed blood culture bottles as the preferred approach for the bacterial culture of PD effluent, which is consistent with the guideline recommendation (3).

Additionally, identifying risk factors associated with *Microbacterium spp.* infection warrants attention. Among our patients, four (four of seven) patients experienced their first peritonitis episode, and all patients had no concomitant catheter-related infections. The average PD duration was 51 months. Meanwhile, given that the incidence of encapsulating peritoneal sclerosis (EPS) increases with the duration of PD, we tried to screen it in our cases. All of our cases lack typical presentations of EPS, such as signs of intestinal obstruction or a high peritoneal transporter status with incipient ultrafiltration failure. In addition, Case 3, whose PD duration was 61 months, underwent a CT scan because of peritonitis relapsing and revealed no evidence of a thickened peritoneal membrane. In terms of occupation, four of seven patients were farmers. Notably, all seven patients were male, which is inconsistent with the literature reports (4/9). It is hard to explain the underlying reasons. Deciphering the above factors may allow for greater progress in prevention and treatment. The CCI was a better predictor than models containing age, diabetes, cardiovascular disease, and albumin and a strong predictor of mortality in incident PD patients. The mortality rate was 50/100 patient-years for patients with a CCI score of 8 or greater (16). In our cases, the CCI of Case 3 was higher than 8

because of cancer and radiotherapy, and he experienced peritonitis relapsing and catheter removal. However, there was no definitive evidence confirming the predictive value of CCI or peritonitis adverse outcomes.

This study had several limitations. It was a single-center experience in treating PDRP caused by *Microbacterium spp*.. The promotion of treatment experience is limited due to the lack of AST. We have communicated with our laboratory in this regard and will promptly enhance the standard operating procedure associated with the AST of *Microbacterium spp.* based on our experiences and the literature reports available.

Conclusion

The treatment experience of PDRP caused by *Microbacterium spp.* is limited, and the treatment effect in the literature is not satisfactory. In this single-center report, seven cases of *Microbacterium spp.* peritonitis were presented for the first time. Our 21-day antibiotic therapy program based on a combination of IP vancomycin and meropenem achieved a relatively high cure rate. To validate our experience, available AST is needed, and further randomized controlled trials are required.

Data availability statement

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, the approval number was XJTU1AF2020LSK-273. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

XYu: Data curation, Investigation, Methodology, Software, Writing—original draft. ZL: Data curation, Writing—original draft. XYa: Data curation, Writing—original draft. XW: Data curation, Writing—original draft. DN: Data curation, Writing—original draft. WL: Investigation, Supervision, Writing—review & editing. JL: Supervision, Writing—review & editing, Investigation. YM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Writing—original draft, Writing—review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This work was supported by Research and Development Fund of the First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China (2022QN-20) for research, authorship and publication. This work was supported by Key Research and Development Program of Shaanxi Province, China (2019KW-040) for publication and research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* (1987) 40:373–83. doi: 10.1016/0021-9681(87)90171-8

2. Ma Y, Geng Y, Jin L, Wang X, Liang C, Xie L, et al. Serum vancomycin levels predict the short-term adverse outcomes of peritoneal dialysis-associated peritonitis. *Perit Dial Int.* (2023) 43:37–44. doi: 10.1177/08968608211064192

3. Li PK, Chow KM, Cho Y, Fan S, Figueiredo AE, Harris T, et al. ISPD peritonitis guideline recommendations: 2022 update on prevention and treatment. *Perit Dial Int.* (2022) 42:110–53. doi: 10.1177/08968608221080586

4. Chow KM, Li PK, Cho Y, Abu-Alfa A, Bavanandan S, Brown EA, et al. ISPD catheter-related infection recommendations: 2023 update. *Peritoneal Dialysis Int.* (2023) 43:201–19. doi: 10.1177/08968608231172740

5. Wybo I, Piérard D, Ichiche M, Vandoorslaer K, Soetens O, Rosseel P, et al. P1947 isolation of *Microbacterium* species in a case of dialysis-associated peritonitis. *Int J Antimic Agents*. (2007) 29:786. doi: 10.1016/S0924-8579(07)71786-7

6. Yim SY, Kang YS, Cha DR, Park DW, Youn YK, Jo YM, et al. Fatal PD peritonitis, necrotizing fasciitis, and bacteremia due to *Shewanella putrefaciens. Perit Dial Int.* (2010) 30:667–9. doi: 10.3747/pdi.2010.00084

7. Miyamoto M, Sakurada T, Oishi D, Koitabashi K, Hanada K, Takemura H, et al. The first case report of peritoneal dialysis related peritonitis caused by *Microbacterium paraoxydans. Clin Nephrol.* (2013) 79:402–6. doi: 10.5414/CN107209

8. Gallois E, Lamy T, Fines-Guyon M, Lobbedez T, Cattoir V. Recurrent peritoneal dialysis-related peritonitis caused by *Microbacterium resistens. Diagn Microbiol Infect Dis.* (2014) 79:111–3. doi: 10.1016/j.diagmicrobio.2013.10.021

9. Yusuf E, Wybo I, Francois K, Pipeleers L, Echahidi F, Covens L, et al. *Microbacterium spp*. as a cause of peritoneal-dialysis-related peritonitis in two patients. *J Microbiol Immunol Infect*. (2016) 49:464–5. doi: 10.1016/j.jmii.2014.03.008

10. Choi HS, Bae EH, Ma SK, Kim SW. Peritoneal dialysis-related peritonitis caused by *Microbacterium paraoxydans*. *Jpn J Infect Dis*. (2017) 70:195–6. doi: 10.7883/yoken.JJID.2016.004

11. Lam PW, Naimark DM, Leis JA. *Microbacterium* peritonitis in peritoneal dialysis: a case report and review. *Peritoneal Dialysis Int*. (2018) 38:9–13. doi: 10.3747/pdi.2017.00121

12. Girişgen I, Kaleli I, Yuksel S. Rare cause of peritoneal dialysis-related peritonitis in a child: *Microbacterium arborescens*. *Ther Apher Dial*. (2019) 23:482–3. doi: 10.1111/1744-9987.12782

13. Gneiding K, Frodl R, Funke G. Identities of *Microbacterium spp*. encountered in human clinical specimens. *J Clin Microbiol*. (2008) 46:3646–52. doi: 10.1128/JCM.01202-08

14. Blumer JL. Meropenem: evaluation of a new generation carbapenem. *Int J Antimicrob Agents*. (1997) 8:73–92. doi: 10.1016/S0924-8579(96)00347-0

15. Takeuchi M, Hatano K. Union of the genera *Microbacterium* Orla-Jensen and *Aureobacterium* Collins et al. in a redefined genus *Microbacterium*. *Int J System Evolut Microbiol*. (1998) 48:739–47. doi: 10.1099/00207713-48-3-739

16. Fried L, Bernardini J, Piraino B. Charlson comorbidity index as a predictor of outcomes in incident peritoneal dialysis patients. *Am J Kidney Dis*. (2001) 37:337–42. doi: 10.1053/ajkd.2001.21300

frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 18 December 2023
DOI 10.3389/fphys.2023.1279578

OPEN ACCESS

EDITED BY
Ying-Yong Zhao,
Northwest University, China

REVIEWED BY
Vassilis L. Tzounakas,
University of Patras, Greece
Yuan Xinxu,
Virginia Commonwealth University, United States

*CORRESPONDENCE
Yang Zhao,
zhaoyang0327@bjmu.edu.cn
Wen Tang,
tanggwen@126.com

†These authors have contributed equally to this work and share first authorship

RECEIVED 18 August 2023
ACCEPTED 05 December 2023
PUBLISHED 18 December 2023

CITATION
Yang Y-H, Saimaiti Y, Zhao Y and Tang W (2023), Plasma phospholipids profiling changes were associated with the therapeutic response to Roxadustat in peritoneal dialysis patients.
Front. Physiol. 14:1279578.
doi: 10.3389/fphys.2023.1279578

Plasma phospholipids profiling changes were associated with the therapeutic response to Roxadustat in peritoneal dialysis patients

Ya-Hui Yang[1†], Yishakejiang Saimaiti[1,2†], Yang Zhao[2*] and Wen Tang[1*]

[1]Department of Nephrology, Peking University Third Hospital, Beijing, China, [2]Department of Laboratory Medicine, Peking University Third Hospital, Beijing, China

Background: Elevated Phospholipids (PLs) and sphingolipid (SM) metabolism relates to with poor clinical status and adverse outcome of end-stage kidney disease patients undergoing peritoneal dialysis (PD). Studies have suggested that the use of hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) (Roxadustat) is associated with altered lipid metabolism. Observing on how PLs and SMs changes after the HIF-PHI treatment in PD patients may help understand the possible effect of HIF-PHI on PD patients besides correcting of anemia.

Materials and methods: Stable peritoneal dialysis (PD) patients treated with Roxadustat for over 3 months were included. Phospholipid and sphingolipid metabolism were measured before and after treatment.

Results: 25 PD patients were included. Overall, phospholipid and sphingolipid metabolism showed a decreasing trend after HIF-PHI treatment. Levels of LysoPC (20:0), 1,2-dilinoleoyl-sn-glycero-3-phosphocholine [CisPC (DLPC) (18:2)], lysophosphatidylethanolamine (LysoPE) (14:0), and sphingomyelin (d18:1/17:0) (17:0) were significantly decreased (all $p < 0.05$). Further regression analyses confirmed the significant relationship between the increased of hemoglobin levels and the decrease in egg lyso PC: phosphatidylethanolamines (PE) (16:0–18:1), PE (16:0–18:2), PE (16:0–22:6), PE (18:0–20:4), PE (18:0–18:2), LysoPE (18:0), LysoPE (18:1), and phosphatidylcholine (PC) (18:1–18:0).

Conclusion: This study demonstrated that phospholipid and sphingolipid metabolism decreased after administration of HIF-PHI and was associated with improvement of anemia.

KEYWORDS

peritoneal dialysis, phospholipids, hypoxia inducible factor prolyl hydroxylase inhibitors, anemia, end-stage kidney disease

Introduction

Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) is a novel small-molecule oral drug used for the treatment of renal anemia (Sanghani and Haase, 2019) that targets all three hypoxia-inducible factor prolyl hydroxylase domain (HIF-PHDs) to a similar extent (Yeh, 2017). Small-molecule prolyl hydroxylase domain (PHD) inhibitors

(PHDIs) stabilize HIF by inhibiting PHD, thereby promoting the secretion of erythropoietin (EPO) to promote hematopoiesis (Rabinowitz, 2013; Duan, 2016).

In addition to the treatment of anemia, several clinical studies have suggested that Roxadustat treatment is accompanied by a reduction in blood lipid levels. Two clinical trials have shown that Roxadustat decreases total, low density lipoprotein (LDL), and high density lipoprotein (HDL) cholesterol levels in patients with non-dialysis-dependent chronic kidney disease (Provenzano, 2016; Chen H., 2017a). Moreover, Chen reported a decrease in triglycerides and very low density lipoprotein (VLDL)-cholesterol in Roxadustat-treated patients with chronic kidney disease (Chen N., 2017b). Interestingly, Zhang showed that the adipocyte HIF-2α reduces atherosclerosis by promoting ceramide catabolism, thus increasing hepatic cholesterol elimination and thermogenesis (Zhang). Atherosclerosis amelioration can be pharmacologically achieved in mice by activating adipose HIF-2α via FG-4592 (Roxadustat).

Sphingolipid metabolites, particularly ceramide and sphingosine-1-phosphate, are signaling molecules that regulate a diverse range of cellular processes that are important in immunity and inflammatory disorders (Maceyka and Spiegel, 2014; Papazoglou, 2022). Phospholipids (PLs) are integral components of the membrane and have important functional, structural, and metabolic roles. Recent reports advocate the involvement of PLs in signaling pathways that modulate pathophysiological disease states, including inflammation, oxidative stress, angiogenesis, and apoptosis. Phosphatidylcholines (PCs) have been proven to independently predict the occurrence of future cardiovascular (CV) events in patients with established CAD (Hilvo, 2020). Moreover, in peritoneal dialysis (PD) patients, our previous study demonstrated that poor volume status was associated with the changes of PE and PC (Li, 2013). In addition, we have found that PD technical failure patients had different plasma PL profiles to non-failure patients using a lipidomic method, predominantly of SM and PC PLs (Tang, 2014a).

Therefore, observation on how PLs and SMs changes after the HIF-PHI treatment in PD patients might help to understand the possible effect of HIF-PHI on PD patients besides correcting of anemia. Novel insights into lipid metabolism could elucidate its mechanism of action and effects on possible PD patients outcome. Thus, in the present study, both serum lipidomics and metabolomics data were analyzed after the clinical use of HIF-PHI for renal anemia treatment in patients with end-stage renal disease who underwent PD.

Methods

Study procedures

This was a single-center retrospective self-controlled observational study. Patients' blood sample were prospectively collected for routine evaluation while patients were retrospectively included according to the inclusion criteria and the blood were tested accordingly. Patients undergoing stable peritoneal dialysis visited our clinic for clinical evaluation, and blood tests were performed between December 2019 and December 2021. They were included according to whether they used HIF-PHIs (Roxadustat) for more than 3 months during the study period. The exclusion criteria were the 1) Discontinuation of HIF-PHI for various reasons during the study period. 2) Severe heart failure [New York Heart Association (NYHA) grade III or above], liver cirrhosis, autoimmune disease, and tumor; 3) Acute complications, such as infection, volume overload, surgery, cardiovascular or cerebrovascular diseases, and blood transfusion due to anemia during Roxadustat treatment; 4) Significant changes in the dialysis dose and the dialysis regimen; 5) The doses of various lipid-decreasing drugs and sevelamer adjusted during the HIF-PHI treatment; and 6) Blood samples before and after Roxadustat treatment were unavailable.

Clinical data, demographic data, laboratory examinations, and use of HIF-PHIs were collected from the available medical records. Biochemical assays and complete blood counts were performed.

Serum lipidomics analysis and metabolomics data processing

Sample pretreatment: Study samples, preserved at −80°C, were thawed at 4°C. Each sample (10 μL) was added, followed by an internal standard solution (10 μL), 0.9% NaCl (10 μL), and chloroform: methanol (2:1) (100 μL). The mixture was vortexed for 20 s and allowed to stand for 30 min at 4°C. After centrifugation for 3 min at 7,800 g, 20 μL of the supernatant was transferred into the insert and concentrated to dryness under nitrogen. Before injection for liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis, the dried samples were re-dissolved in acetonitrile:isopropanol (1:1) (20 μL) and vortexed for 60 s.

LC-MS/MS analysis

The lysophosphatidylcholine (LysoPC) components were identified and quantified using Eksigentultral liquid chromatography 100 coupled with an AB 5600 Triple TOF system (AB SCIEX) and separated using a 2.1 mm × 100 mm XBridge Peptide BEH C18 column (Waters) with a 4 mm × 2.0 mm guard column (Phenomenex). The separation of LysoPC was achieved at a column temperature of 40°C using acetic acid amine (10 mM), formic acid (0.1%, v/v), and water (99.9%, v/v) as mobile phase A, and acetic acid amine (10 mM), formic acid (0.1%, v/v), acetonitrile (49.95%, v/v), and isopropanol (49.95%, v/v) as mobile phase B. The step gradient was as follows: 0.01 min, 35% (v/v) B; 0.01–2 min, 35%–80% (v/v) B; 2–9 min, 80%–100% (v/v) B; 9–15 min, 100% (v/v) B; 15–16 min, 100%–35% (v/v) B; 16–20 min, 35% (v/v) B. The injection volume was 2 μL and the total run-time was 20 min at a flow rate of 0.4 mL/min. The instrument, under the negative model, was set as follows: curtain gas, ion source gas 1, and ion source gas 2 at 30, 50, and 50 psi, respectively; source temperature at 550°C; and ion spray voltage floating at −4,500 V. In the auto MS/MS acquisition, the m/z range for Time of Flight Mass Spectrometer (TOF MS) scan and production of ion scan was 100–1,200 Da and 50–1,200 Da, respectively. The collision energy of the production ion scan was set to −35 ± 15 V and the declustering potential was set to −80 V.

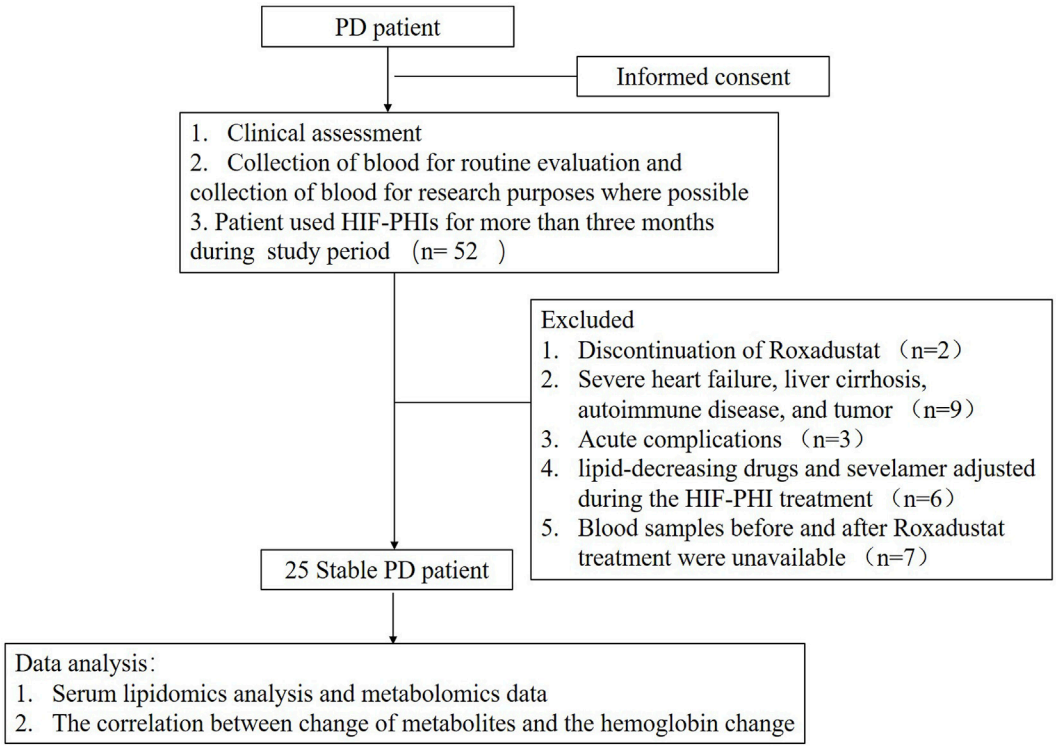


FIGURE 1
STARD diagram depicting the study design and classification of study participants.

TABLE 1 Baseline and follow-up characteristics of study population after Roxadustat treatment.

	Baseline	Follow-up	*p* value
Age (years)	57.91 ± 12.42		
BMI (kg/m^2)	21.64 ± 2.01	21.80 ± 2.53	0.460
Hemoglobin (g/L)	106.00 ± 14.80	115.72 ± 15.02	0.006
RBC count (10^{12}/L)	3.45 ± 0.57	3.73 ± 0.57	0.01
Hematocrit (%)	0.32 ± 0.05	0.36 ± 0.05	0.043
Kt/V Total	1.99 (1.83~2.14)	1.93 (1.63~2.07)	0.086
Ccr Total (ml/min)	73.86 (60.23~88.32)	77.31 (60.74~89.18)	0.67
Creatinine (μmol/L)	851.68 ± 253.47	827.36 ± 228.57	0.09
Urea (mmol/L)	19.00 ± 5.17	18.93 ± 5.35	0.93
TCHO (mmol/L)	4.93 (4.17~5.80)	4.28 ± 1.07	0.008
Triglyceride (mmol/L)	1.60 (1.33~3.04)	1.41 (0.89~2.82)	0.15
LDL-C (mmol/L)	2.27 (1.94~3.05)	2.07 (0.67~3.05)	0.017
HDL-C (mmol/L)	1.12 ± 0.26	0.99 ± 0.29	0.007
Plasma Albumin (g/L)	36.88 ± 4.79	36.22 ± 5.34	0.268
hsCRP (mg/L)	3.08 (0.59,5.36)	1.58 (1.03,6.38)	0.468

BMI, body mass index; RBC, red blood cell; TCHO, total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; hsCRP, hypersensitive C-reactive protein.

Data processing

Peak View 1.2 was used to identify LysoPC, and Multi Quant 2.1 was used to quantify LysoPC based on the m/z value and sample retention time.

Statistical analysis

All statistical analyses in this study were performed using SPSS 26.0. The frequency and percentage were used to describe categorical variables. Categorical results were analyzed using chi-square tests and presented as frequencies and percentages. The mean and standard deviation was used to describe normal distribution continuous variables and unnormal distribution continuous variables were presented as median (25th–75th percentile). The Kolmogorov-Smirnov (K-S) test was used to observe the normality of the two groups of data before and after Roxadustat treatment. In the comparative analysis of before and after Roxadustat administration and the correlation analysis between hemoglobin changes and the lipid metabolite changes, if the K-S test results of both before and after Roxadustat administration obeyed the normal distribution, the paired T-test and Pearson correlation analysis would be used for processing, respectively; if either before or after the Roxadustat groups did not obey the normal distribution, Wilcoxon signed rank test and Spearman correlation analysis were used, respectively. Linear regression analysis was used to observe whether the changes in hemoglobin were significantly correlated with changes in lipid metabolites after excluding the effects of factors, such as age, sex, total kt/v change, total ccr change, and BMI change. Metabolism levels were analyzed using MetaboAnalyst 5.0.

Results

A total of 52 patients were initially enrolled for this study in which twenty-seven patients were excluded due to different reasons and twenty-five peritoneal dialysis (PD) patients were finally included in this study and analyzed (Figure 1). The time between two serum lipidomics analyses was 29 weeks range from 20 to 44 weeks. As shown in Table 1. After Roxadustat treatment, the patient showed a significant improvement in hemoglobin levels. (p = 0.006). Plasma cholesterol levels, including total cholesterol, low-

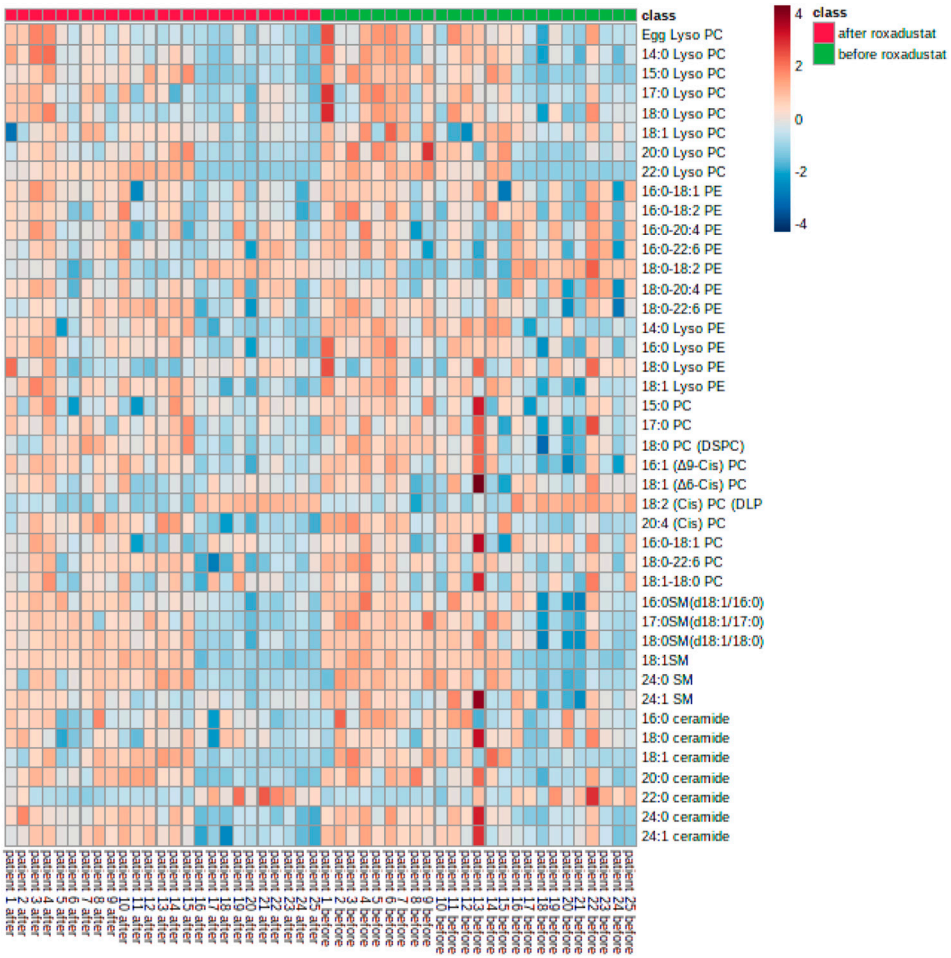


FIGURE 2
Heatmap of phospholipids and sphingolipids metabolism changes before and after Roxadustat treatment.

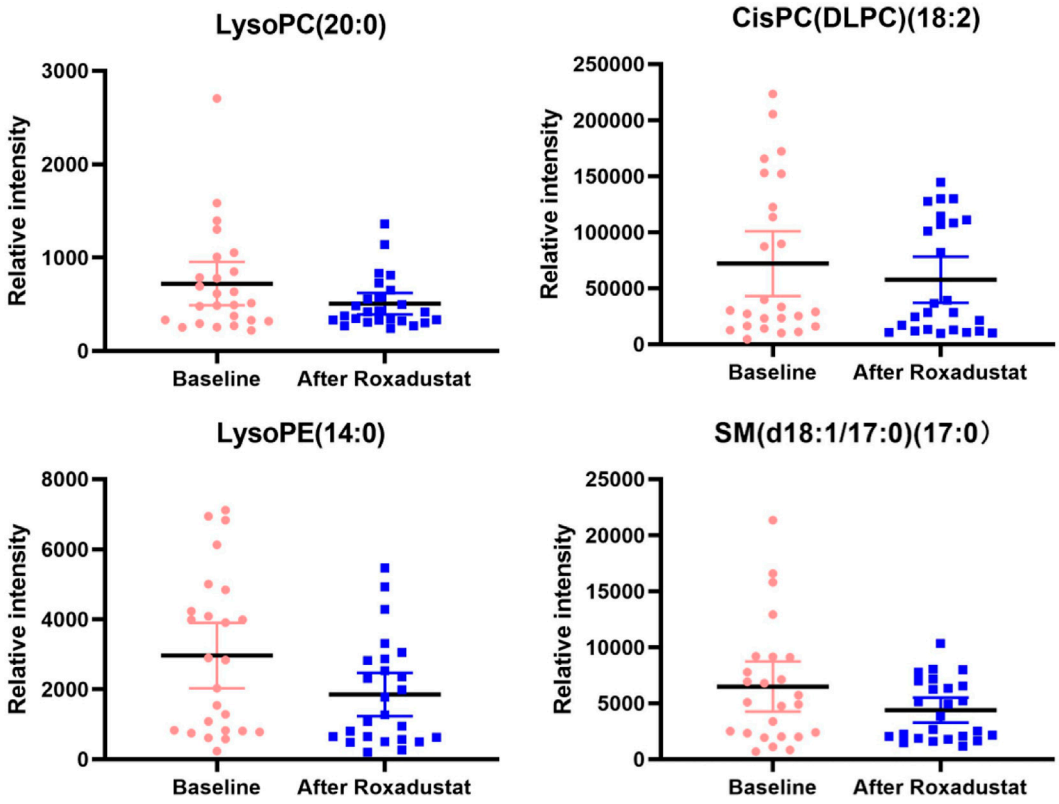


FIGURE 3
This figure presents the boxplots of the significantly changed metabolite levels at baseline and at follow-up after treatment with Roxadustat. The sample means are indicated by the black bars.

TABLE 2 Multiple regression analysis between change of metabolism levels and the hemoglobin change.

Phospholipid change	HGB change			
	β	*t*	R^2	*p*
Change eggLysoPC	−0.685	−3.156	0.486	0.006
Change LysoPC (18:1)	−0.479	−1.784	0.213	0.093
Change PE (16:0–18:1)	−0.671	−3.347	0.561	0.004
Change PE (16:0–18:2)	−0.386	−2.104	0.634	0.052
Change PE (16:0–22:6)	−0.379	−1.79	0.51	0.092
Change PE (18:0–20:4)	−0.598	−3.215	0.623	0.005
Change LysoPE (18:0)	−0.636	−2.976	0.502	0.009
Change PE (18:0–18:2)	−0.594	−3.319	0.651	0.004
Change LysoPE (18:1)	−0.721	−3.439	0.52	0.003
Change PC (18:1)(Δ6Cis)	−0.385	−1.465	0.246	0.162
Change PC (16:0–18:1)	−0.422	−1.587	0.229	0.132
Change PC (18:1–18:0)	−0.590	−2.624	0.448	0.018
Change SM (24:1)	−0.330	−1.213	0.19	0.243

All the initial model included age, gender, total Kt/V change, total Ccr change, BMI change, plasma albumin change and hs-CRP change.

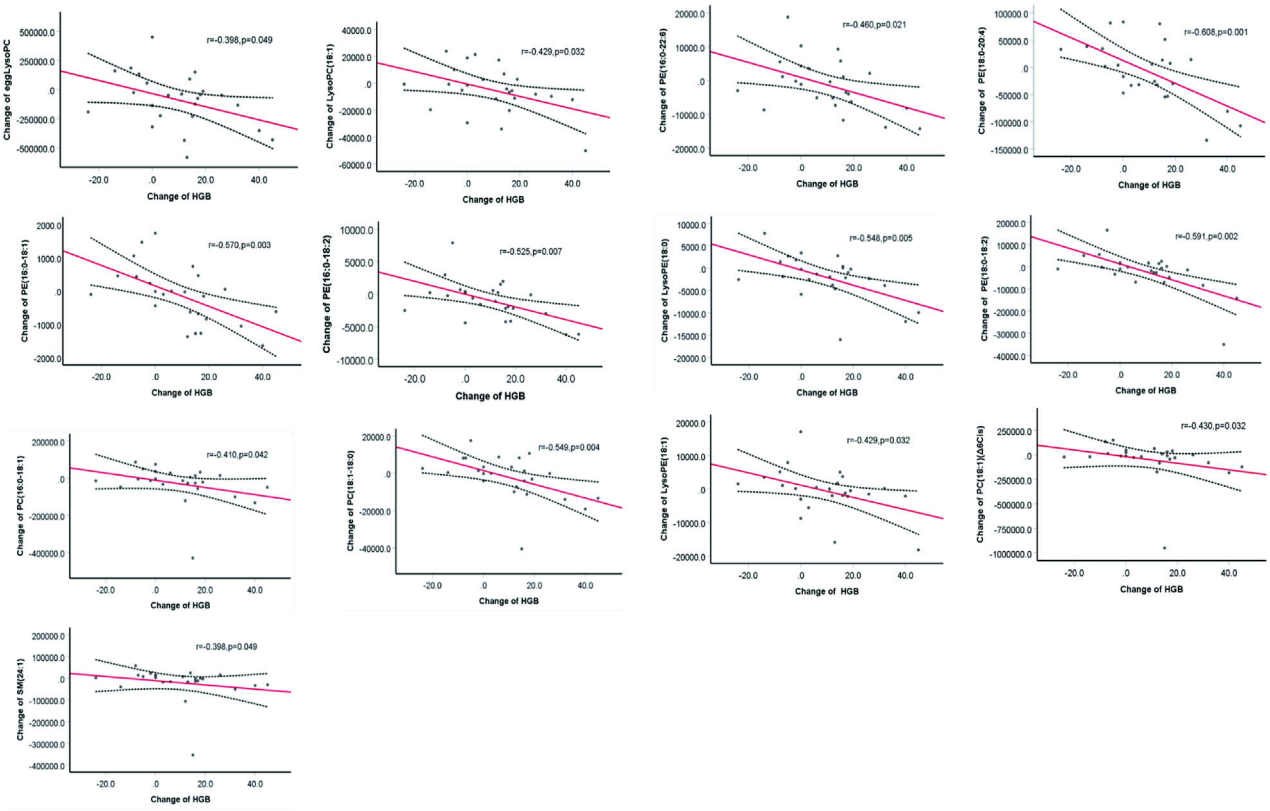


FIGURE 4
The correlation between change of metabolites and the hemoglobin change.

density cholesterol, and high-density cholesterol levels, decreased significantly. The patients' dialysis clearance, as shown by the Kt/V and Ccr, remained stable.

Metabolism levels at baseline and follow-up

As shown in Figure 2. In general, all phospholipid and sphingolipid metabolism showed a decreasing trend after the HIF-PHI (Roxadustat) treatment. Levels of LysoPC (20:0), CisPC (DLPC) (18:2), LysoPE (14:0), and SM (d18:1/17:0) (17:0) were significantly decreased (all $p < 0.05$) after the HIF-PHI (Roxadustat) treatment (Figure 3).

Associations between changes in metabolisms and hemoglobin change from the baseline

Reductions in the levels of eggLysoPC, LysoPC (18:1), PC (18:1) (Δ6Cis), PC (16:0–18:1), PC (18:1–18:0), PE (16:0–18:1), PE (16:0–18:2), PE (16:0–22:6), PE (18:0–20:4), LysoPE (18:0), PE (18:0–18:2), and LysoPE (18:1) SM (24:1) were negatively ($p < 0.05$) associated with the increase in hemoglobin (Figure 4). Further regression analyses confirmed the significant relationship between the increase of hemoglobin level and the decrease of egg lyso PC; PE (16:0–18:1); PE (16:0–18:2); PE (16:0–22:6); PE (18:0–20:4); PE (18:0–18:2); Lyso PE (18:0); LysoPE (18:1) and PC (18:1–18:0) after controlling for age, gender, total Kt/V change, total Ccr change, BMI change, plasma albumin change and high sensitive C- reactive protein change (Table 2).

Discussion

The present study found that patients with end-stage kidney disease (ESKD) who underwent PD showed decreased concentrations of LysoPC (20:0), LysoPE (14:0), PC (18:2) cis dlpc, and SM (17:0) d18:1/18:0 after Roxadustat treatment. In addition, decreased levels of LysoPC, LysoPC (18:1), PC (18:1) (Δ6Cis), PC (16:0–18:1), PC (18:1–18:0), PE (16:0–18:1), PE (16:0–18:2), PE (16:0–22:6), PE (18:0–20:4), LysoPE (18:0), PE (18:0–18:2), LysoPE (18:1), and SM (24:1) were correlated with improvement from anemia. To our knowledge, this is the first study to investigate the changes in phospholipid and sphingolipid metabolism after HIF-PHI.

PLs are integral parts of the membrane and have important functional, structural, and metabolic roles (Liu, 2013). Recently, LC-MS/MS-based lipidomics has provided an opportunity to understand the pathological role of PLs and to develop new predictive biomarkers for distinct diseases.

Sphingolipids are an important class of lipid metabolites and have been confirmed as critical regulators of cardiovascular disease and cancer (Lemaitre, 2018). Abnormal sphingolipid metabolism is common in

patients with uremia. Our previous study found that elevated levels of active sphingolipids are associated with a poor prognosis in end-stage renal disease dialysis (Tang, 2014b; Bai, 2020). Nete also reported that sphingomyelin and phosphatidylcholine species are associated with renal impairment and cause mortality in Type 1 diabetes (Tofte, 2019). In the present study, after Roxadustat treatment, the levels of most plasma sphingomyelin decreased to some extent, whereas only serum SM (d18:1/17:0) decreased significantly ($p < 0.05$).

Chen H. (2017a) reported a significant increase in the serum levels of phospholipids in patients with CKD, which was positively correlated with the level of serum triglycerides and inversely correlated with the levels of total cholesterol and eGFR (Chen H., 2017a). In the present study, we demonstrated that serum LysoPC (20:0), LysoPE (14:0), and PC (18:2) cis-dlpc levels were dramatically decreased after the HIF-PHI treatment. As it is reported that multiple PC, LPC, and LPE are correlated with cardiovascular morbidity (Ferreira-Divino, 2022; Jensen, 2022); thus, our findings that decreased phospholipids after the HIF-PHI treatment, might be suggesting a possible role in cardiovascular protection. However, further studies are required to confirm this hypothesis.

Ceramides are important precursors of other biological sphingolipids. Studies have shown that ceramide levels are increased in chronic kidney disease (CKD) patients (Mantovani, 2021) and are associated with cardiac and renal lipotoxicity (Savira, 2021). Interestingly, adipocyte HIF-2α deficiency exacerbates Western diet-induced atherosclerosis by increasing ceramide levels in adipose tissue, and activation of fatty HIF-2α by the HIF-PHI (Roxadustat) protects against atherosclerosis while simultaneously reducing fat, plasma ceramide, and plasma cholesterol levels (Zhang et al., 2019). In the present study, after the HIF-PHI administration, the levels of most of the plasma ceramides decreased to some extent but not significantly. These decreasing trends may suggest the potential role of the HIF pathway in sphingolipid metabolism; however, future studies with larger sample sizes are needed to confirm this.

One interesting finding in the present study was that decreased levels of phospholipids, lysophospholipids, and SM metabolism were correlated with the improvement of anemia after Roxadustat treatment.

However, the underlying mechanism remains unknown. Studies have shown that the life span of red blood cell (RBC) in patients with renal failure is significantly reduced, indicating that one of the reasons for renal anemia may be the reduction in the life span of RBCs (Vos, 2011; Sato, 2012; Ma, 2017; Li, 2019). In addition, it stabilizes HIF by inhibiting PHD, thereby promoting EPO secretion to improve renal anemia. A previous study also showed that hemodialysis (HD) patients treated with the HIF-PHI had significantly longer RBC longevity than those on rhuEPO therapy (Yang, 2021). Interestingly, both plasma and erythrocyte phospholipid metabolism have been linked to the RBC lifespan in previous studies (Grace, 2012; Dinkla, 2016). Further studies are needed to elucidate the link between phospholipids and RBC life after HIF-PHI treatment.

This study has several limitations. First, the sample size was relatively small, which reduced the statistical power of this study. Second, this is a real-world treatment cohort; although we tried our best to exclude the possible influence of other clinical and treatment factors, we cannot completely rule out the possible impact of some other factors that we did not include. Third, some patients were switched from ESA treatment to Roxadustat therapy, therefore, we could exclude the effect of withdraw of ESA treatment. Forth, despite independent relationship of change of hemoglobin and some of PLs and SMs were discovered after Roxadustat treatment in this study, we could not answer the underline mechanism. Therefore, further study using more advanced method to investigate the potential role of HIF-PHI in PLs and SMs metabolism is need in this area. Despite the above drawbacks our study is the first to investigate PLs and SMs metabolism after the HIF-PHI treatment in a real-world ESKD treatment cohort and may help understand the clinical effect of HIF-PHI in ESKD patients.

Clinical significance

Elevated Phospholipids and sphingolipid (SM) metabolism have been connected with poor clinical status and adverse outcome of end-stage renal disease patients who underwent peritoneal dialysis (PD).

Hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) (Roxadustat) is a novel small-molecule oral drug used for the treatment of renal anemia. Several clinical studies have suggested that treatment by HIF-PHI is accompanied by a reduction in blood lipid levels. Study showed that atherosclerosis amelioration can be pharmacologically achieved in mice by activating adipose HIF-2α via the HIF-PHI (Roxadustat) possible by promoting ceramide catabolism.

This study demonstrated that after HIF-PHI administration, phospholipid and sphingolipid metabolism showed a decreasing trend. Decreased levels of phospholipids, lysophospholipids, and sphingolipid metabolism were correlated with the improvement of anemia after HIF-PHI (Roxadustat) treatment. Our findings that decreased phospholipids and sphingolipid metabolism after Roxadustat treatment, might be suggesting a possible protection role of HIF-PHI for PD patients besides correction of anemia. And provoke further investigation as clinically appropriate.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving humans were approved by the Peking University Third Hospital Medical Science Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was provided by the participants.

Author contributions

Y-HY: Data curation, Investigation, Writing–original draft, Methodology. YS: Data curation, Methodology, Writing–original draft. YZ: Investigation, Conceptualization, Methodology, Validation, Writing–review and editing. WT: Conceptualization, Writing–review and editing, Supervision.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This study was supported by funds from the China International Medical Foundation (No. Z-2017-24-2037), BYSYZD 2019044, BYSY2022051, BMU2023YFJHMX015, and by Project 2020BD030 supported by the PKU-Baidu Fund. The funder had no role in the study design, data collection and analysis, decision to publish, or manuscript preparation.

Acknowledgments

The authors thank the staff of the PD Center, Third Hospital, Peking University.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Bai, Q., Guo, H.-X., Su, C.-Y., Han, Q. F., Wang, T., and Tang, W. (2020). Serum Sphingosine-1-phosphate level and peritonitis in peritoneal dialysis patients. *Ren. Fail.* 42 (1), 829–835. doi:10.1080/0886022x.2020.1805763

Chen, H., Chen, L., Liu, D., Chen, D. Q., Vaziri, N. D., and Yu, X. Y., (2017a). Combined clinical phenotype and lipidomic analysis reveals the impact of chronic kidney disease on lipid metabolism. *J. Proteome Res.* 16 (4), 1566–1578. doi:10.1021/acs.jproteome.6b00956

Chen, N., Qian, J., Chen, J., Yu, X., Mei, C., and Hao, C., (2017b). Phase 2 studies of oral hypoxia-inducible factor prolyl hydroxylase inhibitor FG-4592 for treatment of anemia in China. *Nephrol. Dial. Transpl.* 32 (8), 1373–1386. doi:10.1093/ndt/gfx011

Dinkla, S., van Eijk, L. T., Fuchs, B., Schiller, J., Joosten, I., and Brock, R., (2016). Inflammation-associated changes in lipid composition and the organization of the erythrocyte membrane. *BBA Clin.* 5, 186–192. doi:10.1016/j.bbacli.2016.03.007

Duan, C. (2016). Hypoxia-inducible factor 3 biology: complexities and emerging themes. *Am. J. Physiol. Cell Physiol.* 310 (4), C260–C269. doi:10.1152/ajpcell.00315.2015

Ferreira-Divino, L. F., Suvitaival, T., Rotbain Curovic, V., Tofte, N., Trošt, K., and Mattila, I. M., (2022). Circulating metabolites and molecular lipid species are associated with future cardiovascular morbidity and mortality in type 1 diabetes. *Cardiovasc Diabetol.* 21 (1), 135. doi:10.1186/s12933-022-01568-8

Grace, B. S., Clayton, P. A., Cass, A., and McDonald, S. P. (2012). Transplantation rates for living- but not deceased-donor kidneys vary with socioeconomic status in Australia. *Kidney Int.* 83, 138–145. doi:10.1038/ki.2012.304

Hilvo, M., Meikle, P. J., Pedersen, E. R., Tell, G. S., Dhar, I., and Brenner, H., (2020). Development and validation of a ceramide- and phospholipid-based cardiovascular risk estimation score for coronary artery disease patients. *Eur. Heart J.* 41 (3), 371–380. doi:10.1093/eurheartj/ehz387

Jensen, P. N., Fretts, A. M., Hoofnagle, A. N., McKnight, B., Howard, B. V., and Umans, J. G., (2022). Circulating ceramides and sphingomyelins and the risk of incident cardiovascular disease among people with diabetes: the strong heart study. *Cardiovasc Diabetol.* 21 (1), 167. doi:10.1186/s12933-022-01596-4

Lemaitre, R. N., Yu, C., Hoofnagle, A., Hari, N., Jensen, P. N., and Fretts, A. M., (2018). Circulating sphingolipids, insulin, HOMA-IR, and HOMA-B: the strong heart family study. *Diabetes* 67 (8), 1663–1672. doi:10.2337/db17-1449

Li, J. H., Luo, J. F., Jiang, Y., Ma, Y. J., Ji, Y. Q., and Zhu, G. L., (2019). Red blood cell lifespan shortening in patients with early-stage chronic kidney disease. *Kidney Blood Press Res.* 44 (5), 1158–1165. doi:10.1159/000502525

Li, M., Feng, B., Liang, Y., Zhang, W., Bai, Y., and Tang, W., (2013). Lipid profiling of human plasma from peritoneal dialysis patients using an improved 2D (NP/RP) LC-QToF MS method. *Anal. Bioanal. Chem.* 405 (21), 6629–6638. doi:10.1007/s00216-013-7109-5

Liu, R., Peng, Y., Li, X., Wang, Y., Pan, E., and Guo, W., (2013). Identification of plasma metabolomic profiling for diagnosis of esophageal squamous-cell carcinoma using an UPLC/TOF/MS platform. *Int. J. Mol. Sci.* 14 (5), 8899–8911. doi:10.3390/ijms14058899

Ma, J., Dou, Y., Zhang, H., Thijssen, S., Williams, S., and Kuntsevich, V., (2017). Correlation between inflammatory biomarkers and red blood cell life span in chronic hemodialysis patients. *Blood Purif.* 43 (1-3), 200–205. doi:10.1159/000452728

Maceyka, M., and Spiegel, S. (2014). Sphingolipid metabolites in inflammatory disease. *Nature* 510 (7503), 58–67. doi:10.1038/nature13475

Mantovani, A., Lunardi, G., Bonapace, S., Dugo, C., Altomari, A., and Molon, G., (2021). Association between increased plasma ceramides and chronic kidney disease in patients with and without ischemic heart disease. *Diabetes Metab.* 47 (1), 101152. doi:10.1016/j.diabet.2020.03.003

Papazoglou, A. S., Stalikas, N., Moysidis, D. V., Otountzidis, N., Kartas, A., and Karagiannidis, E., (2022). CERT2 ceramide- and phospholipid-based risk score and major adverse cardiovascular events: a systematic review and meta-analysis. *J. Clin. Lipidol.* 16 (3), 272–276. doi:10.1016/j.jacl.2022.02.001

Provenzano, R., Besarab, A., Sun, C. H., Diamond, S. A., Durham, J. H., and Cangiano, J. L., (2016). Oral hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) for the treatment of anemia in patients with CKD. *Clin. J. Am. Soc. Nephrol.* 11 (6), 982–991. doi:10.2215/CJN.06890615

Rabinowitz, M. H. (2013). Inhibition of hypoxia-inducible factor prolyl hydroxylase domain oxygen sensors: tricking the body into mounting orchestrated survival and repair responses. *J. Med. Chem.* 56 (23), 9369–9402. doi:10.1021/jm400386j

Sanghani, N. S., and Haase, V. H. (2019). Hypoxia-inducible factor activators in renal anemia: current clinical experience. *Adv. Chronic Kidney Dis.* 26 (4), 253–266. doi:10.1053/j.ackd.2019.04.004

Sato, Y., Mizuguchi, T., Shigenaga, S., Yoshikawa, E., Chujo, K., and Minakuchi, J., (2012). Shortened red blood cell lifespan is related to the dose of erythropoiesis-stimulating agents requirement in patients on hemodialysis. *Ther. Apher. Dial.* 16 (6), 522–528. doi:10.1111/j.1744-9987.2012.01089.x

Savira, F., Magaye, R., Scullino, C. V., Flynn, B. L., Pitson, S. M., and Anderson, D., (2021). Sphingolipid imbalance and inflammatory effects induced by uremic toxins in heart and kidney cells are reversed by dihydroceramide desaturase 1 inhibition. *Toxicol. Lett.* 350, 133–142. doi:10.1016/j.toxlet.2021.07.012

Tang, W., Li, M., Lu, X. H., Liu, H. W., and Wang, T. (2014a). Phospholipids profiling and outcome of peritoneal dialysis patients. Biomarkers: biochemical indicators of exposure, response, and susceptibility to chemicals. *Biomarkers* 19 (6), 505–508. doi:10.3109/1354750X.2014.943290

Tang, W., Li, M., Lu, X.-H., Liu, H. W., and Wang, T. (2014b). Phospholipids profiling and outcome of peritoneal dialysis patients. *Biomarkers* 19 (6), 505–508. doi:10.3109/1354750x.2014.943290

Tofte, N., Suvitaival, T., Ahonen, L., Winther, S. A., Theilade, S., and Frimodt-Møller, M., (2019). Lipidomic analysis reveals sphingomyelin and phosphatidylcholine species associated with renal impairment and all-cause mortality in type 1 diabetes. *Sci. Rep.* 9 (1), 16398. doi:10.1038/s41598-019-52916-w

Vos, F. E., Schollum, J. B., Coulter, C. V., Doyle, T. C. A., Duffull, S. B., and Walker, R. J. (2011). Red blood cell survival in long-term dialysis patients. *Am. J. Kidney Dis.* 58 (4), 591–598. doi:10.1053/j.ajkd.2011.03.031

Yang, X., Zhao, B., Wang, J., Wang, L., Tao, M., and Lu, J., (2021). Red blood cell lifespan in long-term hemodialysis patients treated with roxadustat or recombinant human erythropoietin. *Ren. Fail.* 43 (1), 1428–1436. doi:10.1080/0886022X.2021.1988968

Yeh, T. L., Leissing, T. M., Abboud, M. I., Thinnes, C. C., Atasoylu, O., and Holt-Martyn, J. P., (2017). Molecular and cellular mechanisms of HIF prolyl hydroxylase inhibitors in clinical trials. *Chem. Sci.* 8 (11), 7651–7668. doi:10.1039/c7sc02103h

Zhang, X., Zhang, Y., Wang, P., Zhang, S. Y., Dong, Y., and Zeng, G., (2019). Adipocyte hypoxia-inducible factor 2α suppresses atherosclerosis by promoting adipose ceramide catabolism. *Cell metab.* 30 (5), 937–951 e5. doi:10.1016/j.cmet.2019.09.016

frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 10 July 2024
DOI 10.3389/fphys.2024.1339762

OPEN ACCESS

EDITED BY
Rosilene M. Elias,
University of São Paulo, Brazil

REVIEWED BY
Pedro Henrique Franca Gois,
The University of Queensland, Australia
Ramesh Khannaa,
University of Missouri, United States

*CORRESPONDENCE
Joanna Stachowska-Pietka,
jstachowska@ibib.waw.pl,
joanna.stachowskapietka@ki.se

RECEIVED 16 November 2023
ACCEPTED 16 May 2024
PUBLISHED 10 July 2024

CITATION
Stachowska-Pietka J, Waniewski J, Olszowska A, Garcia-Lopez E, Yan J, Yao Q, Wankowicz Z and Lindholm B (2024), Can one long peritoneal dwell with icodextrin replace two short dwells with glucose?
Front. Physiol. 15:1339762.
doi: 10.3389/fphys.2024.1339762

Can one long peritoneal dwell with icodextrin replace two short dwells with glucose?

Joanna Stachowska-Pietka[1,2]*, Jacek Waniewski[1], Anna Olszowska[3], Elvia Garcia-Lopez[2], Junfei Yan[4], Qiang Yao[4], Zofia Wankowicz[3] and Bengt Lindholm[2]

[1]Nalecz Institute of Biocybernetics and Biomedical Engineering, Polish Academy of Sciences, Warsaw, Poland, [2]Department of Clinical Science, Intervention and Technology, Division of Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden, [3]Central Clinical Hospital of the Ministry of National Defence, Military Institute of Medicine, Warsaw, Poland, [4]Baxter Healthcare Corporation, Shanghai, China

Background: Due to the slower dissipation of the osmotic gradient, icodextrin-based solutions, compared to glucose-based solutions, can improve water removal. We investigated scenarios where one icodextrin-based long dwell (Extraneal) replaced two glucose-based exchanges.

Methods: The three-pore model with icodextrin hydrolysis was used for numerical simulations of a single exchange to investigate the impact of different peritoneal dialysis schedules on fluid and solute removal in patients with different peritoneal solute transfer rates (PSTRs). We evaluated water removal (ultrafiltration, UF), absorbed mass of glucose (AbsGluc) and carbohydrates (AbsCHO, for glucose and glucose polymers), ultrafiltration efficiency (UFE = UF/AbsCHO) per exchange, and specified dwell time, and removed solute mass for sodium (ReNa), urea (ReU), and creatinine (ReCr) for a single peritoneal exchange with 7.5% icodextrin (Extraneal®) and glucose-based solutions (1.36% and 2.27%) and various dwell durations in patients with fast and average PSTRs.

Results: Introducing 7.5% icodextrin for the long dwell to replace one of three or four glucose-based exchanges per day leads to increased fluid and solute removal and higher UF efficiency for studied transport groups. Replacing two glucose-based exchanges with one icodextrin exchange provides higher or similar water removal and higher daily sodium removal but slightly lower daily removal of urea and creatinine, irrespective of the transport type present in the case of reference prescription with three and four daily exchanges.

Conclusion: One 7.5% icodextrin can replace two glucose solutions. Unlike glucose-based solutions, it resulted only in minor differences between PSTR groups in terms of water and solute removal with UFE remaining stable up to 16 h.

KEYWORDS

chronic kidney disease, peritoneal dialysis, icodextrin, ultrafiltration, sodium removal, glucose absorption, ultrafiltration efficiency

1 Introduction

The removal of excess water and uremic toxins is the main goal of peritoneal dialysis (PD). In conventional PD solutions, glucose at different concentrations is used as an osmotic agent to provide sufficient water removal (ultrafiltration, UF), together with solute removal. The higher the glucose concentration, the higher the osmotic gradient, which induces greater UF; however, glucose absorption increases. Moreover, the prolonged exposure to a higher glucose concentration might trigger local structural and functional changes within the peritoneal membrane that, in the long-term, may lead to insufficient water removal and, possibly, UF failure. As an alternative, to ameliorate these problems, an isosmotic solution (Extraneal®, Baxter) containing glucose polymers (7.5% icodextrin) instead of glucose as the primary osmotic agent can be used in longer dwells or in patients with insufficient UF to increase and prolong water removal due to the slower dissipation of the osmotic gradient created by icodextrin and to decrease the exposure to glucose.

The efficiency of water and solute removal is directly related to the characteristics of the peritoneal membrane and its transport capacity (permeability) that varies among patients and may change over time in long-term dialysis. Although recently more emphasis was given to fluid removal, the typical assessment of peritoneal membrane transport properties is based on small-solute transport and classification of individual patients according to their peritoneal small solute transfer rates (PSTRs) as fast, average, and slow transporters based on the peritoneal equilibration test (Morelle et al., 2021). This is partly due to the fact that, in the case of dwells with glucose-based solutions, a faster PSTR not only results in the faster and earlier equilibration of solutes but also the faster absorption of glucose and, consequently, lower UF, which, in turn, leads to the lower removal of urea and creatinine during the latter part of the dwell (Wang et al., 1998). This is in contrast to long icodextrin-based dwells, for which numerical simulations and also clinical trials suggest the lower dependence of UF on the PSTR and tendency to equalize water and sodium removal, especially among patients characterized by a fast and average PSTR (Lin et al., 2009; Akonur et al., 2016).

The current consensus is that small-solute removal should not be considered so strictly and treated as the only indicator of treatment adequacy, and that other factors should be also taken into account (Brown et al., 2020). Nowadays, modern PD prescriptions allow more possibilities to modify and optimize standard PD treatment regimens in order to not only provide effective treatment outcome in terms of fluid and solute removal but also to decrease glucose exposure that may harm the peritoneal membrane or reduce the number of exchanges as these changes may potentially protect residual renal function and increase the patient quality of life. The recent trend of the growing popularity of incremental dialysis is also consistent with the above fact (Blake et al., 2020). Incremental PD consists in the earlier initiation of PD with less frequent exchanges and/or with lower doses, with further modifications following changes occurring in membrane and renal function at the time of PD. It is very common to initiate PD therapy with only 2–3 exchanges per day, especially in Asia (Lo et al., 2001; Yan et al., 2022).

Various clinical studies suggest that icodextrin improved UF and lowered daily glucose absorption levels compared to glucose-based solutions (Goossen et al., 2020). In addition, the differences in mechanisms involved in the water removal for icodextrin and glucose-based solutions were investigated experimentally and using mathematical modeling (Morelle et al., 2018; Morelle et al., 2023); however, the magnitude of its superiority requires further research. In this study, we applied the three-pore model to simulate various PD schedules and their impact on fluid and solute removal under well-specified and controlled conditions to investigate whether glucose-based exchanges can be replaced with 7.5% icodextrin in the same patients and, if yes, to which extent? We especially address one question: can one icodextrin-based long dwell replace two exchanges with glucose-based solutions? Since the problem of insufficient water removal is mainly observed in patients with a fast PSTR, we primarily focus on this group, but we also verify to which extent answers to this question are transferable to patients with other transport status.

2 Materials and methods

2.1 Model overview

All simulations presented in this study are based on the extended version of the three-pore model for peritoneal transport (including dwells with 7.5% icodextrin) described in detail below. The proposed model is based on the classical three-pore approach applied to describe the peritoneal transport of water and solutes. In addition, icodextrin hydrolysis and its impact on peritoneal transport are taken into account; in the present study, we used a minimal model, i.e., a simplified version of the models of icodextrin hydrolysis by α-amylase proposed by Akonur et al. (2015) and Stachowska-Pietka et al. (2023), which is still sufficient to provide an accurate description of clinical data.

The applied model describes changes in the intraperitoneal volume and solute concentrations in the dialysate. The following solutes are considered in the model: small solutes (urea, creatinine, glucose, and sodium) and icodextrin polysaccharides [aggregated into seven fractions, i.e., glucose polymer-size classes, with molecular weight cut-off values up to 1.08 kDa (fraction 1), 4.44 kDa (fraction 2), 9.89 kDa (fraction 3), 21.4 kDa (fraction 4), 43.5 kDa (fraction 5), 66.7 kDa (fraction 6), and over 66.7 kDa (fraction 7), as described in Stachowska-Pietka et al. (2023)].

2.2 Model-based simulations

Numerical simulations of peritoneal transport during a single exchange were carried out for a typical patient with an average PSTR according to PET. The characteristics of a "typical peritoneal membrane" were taken based on the adjustment of the model to the clinical data of nine patients undergoing PD with glucose 2.27% solution, described previously in Heimburger et al. (1992). More precisely, the fractional small-pore UF coefficient (α_{SP}) and unrestricted pore area over the (unit) diffusion path length distance ($A_0/\Delta x$) were adjusted to clinical data from Heimburger et al. (1992), and peritoneal fluid absorption of 1.2 mL/min was

taken into account based on the volume marker absorption from the peritoneal cavity. For each solute, the diffusive permeability of the peritoneal membrane (PS) was calculated according to the standard formulas from the three-pore approach, as proposed and applied previously based on the adjusted value of $A_0/\Delta x$ (Rippe and Levin, 2000; Rippe et al., 2004; Waniewski, 2013). The diffusive permeability of urea was adjusted separately to $A_0/\Delta x$ (with a slightly higher value than the theoretical one) to obtain a precise description of urea removal during the peritoneal exchange. This remains in agreement with clinical observations that higher values of diffusive transport parameters for urea were observed during PD exchanges related to its transport across the peritoneal tissue cells. The model describes data with high accuracy with an average relative error per measurement point of 0.01, as presented in Supplementary Figure S1.

The obtained characteristics of the peritoneal membrane were taken to provide the simulation of glucose and icodextrin exchanges. The typical values of the peritoneal fluid absorption rate measured using a volume marker range from 0.7 up to 1.6 mL/min but typically remain below 1 mL/min (Waniewski, 2013). The mean value of peritoneal absorption measured in Heimburger et al. (1992) was 1.2 ± 0.6 mL/min, whereas a lower mean value of 0.67 ± 0.39 mL/min was found in Stachowska-Pietka et al. (2023). Therefore, to provide reliable simulations for a typical patient, we considered an average value of those two, 0.9 mL/min. The typical parameters for icodextrin hydrolysis by amylase were taken based on the average values obtained using the minimal model for the analysis of clinical data on long-term icodextrin-exposed patients undergoing 16-h 7.5% icodextrin dwells, published previously by Olszowska et al. (2019). The simulation of a single exchange of 2 L dialysis fluid with 2.27% and 1.36% glucose lasting up to 8 h and with 7.5% icodextrin lasting up to 16 h was performed with parameters as presented in Supplementary Table S1.

The simulation of a single exchange of 2 L dialysis fluid with 2.27% and 1.36% glucose lasting up to 8 h and with 7.5% icodextrin lasting up to 16 h was performed with parameters as presented in Supplementary Table S1. The initial concentrations of the solutes in the dialysate were calculated taking into account the dilution of solute concentrations in fresh dialysis fluid (according to specifications by the manufacturer) by the residual peritoneal volume. Numerical simulations for a patient with a fast PSTR were performed with the rescaled solute diffusive permeabilities of the peritoneal membrane (PSs), following the changes in $A_0/\Delta x$ (increased by a factor of 1.6), as previously proposed by Oberg (2021).

2.3 Minimal three-pore model for icodextrin transport

In order to simulate peritoneal dwells with icodextrin, the classical three-pore model was extended. Since the modeling of hydrolysis was out of scope of this study, we applied a model that would describe the kinetics of icodextrin fractions without a detailed description of its hydrolysis. We call this model a minimal model as it is a simplified version of the models that take into account icodextrin hydrolysis by α-amylase proposed by Akonur et al. (2015) and Stachowska-Pietka et al. (2023), which is still sufficient to provide an accurate description of clinical data.

A simplified kinetics was proposed using pseudo-first-order degradation kinetics to describe the net decrease in icodextrin fraction mass in the dialysate (fractions 2–7) that was related to the hydrolysis with a constant degradation rate k_i (Akonur et al., 2015; Stachowska-Pietka et al., 2023). Therefore, in addition to peritoneal kinetics, a decrease in the mass of fractions 2–7 corresponding to the hydrolysis can be calculated as $k_i \cdot C_{D,amylase} \cdot (V_D \cdot C_{D,Ico_i})$, where $V_D \cdot C_{D,Ico_i}$ denotes the mass of fraction i. Similar to the previous approaches, we assume additionally that the degradation rate depends on the amylase concentration in dialysate $C_{D,amylase}$. The (net) mass of icodextrin polymers from fractions 2 to 7 degraded by the amylase activity (expressed in moles/min) would increase the molar mass of fraction 1 (by $2 \sum_{i=2,\ldots,7} k_i \cdot C_{D,amylase} \cdot (V_D \cdot C_{D,Ico_i})$) additionally to its increase related to the degradation of polymers present already in fraction 1 ($k_1 \cdot C_{D,amylase} \cdot (V_D \cdot C_{D,Ico_1})$.

Similar to the classical three-pore model, the minimal model was adjusted to the clinical data on long-term icodextrin-exposed patients undergoing 16-h 7.5% icodextrin dwells, published previously by Olszowska et al. (2019). The individual kinetics of the intraperitoneal volume and the concentration of glucose, urea, creatinine, and icodextrin fractions 1–7 were taken into account. The goodness of the minimal model to predict peritoneal transport in icodextrin dwells was high with an average relative error per measurement point of 0.032 (Supplementary Figures S2, S3).

2.4 Calculation of treatment efficiency

For each session, the removal of urea, creatinine, and sodium (ReU, ReCr, and ReNa, respectively) was calculated as the difference between the mass of the solute removed in the spent dialysate and the solute mass instilled. The absorption of glucose from glucose-based solutions and carbohydrates (polysaccharides) from icodextrin-based solution during the peritoneal exchange was calculated as the difference between the solute mass infused in the fresh solution and its mass removed in the drained fluid. The total absorption of carbohydrates, AbsCHO, was calculated as the total mass of glucose absorbed (in the case of glucose-based solution) or the sum of the total glucose and carbohydrate mass absorbed (for 7.5% icodextrin) during a single session or for a whole schedule. In addition, the total mass of glucose absorbed, AbsGluc, was calculated for each schedule.

The removal of fluid was evaluated based on the UF and calculated as the difference between the final volume decreased by the residual volume and the infused volume. The efficiency of dialysis solution to remove water, i.e., ultrafiltration efficiency UFE, was defined as UF divided by the total absorption of carbohydrates, AbsCHO, during a specified time—a single exchange with various dwell times or daily.

2.5 Numerical simulations

The parameters for the classical and minimal three-pore model were estimated using the "lsqnonlin" function implemented with the

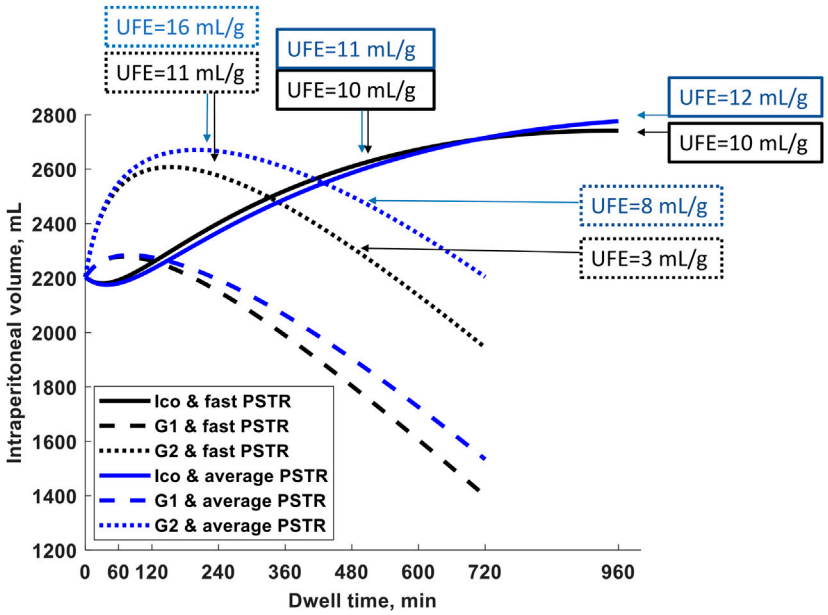


FIGURE 1
Intraperitoneal volume as a function of dwell time during a 12-h exchange with 1.36% (G1) and 2.27% glucose (G2) and during a 16-h exchange with Extraneal (Ico, 7.5% icodextrin-based solution) for a patient with fast peritoneal solutes transfer rate (PSTR) and average PSTR. The figure shows marked differences between the three solutions in the intraperitoneal volume with transitory increases in the two glucose-based solutions that are accentuated by a faster PSTR, while the steady increase of volume up to 14–16 h with 7.5% icodextrin (Extraneal) is not influenced much by the PSTR. The ultrafiltration efficiency, UFE (volume of water removed in mL per gram absorbed carbohydrates), for G2 and 7.5% icodextrin (Extraneal) and for both PSTR groups is noted at specified dwell times (4 and 8 h for G2 and 8 and 16 h for Ico), showing a decrease in UFE in glucose-based solutions already after the 4-h dwell, whereas UFE remains stable even up to 16 h in the icodextrin-based solution.

trust–region–reflective algorithm implemented to minimize the sum of squared differences between the modeled and measured values for the intraperitoneal volume and concentration of glucose, urea, creatinine, and icodextrin fractions (for the minimal model only) in the dialysate.

The numerical simulation of glucose and icodextrin-based dwells was performed using the minimal three-pore model that was implemented and solved using the commercial software package MATLAB with the built-in function "ode45," which is based on an explicit Runge–Kutta formula with variable step size. Computer-based simulations were performed according to the concept presented in Sections 2.1–2.4 and with the parameters presented in Supplementary Table S1.

3 Results

The changes in the intraperitoneal volume during a single exchange with 2.27% and 1.36% glucose and icodextrin-based (Extraneal) solutions are presented in Figure 1 for patients with an average and fast PSTR. In the case of shorter exchanges, glucose-based solutions are more efficient in water removal than 7.5% icodextrin, whereas icodextrin provides greater UF for longer dwells (Figure 1). Initially, for glucose-based solutions, the intraperitoneal volume increases. However, the dominance of peritoneal fluid absorption over ultrafiltration during the later phase of the peritoneal dwell results in the thereafter observed steady decrease in the intraperitoneal volume and, thus, the appearance of negative ultrafiltration for long-enough dwells (Figure 1). The appearance of negative ultrafiltration, corresponding to the absorption of fluid, can be observed earlier in the case of solutions with a lower glucose concentration, as well as in patients with faster transport status, due to the faster dissipation of the osmotic gradient (Table 1). This is in contrast to the icodextrin-based exchanges for which the intraperitoneal volume gradually increases up to 14–16 h of the peritoneal dwell (Figure 1; Table 1). However, the model predicts that for long-enough dwells with 7.5% icodextrin (exceeding 14–16 h), the fluid absorption rate will finally exceed the UF rate, eventually leading to a slow decrease in the intraperitoneal volume (instead of the observed increase) that would occur sooner in the case of patients with a faster PSTR. In contrast to glucose-based solutions, the changes in the intraperitoneal volume during dwells with 7.5% icodextrin are similar among patients from different transfer groups (difference in UF for a single exchange is smaller than 65 mL) (Figure 1; Table 1).

During peritoneal dwells, the concentration of the osmotic agents in dialysate, glucose and icodextrin, slowly decreases. The absorption of glucose occurs during the whole dwell period with glucose-based solutions, with 42 g and 25 g of glucose being absorbed after 12 h for a patient with a fast PSTR and 2.27% and 1.36% glucose, respectively, as presented in Table 1. In the case of icodextrin-based solutions, the amount of carbohydrates absorbed during the peritoneal dwell, AbsCHO, is mainly related to the absorption of glucose polymers composing icodextrin, while glucose is removed from the body in the dialysis fluid. After a 16-h dwell, the absorption of carbohydrates reaches net AbsCHO = 55 g for fast transporters (including an estimated amount of 5 g of

10.3389/fphys.2024.1339762

TABLE 1 Simulated ultrafiltration (UF), absorbed carbohydrates (AbsCHO for glucose and glucose polymers), ultrafiltration efficiency (UFE = UF/AbsCHO) per single exchange and specified dwell time, and removed solute mass calculated for sodium (ReNa), urea (ReU), and creatinine (ReCr) for a single peritoneal exchange with icodextrin-based (Extraneal) and glucose-based solutions (2.27% and 1.36%) and different dwell durations for a patient with a fast and average peritoneal solute transfer rate (PSTR). NA, not applicable due to net fluid absorption.

Solution	Icodextrin			Glucose 2.27%					Glucose 1.36%				
Dwell duration	10 h	12 h	16 h	4 h	6 h	8 h	10 h	12 h	4 h	6 h	8 h	10 h	12 h
Transfer group	Fast PSTR												
UF, mL	469	510	538	373	262	109	−68	−258	−53	−214	−399	−598	−804
AbsCHO, g	45.2	50.1	54.8	34.0	37.8	39.9	41.2	42.0	20.8	22.8	23.9	24.5	25.0
UFE, mL/g	10.4	10.2	9.8	11.0	6.9	2.7	NA	NA	NA	NA	NA	NA	NA
ReNa, mmoL	75.1	80.9	85.2	51.1	42.2	24.5	1.9	−23.5	0.1	−19.2	−43.4	−70.2	−98.5
ReU, g	2.65	2.70	2.74	2.5	2.4	2.3	2.1	1.9	2.1	1.9	1.7	1.5	1.3
ReCr, g	0.21	0.21	0.22	0.17	0.18	0.18	0.16	0.15	0.15	0.15	0.14	0.12	0.10
Transfer group	Average PSTR												
UF, mL	457	512	573	463	403	297	160	1	−10	−140	−299	−478	−669
AbsCHO, g	39.7	43.9	47.9	28.3	32.8	36.0	38.3	39.9	18.1	20.7	22.4	23.6	24.4
UFE, mL/g	11.5	11.7	12.0	16.4	12.3	8.2	4.2	0.0	NA	NA	NA	NA	NA
ReNa, mmoL	73.4	80.8	89.3	51.7	51.4	42.6	27.9	8.7	0.9	−13.1	−32.3	−55.2	−80.7
ReU, g	2.6	2.7	2.8	2.3	2.4	2.4	2.3	2.2	2.0	1.9	1.8	1.7	1.4
ReCr, g	0.20	0.21	0.22	0.15	0.17	0.17	0.17	0.16	0.13	0.14	0.14	0.13	0.11

glucose removed from blood to the dialysate) and AbsCHO = 48 g for patients with an average PSTR (Table 1). Moreover, the efficiency of icodextrin to remove water, UFE, remains relatively stable with values close to 10 mL/g for a fast PSTR and 11–12 mL/g for average transporters. Unlike for 7.5% icodextrin, the efficiency of glucose-based solutions, UFE, does not remain stable but decreases with the dwell length, being higher in the case of dialysis fluid with higher tonicity (Table 1).

Sodium removal follows water transport, being the highest in the case of dwells with 7.5% icodextrin for dwells longer than 6 h in patients with a fast and average PSTR, Table 1. Moreover, in the case of the usage of icodextrin-based solutions, sodium removal increases with dwell time, while the removal of sodium in dwells with glucose-based solutions increases initially but then decreases after 4–6 h of peritoneal dwells due to the decrease in the peritoneal dialysate volume (Table 1). Consequently, for long-enough dwells, effective absorption of sodium among fast transporters is predicted by the model to occur after 12 h and 6 h for 2.27% and 1.36% glucose, respectively, as indicated by negative values of ReNa in Table 1. In patients with a fast PSTR, the removal of urea and creatinine already decreases after 4 h of glucose dwells (Table 1). In the case of patients with an average PSTR, the corresponding decrease in the urea and creatinine mass removed is observed later, after 6–8 h (Table 1). This is in contrast to 7.5% icodextrin, for which a slight increase in the urea and creatinine mass removed is observed throughout the dwell time and for patients with all transfer types (Table 1). Furthermore, when comparing the removal of small solutes for dwells with the same duration, the removal of solutes is higher with 2.27% glucose than with 7.5% icodextrin in the case of shorter dwells, while for longer dwells, superiority of icodextrin-based solution in terms of the solute mass removed is observed for patients with all types of peritoneal transfer (Table 1) (not shown for slow transporters).

Let us consider a patient with a fast PSTR undergoing initially three 8-h exchanges per day with 2 L of 1.36% or 2.27% glucose-based solution (presented as reference prescriptions in Table 2) and compare it with new scenarios in which one glucose-based exchange (A_1 and C_1, and B_1 with an additional change in glucose concentration in one exchange) or two glucose dwells (scenarios D_1 and E_1) were replaced by one exchange of 7.5% icodextrin. In scenarios A_1–C_1, a single 12-h exchange with the icodextrin-based solution is assumed, followed by two 6-h exchanges with 1.36% or 2.27% glucose-based solutions, whereas in scenarios D_1 and E_1, two glucose 8-h exchanges are replaced by one 16-h dwell with 7.5% icodextrin (Table 2). Based on the results presented in Table 1, the corresponding fluid and solute removals for all theoretical schedules were calculated and presented in Table 2. As expected, the reference prescription with 2.27% glucose provides the higher removal of fluid and solutes with daily UFE = 2.7 mL/g if compared to 1.36% glucose, for which the net absorption of fluid and sodium is predicted (negative UF and ReNa) (Table 2). However, the higher water removal for 2.27% glucose is accompanied by higher glucose absorption (>48 g daily) (Table 2). The substitution of one glucose dwell (from the reference prescription) by one icodextrin dwell leads to the increased removal of water and solutes, even in the case of shorter dwells of glucose solutions, as well as higher daily UFE (scenarios A_1 and C_1; Table 2). Moreover, although the total absorption of carbohydrates increases, the daily absorption of glucose for scenarios A_1 and C_1 is lower than in all reference

TABLE 2 Comparison of reference prescription of three exchanges/day with 2L of glucose 1.36% (G1) or 2.27% (G2) solution with new scenarios (A_1–E_1), where one icodextrin-based exchange replaces one or two glucose-based exchanges, in terms of fluid and solute removal[a] for patients with a fast peritoneal transfer rate (PSTR).

	Reference prescription Fast PSTR		New scenarios				
			A_1	B_1	C_1	D_1	E_1
No. of dwells	Three exchanges/day		Three exchanges/day			Two exchanges/day	
Dwell time[b]	8 h 8 h 8 h		12 h 6 h 6 h			16 h 8 h	
Dialysis fluid	3xG1	3xG2	1xIco+2xG1	1xIco+1xG1+1xG2	1xIco+2xG2	1xIco+1xG1	1xIco+1xG2
UF, mL	−1,198	326	82	558	1,034	139	647
AbsGluc, g	71.6	119.8	40.8	55.9	70.9	19.1	35.1
AbsCHO, g	71.6	119.8	95.6	110.7	125.7	78.6	94.7
UFE, mL/g	N.A.	2.7	0.9	5.0	8.2	1.8	6.8
ReNa, mmol	−130.2	73.6	42.5	103.9	165.3	41.8	109.7
ReU, g	5.2	6.9	6.6	7.1	7.6	4.5	5.0
ReCr, g	0.41	0.53	0.51	0.54	0.58	0.35	0.39

[a]Ultrafiltration (UF), absorbed glucose (AbsGluc), and carbohydrates (AbsCHO for glucose and glucose polymers), ultrafiltration efficiency (UFE), and removed solute mass for sodium (ReNa), urea (ReU), and creatinine (ReCr) were calculated for the whole schedule.
[b]Glucose-based exchanges are denoted by dark blue, and icodextrin-based exchanges by light blue.

10.3389/fphys.2024.1339762

TABLE 3 Comparison of the reference prescription of four exchanges/day with 2L of glucose 1.36% (G1) or 2.27% (G2) solution with new scenarios (A_2–F_2), where one icodextrin-based exchange replaces one or two glucose-based exchanges, in terms of fluid and solute removal[a] for patients with a fast peritoneal transfer rate (PSTR).

	Reference prescription Fast PSTR		New scenarios					
			A_2	B_2	C_2	D_2	E_2	F_2
No. of dwells	Four exchanges/day		Four exchanges/day				Three exchanges/day	
Dwell time[b]	12 h | 4 h | 4 h | 4 h		12 h | 4 h | 4 h | 4 h				12 h | 6 h | 6 h	
Dialysis fluid	4xG1	4xG2	1xIco+3xG1	1xIco+2xG1+1xG2	1xIco+1xG1+2xG2	1xIco+3xG2	1xIco+2xG1	1xIco+2xG2
UF, mL	−963	860	351	777	1,203	1,628	82	1,034
AbsGluc, g	87.3	143.9	57.6	70.8	84.0	97.2	40.8	70.9
AbsCHO, g	87.3	143.9	112.4	125.6	138.8	152.0	95.6	125.7
UFE, mL/g	N.A.	6.0	3.1	6.2	8.7	10.7	0.9	8.2
ReNa, mmol	−98.1	129.9	81.3	132.3	183.3	234.3	42.5	165.3
ReU, g	7.5	9.3	8.9	9.3	9.7	10.1	6.6	7.6
ReCr, g	0.55	0.67	0.66	0.68	0.71	0.73	0.51	0.58

[a]Ultrafiltration (UF), absorbed glucose (AbsGluc), and carbohydrates (AbsCHO for glucose and glucose polymers), ultrafiltration efficiency (UFE), and removed solute mass for sodium (ReNa), urea (ReU), and creatinine (ReCr) were calculated for the whole schedule.
[b]Glucose-based exchanges are denoted by dark blue, and icodextrin-based exchanges, by light blue.

10.3389/fphys.2024.1339762

TABLE 4 Comparison of the reference prescription of three exchanges/day with 2L of glucose 1.36% (G1) or 2.27% (G2) solution with new scenarios (A_1–E_1), where one icodextrin-based exchange replaces one or two glucose-based exchanges, in terms of fluid and solute removal[a] for patients with an average peritoneal transfer rate (PSTR).

	Reference prescription Average PSTR		New scenarios				
			A_1	B_1	C_1	D_1	E_1
No. of dwells	Three exchanges/day		Three exchanges/day			Two exchanges/day	
Dwell time[b]	8 h 8 h 8 h		12 h 6 h 6 h			16 h 8 h	
Dialysis fluid	3xG1	3xG2	1xIco+2xG1	1xIco+1xG1+1xG2	1xIco+2xG2	1xIco+1xG1	1xIco+1xG2
UF, mL	−897	891	232	775	1,318	274	870
AbsGluc, g	67.2	108.1	36.8	49.0	61.2	17.6	31.3
AbsCHO, g	67.2	108.1	85.2	97.4	109.5	70.3	83.9
UFE, mL/g	N.A.	8.2	2.7	8.0	12.0	3.9	10.4
ReNa, mmol	−96.9	127.9	54.6	119.1	183.5	57.0	132.0
ReU, g	5.5	7.3	6.6	7.1	7.6	4.6	5.2
ReCr, g	0.41	0.52	0.48	0.51	0.54	0.35	0.39

[a]Ultrafiltration (UF), absorbed glucose (AbsGluc), and carbohydrates (AbsCHO for glucose and glucose polymers), ultrafiltration efficiency (UFE), and removed solute mass for sodium (ReNa), urea (ReU), and creatinine (ReCr) were calculated for the whole schedule.
[b]Glucose-based exchanges are denoted by dark blue, and icodextrin-based exchanges, by light blue.

10.3389/fphys.2024.1339762

TABLE 5 Comparison of the reference prescription of four exchanges/day with 2L of glucose 1.36% (G1) or 2.27% (G2) solution with new scenarios (A_2–F_2), where one icodextrin-based exchange replaces one or two glucose-based exchanges, in terms of fluid and solute removal[a] for patients with an average peritoneal transfer rate (PSTR).

	Reference prescription Average PSTR		New scenarios					
			A_2	B_2	C_2	D_2	E_2	F_2
No. of dwells	Four exchanges/day		Four exchanges/day				Three exchanges/day	
Dwell time[b]								
Dialysis fluid	4xG1	4xG2	1xIco+3xG1	1xIco+2xG1+1xG2	1xIco+1xG1+2xG2	1xIco+3xG2	1xIco+2xG1	1xIco+2xG2
UF, mL	−699	1,390	483	955	1,428	1901	232	1,318
AbsGluc, g	78.6	124.7	49.7	59.9	70.1	80.3	36.8	61.2
AbsCHO, g	78.6	124.7	98.1	108.3	118.5	128.7	85.2	109.5
UFE, mL/g	N.A.	11.1	4.9	8.8	12.1	14.8	2.7	12.0
ReNa, mmol	−77.9	163.8	83.6	134.3	185.1	235.8	54.6	183.5
ReU, g	7.3	9.1	8.5	8.9	9.3	9.6	6.6	7.6
ReCr, g	0.50	0.61	0.59	0.61	0.63	0.65	0.48	0.54

[a]Ultrafiltration (UF), absorbed glucose (AbsGluc), and carbohydrates (AbsCHO for glucose and glucose polymers), ultrafiltration efficiency (UFE), and removed solute mass for sodium (ReNa), urea (ReU), and creatinine (ReCr) were calculated for the whole schedule.
[b]Glucose-based exchanges are denoted by dark blue, and icodextrin-based exchanges, by light blue.

10.3389/fphys.2024.1339762

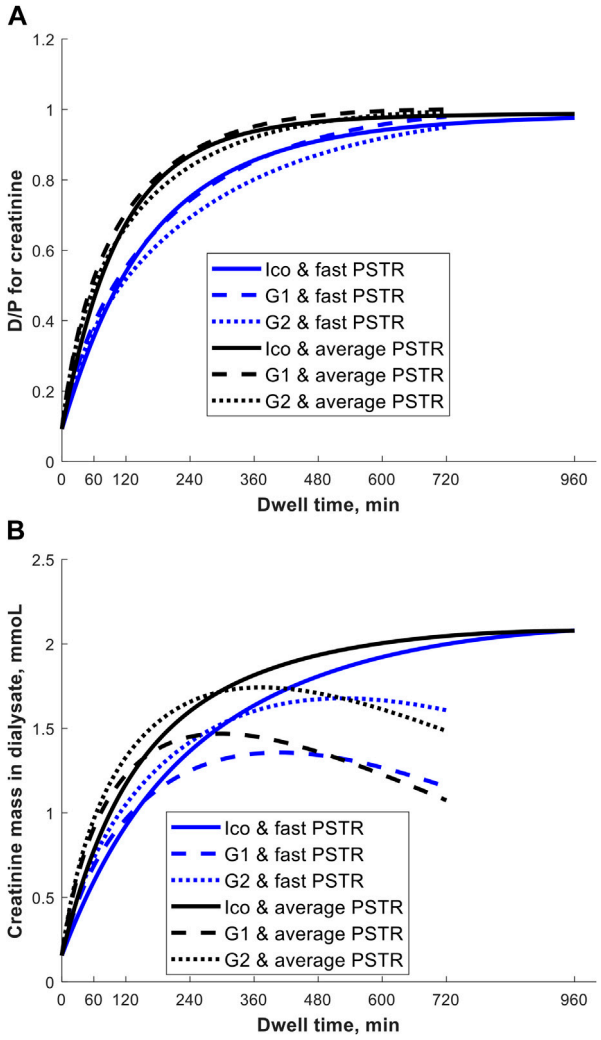


FIGURE 2
Creatinine dialysate-to-plasma concentration, D/P (panel A), and creatinine mass in dialysate (panel B) as a function of dwell time during the 12-h exchange with 1.36% (G1) or 2.27% (G2) glucose-based solution and 16-h exchange with 7.5% icodextrin-based solution (Ico, Extraneal®) in a patient with a fast and average PSTR.

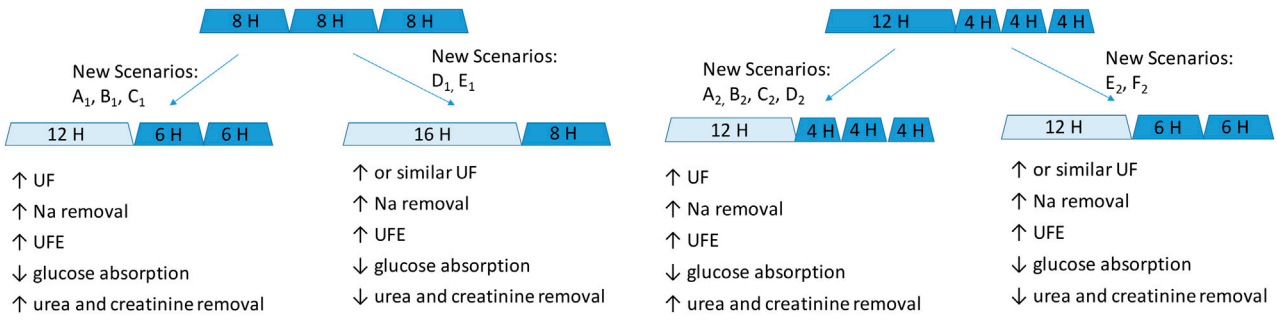


FIGURE 3
Schematic representation of the impact of replacing one or two glucose-based solutions with one long icodextrin exchange in patients with a fast and average PSTR. Glucose-based exchanges are denoted by dark blue, and icodextrin-based exchanges, by light blue. New scenarios refer to the detailed data presented in Tables 2–5.

prescriptions, i.e., 40.8 g and 70.9 g for scenarios A_1 and C_1, respectively. Furthermore, in the case of reference prescription with 2.27% glucose, the fluid and solute removal is also higher when replacing one glucose exchange by one exchange with icodextrin, together with a lowering glucose concentration in one of the two remaining glucose-based exchanges, scenario B_1 (Table 2). Similarly, in the case of a patient with an average PSTR, the removal of water and solutes is also higher for scenarios A_1 and C_1, as can be calculated from the results presented in Table 1.

The substitution of two glucose-based exchanges from the reference prescription with 1.36% and 2.27% glucose by one 16-h icodextrin exchange leads to an increase in UF from −1,198 and 326 mL to 139 (+1,337 mL) and 647 (+321 mL) mL, respectively (scenarios D_1 and E_1; Table 2). This change also leads to improved sodium removal (increase of ReNa by 172 and 36 mmol for 1.36% and 2.27% glucose, respectively) and higher UFE (Table 2). The observed increase in AbsCHO for scenario D_1 and decrease for E_1 correspond to the increased total absorption of carbohydrates, whereas glucose absorption per day is lower (only 19 g and 35 g, respectively, for scenarios D_1 and E_1). However, the corresponding removal of urea and creatinine decreases in scenarios D_1 and E_1 by 13% and 15%, respectively, for 1.36% glucose solution and by 28% and 26% for 2.27% glucose solution (Table 2). Similarly, when substituting two glucose exchanges by one long dwell with the icodextrin-based solution in a patient with an average PSTR, this results in higher UF and higher UFE and sodium removal but not higher urea and creatinine removal.

Table 3 shows water and solute removal for a patient with a fast PSTR undergoing four daily exchanges as reference prescription, three short 4-h exchanges and one long 12-h exchange each with 2 L of solution. We consider different scenarios—A_2 and D_2—replacing one glucose exchange from initial reference scenarios by one icodextrin dwell, and scenarios B_2 and C_2 additionally with a different mix use of 1.36% and 2.27% exchanges (Table 3). In general, 7.5% icodextrin is more effective in fluid and solute removal not only if one long glucose dwell is replaced by one icodextrin dwell, scenarios A_2 and D_2, but also if additionally, the concentration in one glucose exchange is decreased (scenario C_2 in Table 3). However, a further decrease in glucose concentration, as in scenario B_2, although resulting in similar or slightly higher removal of solutes and higher UFE, leads to lower UF than reference prescription with glucose 2.27% (Table 3).

The replacement of two glucose exchanges by one icodextrin exchange, without changing the glucose concentration in the remaining exchanges, leads to an increase in water and sodium removal, which is higher for 2.27% than for 1.36% solutions, scenarios E_2 and F_2 (Table 3). It also results in lower glucose uptake (41 g and 71 g for scenarios E_2 and F_2, respectively, although AbsCHO is lower only in the case of 2.27% glucose) and higher UFE (Table 3). However, such a replacement also leads to the lower removal of urea and creatinine by 12% and 7%, respectively, for 1.36% glucose (scenario E_2) and by 18% and 15%, respectively, for 2.27% glucose (scenario F_2) (Table 3). A further increase in the effectiveness of water removal can be obtained by prolonging icodextrin exchange and shortening glucose dwells, for example, from 12 h + 2 × 6 h to 16 h + 2 × 4 h (UFE equal to 4.5 and 10.5 mL/g for 1.36% and 2.27% glucose, respectively, calculated based on Table 1). On the other hand, although scenario E_2 is more efficient in water and sodium removal than reference prescription with initial exchanges with 2.27% glucose (Table 3), an additional decrease in the glucose concentration in one of the remaining exchanges (scenario B_1 in Table 2) leads to lower water and sodium removal. Similarly, a beneficial effect of icodextrin in water and sodium removal (in case of scenarios E_2 and F_2) is also present if considering patients with an average PSTR.

Detailed results for patients with an average PSTR having 3–4 exchanges per day have a similar trend and are presented in Tables 4, 5.

4 Discussion

This study shows that in PD patients who receive 3–4 daily exchanges with 1.36% or 2.27% glucose-based solutions, one icodextrin-based long dwell can replace two exchanges with glucose-based solutions in terms of the removal of fluid and sodium. Such a change in the prescription was found to provide higher or similar removal of water and sodium but slightly lower daily removal of urea and creatinine, independent of the PSTR. Consequently, there could be potential positive clinical implications linked to the better control of fluid status and improved quality of life because of less intrusion in regular life due to reduced number of exchanges. These potential advantages should be weighed against the potential disadvantage of the lower removal of urea and creatinine and other uremic toxins.

The introduction of icodextrin into reference prescriptions comprising 3–4 exchanges per day of glucose-based solutions leads to substantial increase in fluid and solute removal, lower glucose absorption, and higher UF efficiency for patients from all transport groups. The observed higher values of AbsCHO in the new prescriptions with icodextrin (although glucose absorption was lower) were related not only to the larger infused mass of CHO but also dwell duration. In fact, AbsCHO for icodextrin predicted for the same dwell duration and irrespective of transport groups was similar to that for 2.27% glucose being 39–44 g/8-h and 36–40 g/8-h dwell, respectively, and similar to the values of AbsCHO found in the MIDAS study—38 g/8-h and 39 g/8-h dwell, respectively (Mistry et al., 1994). Moreover, in contrast to dwells with the glucose-based solution, the absorption of icodextrin metabolites does not result in the observed hyperglycemia and hyperinsulinemia (Gokal et al., 2002). This is mainly due to the fact that during peritoneal dwell, icodextrin is hydrolyzed by α-amylase to maltose and larger glucose polymers, and further metabolism to glucose by maltase occurs rather intracellularly (Mistry et al., 1994; Gokal et al., 2002). The results for other treatment schedules, i.e., with different numbers and duration of dwells, can be easily calculated based on the results given in Table 1. Our predictions of the effects of the usage of icodextrin vs. glucose-based solutions in terms of fluid and solute (sodium, urea, and creatinine) removal agree with the clinical observations in randomized control studies in different groups of patients with the same dialysis dosage (Lin et al., 2009; Qi et al., 2011; Goossen et al., 2020). Similar results were previously predicted by numerical simulations of automated

PD (APD) and continuous ambulatory PD (CAPD) with glucose and icodextrin solutions (Akonur et al., 2016). The tendency of icodextrin to equalize water and sodium removal among patients with different PSTRs is in contrast to the glucose-based solutions in which the lower removal of water, urea, and creatinine is observed in patients with a fast PSTR and longer dwells (Wang et al., 1998). Moreover, a study looking within the same group of patients at the effect on fluid and solute removal of a night exchange of icodextrin vs. a night exchange of 1.36%, 2.27%, or 3.86% glucose demonstrated that UF and weekly removal of creatinine and urea were superior with icodextrin (Paniagua et al., 2012). Another advantage of using icodextrin is the reduction in the metabolic burden of glucose overexposure, which may be especially significant in the management of fast transport diabetic patients on PD by facilitating metabolic control (Paniagua et al., 2009).

Although we did not specifically analyze consequences for PD patients undergoing APD, our results are also relevant for APD patients using the icodextrin-based solution for the long daytime dwell (Plum et al., 2002). Interestingly, a study showed that a CAPD regimen with one icodextrin-containing and two glucose-containing solutions may contribute to a better preservation of residual renal function and a more biocompatible regimen, with similar dialysis adequacy to a regimen of four daily glucose-containing exchanges (Yoon et al., 2014). This is well-aligned with the study result in our math model. Another recent application is to use one 7.5% icodextrin (Extraneal) solution to replace two glucose-containing solutions as part of the prescription for incremental PD (Fernandes et al., 2023). By using the modified three-pore model, Guest et al. evaluated incremental CAPD prescriptions with 1–3 dwells/day using 2 L of icodextrin and glucose-based solutions and found that two dwells/day (including one Extraneal and one glucose solution) in patients with a glomerular filtration rate of at least 6 mL/min per 1.73 m^2 are sufficient to achieve clearance goals in all four types of peritoneal transport (Guest et al., 2017).

Why could one exchange of 7.5% icodextrin replace two shorter exchanges of 1.36% or 2.27% glucose solutions? First, this prescription change results in adequate fluid removal. Numerical simulations in our study suggest higher efficiency of icodextrin in water removal, i.e., higher UFE, in the case of longer dwells with a duration of over 10 h, whereas glucose-based solutions are more beneficial in the case of shorter dwells (Figure 1). Unlike glucose-based solutions, icodextrin resulted only in minor differences between transport groups in terms of water and solute removal, with UFE remaining stable up to 16 h (Table 1). Second, the introduction of 7.5% icodextrin also brings relative sufficient solute removal. Although the equilibration rates (in terms of the dialysate to the plasma concentration rate) for urea and creatinine are similar for icodextrin and glucose solutions, the water transport influences the observed removal of urea and creatinine (Figure 2). In consequence, a decrease in ReU and ReCr with increased dwell duration is observed for glucose-based solutions, whereas a persistent increase occurs during icodextrin dwells. Furthermore, despite higher removal during shorter glucose dwells, more efficient removal of urea and creatinine is provided by icodextrin in the case of longer dwells (Figure 2; Table 1). Based on the latest ISPD guideline (Brown et al., 2020), we shall consider more aspects regarding dialysis adequacy, including patient reported outcomes, fluid removal, and nutrition, whereas the view that small-solute removal (urea, creatinine, etc.) is the only important index to consider when evaluating dialysis quality is no longer valid. However, we need further clinical studies to verify if the new prescription provides patient benefits. Obviously, the replacement of two glucose exchanges by a single exchange with icodextrin solution provides higher or similar water removal and higher sodium daily removal for patients from average and fast transfer groups. Third, the use of one 7.5% icodextrin solution instead of two glucose solutions also leads to lower glucose uptake, slower dissipation of the osmotic agent, and higher UF efficiency (Table 2). However, this change leads also to a slightly lower daily removal of urea and creatinine, irrespective of the transport type in the case of reference prescriptions with 3–4 daily glucose-based exchanges (Tables 2, 3). The direction of changes induced by the replacement of 1–2 glucose-based exchanges by one long dwell with 7.5% icodextrin is the same for all investigated reference prescriptions with 3–4 exchanges per day and patients with a fast and average PSTR, as summarized in Figure 3.

Recently reported findings showed that the method of steady-concentration PD performed using a device providing continuous glucose infusion to maintain a high intraperitoneal glucose concentration resulted in higher UF rates, more efficient use of glucose (increased ultrafiltration volume/gram glucose absorbed), and greater sodium removal than those when using standard 2.5% dextrose CAPD dwell (Heimburger et al., 2023). However, while the strategy of PD with a steady glucose concentration means a more efficient use of glucose as an osmotic agent, it is associated with increased exposure to glucose, which may have disadvantages because of harmful metabolic effects and negative effects on the peritoneum.

Our study has several limitations. First, the daily fluid and solute removal calculated in this study represents the removal related purely to peritoneal dialysis, without renal clearance taken into account, and we did not analyze the impact of dry/wet periods. Moreover, the presented simulations consider only the dwell time, whereas the impact of the infusion and drainage procedures on fluid and solute transport was not included in the present model. We also do not provide results of simulations with 3.86% glucose, a solution which is highly efficient in terms of fluid and solute removal in short dwells also in patients with a fast PSTR since this was outside the scope of our study. Strengths of the study include the use of detailed clinical data on fluid and solute transfer from studies in patients using glucose-based (Heimburger et al., 1992) and icodextrin-based (Olszowska et al., 2019) solutions that were incorporated in a modified three-pore model with icodextrin hydrolysis taken into account (Akonur et al., 2015; Stachowska-Pietka et al., 2023).

In summary, simulations of the peritoneal transfer of fluid and solutes in patients with a fast or average PSTR who used 3–4 glucose-based (1.36% and 2.27%) exchanges per day showed that one icodextrin solution could replace two glucose-based exchanges. Although the new prescriptions with icodextrin resulted in increased water and sodium removal independent of the PSTR, there was only a minor reduction in urea and creatinine removal in the case of the replacement of two glucose-based exchanges. Unlike glucose-based dwells for which the removal of fluid and solutes becomes negative after 4–6 h in patients with a fast PSTR, icodextrin was associated with only minor differences between PSTR groups in terms of water and solute removal, which increased on average steadily throughout the long dwell up to 16 h, with UFE remaining close to 10 mL/g. These results suggest that dialysis schedules using

one 7.5% icodextrin (Extraneal) exchange instead of two exchanges of glucose-based solutions might be a strategic prescription to provide adequate dialysis and potential benefits to the patient quality of life with less exposure to glucose. Further clinical studies are needed to confirm these findings.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Author contributions

JS-P: software, investigation, formal analysis, writing–review and editing, writing–original draft, visualization, methodology, and conceptualization. JW: writing–review and editing, supervision, investigation, and conceptualization. AO: writing–review and editing and data curation. EG-L: writing–review and editing and data curation. JY: writing–review and editing, investigation, and conceptualization. QY: writing–review and editing, investigation, and conceptualization. ZW: writing–review and editing and data curation. BL: writing–review and editing, supervision, investigation, and conceptualization.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. Clinical data from dwells with Extraneal used in this study were collected within a study funded by the Ministry of Science and Higher Education, Warsaw, Poland, grant 2PO5B 01129. Baxter Novum is the result of a grant from Baxter Healthcare Corporation to Karolinska Institutet.The funders were not involved in the study design, collection, analysis, interpretation of data, the writing of this article, or the decision to submit it for publication.

Acknowledgments

Baxter Novum is the result of a grant from Baxter Healthcare to Karolinska Institute.

Conflict of interest

Authors JY and QY were employed by Baxter Healthcare Corporation.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2024.1339762/full#supplementary-material

References

Akonur, A., Holmes, C. J., and Leypoldt, J. K. (2015). Predicting the peritoneal absorption of icodextrin in rats and humans including the effect of α-amylase activity in dialysate. *Perit. Dial. Int.* 35 (3), 288–296. doi:10.3747/pdi.2012.00247

Akonur, A., Sloand, J., Davis, I., and Leypoldt, J. (2016). Icodextrin simplifies PD therapy by equalizing UF and sodium removal among patient transport types during long dwells: a modeling study. *Perit. Dial. Int.* 36 (1), 79–84. doi:10.3747/pdi.2013.00081

Blake, P. G., Dong, J., and Davies, S. J. (2020). Incremental peritoneal dialysis. *Perit. Dial. Int.* 40 (3), 320–326. doi:10.1177/0896860819895362

Brown, E. A., Blake, P. G., Boudville, N., Davies, S., de Arteaga, J., Dong, J., et al. (2020). International Society for Peritoneal Dialysis practice recommendations: prescribing high-quality goal-directed peritoneal dialysis. *Perit. Dial. Int.* 40 (3), 244–253. doi:10.1177/0896860819895364

Fernandes, A., Matias, P., and Branco, P. (2023). Incremental peritoneal dialysis-definition, prescription, and clinical outcomes. *Kidney360* 4 (2), 272–277. doi:10.34067/KID.0006902022

Gokal, R., Moberly, J., Lindholm, B., and Mujais, S. (2002). Metabolic and laboratory effects of icodextrin. *Kidney Int. Suppl.* 62 (81), S62–S71. doi:10.1046/j.1523-1755.62.s81.9.x

Goossen, K., Becker, M., Marshall, M. R., Buhn, S., Breuing, J., Firanek, C. A., et al. (2020). Icodextrin versus glucose solutions for the once-daily long dwell in peritoneal dialysis: an enriched systematic review and meta-analysis of randomized controlled trials. *Am. J. Kidney Dis.* 75 (6), 830–846. doi:10.1053/j.ajkd.2019.10.004

Guest, S., Leypoldt, J. K., Cassin, M., and Schreiber, M. (2017). Kinetic modeling of incremental ambulatory peritoneal dialysis exchanges. *Perit. Dial. Int.* 37 (2), 205–211. doi:10.3747/pdi.2016.00055

Heimburger, O., Hegbrant, J., Martus, G., Wilkie, M., De Leon, C., Carlsson, O., et al. (2023). Effects of steady glucose concentration peritoneal dialysis on ultrafiltration volume and sodium removal: a pilot crossover trial. *Clin. J. Am. Soc. Nephrol.* 19, 224–232. doi:10.2215/CJN.0000000000000342

Heimburger, O., Waniewski, J., Werynski, A., and Lindholm, B. (1992). A quantitative description of solute and fluid transport during peritoneal dialysis. *Kidney Int.* 41 (5), 1320–1332. doi:10.1038/ki.1992.196

Lin, A., Qian, J., Li, X., Yu, X., Liu, W., Sun, Y., et al. (2009). Randomized controlled trial of icodextrin versus glucose containing peritoneal dialysis fluid. *Clin. J. Am. Soc. Nephrol.* 4 (11), 1799–1804. doi:10.2215/CJN.02950509

Lo, W. K., Tong, K. L., Li, C. S., Chan, T. M., Wong, A. K., Ho, Y. W., et al. (2001). Relationship between adequacy of dialysis and nutritional status, and their impact on patient survival on CAPD in Hong Kong. *Perit. Dial. Int.* 21 (5), 441–447. doi:10.1177/089686080102100504

Mistry, C. D., Gokal, R., and Peers, E. (1994). A randomized multicenter clinical trial comparing isosmolar icodextrin with hyperosmolar glucose solutions in CAPD. MIDAS Study Group. Multicenter Investigation of Icodextrin in Ambulatory Peritoneal Dialysis. *Kidney Int.* 46 (2), 496–503. doi:10.1038/ki.1994.300

Morelle, J., Lambie, M., Oberg, C. M., and Davies, S. (2023). The peritoneal membrane and its role in peritoneal dialysis. *Clin. J. Am. Soc. Nephrol.* 19, 244–253. doi:10.2215/CJN.0000000000000282

Morelle, J., Sow, A., Fustin, C. A., Fillee, C., Garcia-Lopez, E., Lindholm, B., et al. (2018). Mechanisms of crystalloid versus colloid osmosis across the peritoneal membrane. *J. Am. Soc. Nephrol.* 29 (7), 1875–1886. doi:10.1681/ASN.2017080828

Morelle, J., Stachowska-Pietka, J., Oberg, C., Gadola, L., La Milia, V., Yu, Z., et al. (2021). ISPD recommendations for the evaluation of peritoneal membrane dysfunction

in adults: classification, measurement, interpretation and rationale for intervention. *Perit. Dial. Int.* 41 (4), 352–372. doi:10.1177/0896860820982218

Oberg, C. M. (2021). Optimization of bimodal automated peritoneal dialysis prescription using the three-pore model. *Perit. Dial. Int.* 41 (4), 381–393. doi:10.1177/08968608211010055

Olszowska, A., Waniewski, J., Stachowska-Pietka, J., Garcia-Lopez, E., Lindholm, B., and Wankowicz, Z. (2019). Long peritoneal dialysis dwells with icodextrin: kinetics of transperitoneal fluid and polyglucose transport. *Front. Physiol.* 10, 1326. doi:10.3389/fphys.2019.01326

Paniagua, R., Debowska, M., Ventura, M. D., Avila-Diaz, M., Prado-Uribe, C., Mora, C., et al. (2012). Ultrafiltration and dialysis adequacy with various daily schedules of dialysis fluids. *Perit. Dial. Int.* 32 (5), 545–551. doi:10.3747/pdi.2011.00048

Paniagua, R., Ventura, M. D., Avila-Diaz, M., Cisneros, A., Vicente-Martinez, M., Furlong, M. D., et al. (2009). Icodextrin improves metabolic and fluid management in high and high-average transport diabetic patients. *Perit. Dial. Int.* 29 (4), 422–432. doi:10.1177/089686080902900409

Plum, J., Gentile, S., Verger, C., Brunkhorst, R., Bahner, U., Faller, B., et al. (2002). Efficacy and safety of a 7.5% icodextrin peritoneal dialysis solution in patients treated with automated peritoneal dialysis. *Am. J. Kidney Dis.* 39 (4), 862–871. doi:10.1053/ajkd.2002.32009

Qi, H., Xu, C., Yan, H., and Ma, J. (2011). Comparison of icodextrin and glucose solutions for long dwell exchange in peritoneal dialysis: a meta-analysis of randomized controlled trials. *Perit. Dial. Int.* 31 (2), 179–188. doi:10.3747/pdi.2009.00264

Rippe, B., and Levin, L. (2000). Computer simulations of ultrafiltration profiles for an icodextrin-based peritoneal fluid in CAPD. *Kidney Int.* 57 (6), 2546–2556. doi:10.1046/j.1523-1755.2000.00114.x

Rippe, B., Venturoli, D., Simonsen, O., and de Arteaga, J. (2004). Fluid and electrolyte transport across the peritoneal membrane during CAPD according to the three-pore model. *Perit. Dial. Int.* 24 (1), 10–27. doi:10.1177/089686080402400102

Stachowska-Pietka, J., Waniewski, J., Olszowska, A., Garcia-Lopez, E., Wankowicz, Z., and Lindholm, B. (2023). Modelling of icodextrin hydrolysis and kinetics during peritoneal dialysis. *Sci. Rep.* 13 (1), 6526. doi:10.1038/s41598-023-33480-w

Wang, T., Heimburger, O., Waniewski, J., Bergstrom, J., and Lindholm, B. (1998). Increased peritoneal permeability is associated with decreased fluid and small-solute removal and higher mortality in CAPD patients. *Nephrol. Dial. Transpl.* 13 (5), 1242–1249. doi:10.1093/ndt/13.5.1242

Waniewski, J. (2013). Peritoneal fluid transport: mechanisms, pathways, methods of assessment. *Arch. Med. Res.* 44 (8), 576–583. doi:10.1016/j.arcmed.2013.10.010

Yan, H., Abreu, Z., and Bargman, J. M. (2022). Incremental peritoneal dialysis in incident end-stage kidney disease patients. *Perit. Dial. Int.* 42 (4), 387–393. doi:10.1177/08968608211036796

Yoon, H. E., Chang, Y. K., Shin, S. J., Choi, B. S., Kim, B. S., Park, C. W., et al. (2014). Benefits of a continuous ambulatory peritoneal dialysis (CAPD) technique with one icodextrin-containing and two biocompatible glucose-containing dialysates for preservation of residual renal function and biocompatibility in incident CAPD patients. *J. Korean Med. Sci.* 29 (9), 1217–1225. doi:10.3346/jkms.2014.29.9.1217

frontiers | Frontiers in Physiology

TYPE Review
PUBLISHED 13 August 2024
DOI 10.3389/fphys.2024.1322493

OPEN ACCESS

EDITED BY
Guoshuang Xu,
Air Force Medical University, China

REVIEWED BY
Luciano D'Apolito,
BioGeM Institute, Italy
Manuel Lopez-Cabrera,
Spanish National Research Council (CSIC), Spain

*CORRESPONDENCE
Raymond T. Krediet,
r.t.krediet@amsterdamumc.nl

RECEIVED 16 October 2023
ACCEPTED 10 July 2024
PUBLISHED 13 August 2024

CITATION
Krediet RT (2024), Physiology of peritoneal dialysis; pathophysiology in long-term patients. *Front. Physiol.* 15:1322493.
doi: 10.3389/fphys.2024.1322493

Physiology of peritoneal dialysis; pathophysiology in long-term patients

Raymond T. Krediet*

Academic Medical Center, Amsterdam, Netherlands

The microvascular wall of peritoneal tissues is the main barrier in solute and water transport in the initial phase of peritoneal dialysis (PD). Small solute transport is mainly by diffusion through inter-endothelial pores, as is hydrostatic fluid transport with dissolved solutes. Water is also transported through the intra-endothelial water channel aquaporin-1(AQP-1) by a glucose-induced crystalloid osmotic gradient (free water transport). In the current review the physiology of peritoneal transport will be discussed both during the first years of PD and after long-term treatment with emphasis on the peritoneal interstitial tissue and its role in free water transport. Attention will be paid to the role of glucose-induced pseudohypoxia causing both increased expression of fibrogenetic factors and of the glucose transporter GLUT-1. The former leads to peritoneal fibrosis, the latter to a reduced crystalloid osmotic gradient, explaining the decrease in free water transport as a cause of ultrafiltration failure. These phenomena strongly suggest that the extremely high dialysate glucose concentrations are the driving force of both morphologic and functional peritoneal alterations that may develop during long-term PD.

KEYWORDS

peritoneal dialysis, pseudohypoxia, glucose, GLUT-1, ultrafiltration failure, free water transportr, peritoneal fibrosis, long-term PD

Introduction

Peritoneal dialysis (PD) as replacement of some aspects of kidney function is limited to removal of potentially toxic solutes that accumulate in severely impaired kidney function, and removal of excess of fluid that can also be present. It should be appreciated that the peritoneum in this condition is not only composed of the mesothelium that covers all abdominal organs, but also includes the submesothelial tissue. This so-called interstitium is composed of a ground substance of hyaluronan and glycosaminoglycans, forming a collagenous network that serves as a skeleton for embedded structures, like microvessels of the circulation and also lymphatic vessels. The interstitium contains a limited number of cells, mainly adipocytes and a few fibroblasts. Overall the interstitium looks rather "empty" at the start of (PD). The mesothelial layer is not a barrier to osmotic fluid transport induced by the glucose content of the intraperitoneal dialysis solution (Flessner, 1994). Therefore, the microvascular wall is likely to be the main barrier for the transport of solutes and fluid from the circulation to the dialysate-filled peritoneal cavity. After a description of the mechanisms of peritoneal transport in the initial phase of PD, the present review will focus on the alterations in peritoneal morphology and transport that can develop in patients after more than 2–4 years of PD, their interrelationships and pathogenesis. Especially the role of the interstitium will be discussed.

Physiology of solute transport

Solutes can pass the microvascular wall through a system of interendothelial pores. These interendothelial cell clefts comprise 90% of all pores and have radii of about 40 Å (Rippe, 1993). The hydrostatic pressure gradient in the normal situation-so without PD-averages 30 mmHg, but decreases to about zero from the arteriolar to the venous part of the microcirculation (Hall, 2016). Therefore hydrostatic ultrafiltration will be largest in the proximal part of the microcirculation. Using a dialysis solution without an osmotic agent and dextran 70 as intraperitoneal volume marker it could be estimated that peritoneal hydrostatic ultrafiltration in PD patients averages 0.5 mL/min (Struijk et al., 1996). Small solutes like urea, creatinine and glucose have radii of 2 to 3 Å, meaning that their transport through pores of 40 Å is unlikely to be size-selectively hindered and that they pass the small pores by convection to the interstitial tissue. When no PD is applied, the interstitial concentration of these small solutes will be similar to that in the microcirculation, but in case of the presence of a dialysis solution the concentrations of urea and creatinine will be zero. This concentration difference induces diffusion through the same small pore system, which-is a much more efficient process for the removal of small solutes than convection. For instance the solute removal rate averages 17 mL/min for urea and 8 mL/min for creatinine (Smit et al., 2003). As the diffusion rate of a molecule is dependent on its molecular weight, a convection rate of 0.5 mL/min is quantitatively unimportant for small solutes, but this is different for large ones like serum proteins. For instance the transport rate of β_2-microglobulin from the circulation to the dialysate averages 1 mL/min, half of which is by convection and half by diffusion (Krediet et al., 2022). The diffusion velocity of a solute is dependent on its size, meaning that low molecular weight solutes diffuse faster than those with a higher molecular weight, so urea (MW 60 D)> creatinine (MW 113 D)> glucose (MW 180 D). Besides the concentration gradient between plasma and intra-abdominal dialysate, the small pore density - so the number of perfused peritoneal micro-vessels - is a determinant of over-all diffusion. This parameter is also called the effective peritoneal surface area (EPSA). The dialysate/plasma (D/P) ratio of creatinine is often used as a functional parameter of EPSA. A mean value of 0.72 after a dwell of 4 h has been reported, but with a 95% confidence interval of 0.52–0.90, indicating a marked inter-individual variability (Smit et al., 2003). These values include an intra-individual variability of 7% (Imholz et al., 1998). Based on D/P creatinine, patients have been categorized in four groups: high and low transporters and high and low average transporters (Twardowski et al., 1987). More recently high and low have been changed to fast and slow. The majority of patients are in the average groups, slow transport rates are rare. Morphological studies on relationships between blood vessel density and peritoneal solute transport have shown equivocal results (Sherif et al., 2006; Schaefer et al., 2018; Nakano et al., 2020). An association has been reported in some, but not confirmed in others. A relationship between over-all estimated blood vessel density by sublingual sidestream darkfield imaging and peritoneal solute transport was found for peritoneal glucose absorption in a limited number of PD patients, excluding the fast transporter group (Vlahu et al., 2014), but this needs further confirmation. These findings suggest that in most patients peritoneal transport is dependent on the vascular density, but that fast transporters additionally have peritoneal vasodilation, which will increase EPSA.

Physiology of fluid transport

Fluid transport during PD is the difference between transcapillary ultrafiltration and back absorption. As stated above, the hydrostatic pressure gradient will induce about 0.5 mL/min ultrafiltration, which is counterbalanced by 0.4 mL/min backfiltration due to the colloid osmotic pressure gradient (4). To withdraw excess fluid from patients with kidney failure additional crystalloid osmosis is applied by the addition of glucose to the dialysis fluid in high doses, leading to an osmolarity of maximal 500 mosmol/L. Part of the glucose will be absorbed during a dialysis dwell. On average this is 60% of the instilled quantity after 4 h. It means that glucose is unable to create a crystalloid osmotic gradient in the small inter-endothelial pores. The presence of the intra-endothelial water channel aquaporin-1 (AQP-1) in peritoneal capillaries and especially venules explains the crystalloid osmotic gradient, because this water channel only allows water to pass and restricts all solutes. So, AQP-1 induces free water transport (FWT) which is different from fluid transport through the small inter-endothelial pores (SPFT) that is composed of water and solutes. The AQP-1 genotype has some effect on its function. The TT genotype is associated with lower ultrafiltration than the CC genotype (Morelle et al., 2021).

FWT will decrease dialysate sodium concentration, the so-called sodium sieving. This is usually assessed after 60 min of a dwell. When the intraperitoneal volume at this time is known, the sodium clearance from the dialysate can be used to calculate FWT and SPFT separately (Smit et al., 2004; La Milia et al., 2005). During the first hour of a hypertonic dialysis dwell 40% of transcapillary ultrafiltration is by FWT and 60% by SPFT (Parikova et al., 2005). The presence of a large EPSA is associated with a high value for SPFT, but with a low FWT and over-all transcapillary ultrafiltration, pointing to the importance of the crystalloid osmotic pressure in peritoneal ultrafiltration (Krediet, 2018).

Due to the problems associated with the extremely high glucose load, glucose polymers have been investigated. Icodextrin is the only available glucose polymer (mainly α1-4 linkages, average molecular weight 16,000 D). The 7% solution is not hypertonic, but induces colloid osmosis, i.e., it induces fluid transport through the small inter-endothelial pores, not through AQP-1. Therefore no sodium sieving is present, and a large EPSA is associated with high ultrafiltration rates (Ho-dac-Pannekeet et al., 1996). The large size of icodextrin molecules imply a slow absorption, making it especially effective during long dwells.

Early alterations of the peritoneal membrane

Already after a few months peritoneal accumulation of advanced glycosylation end products can be found, first submesothelially, later also perivascular (Yamada et al., 1994). This event is associated with the formation of immature capillaries and with an increase in

postcapilillary vessel wall thickness (Nakano et al., 2020). Epithelial-to-mesenchymal transition of mesothelial cells (EMT) is another morphological change. This phenomenon has first been described in 2003 and consists of a transition of the usual epithelial phenotype to a mesenchymal one with loss of cytokeratin expression. EMT in peritoneal biopsies is characterized by the presence of cytokeratin-positive fibroblasts-like cells in the submesothelial interstitial tissue (Yanez-Mo et al., 2003). The prevalence of EMT is highest between 1.5 and 2 years, when it is present in about one-third of patients (Del et al., 2008). Both phenomena may be involved in the early reduction of ultrafiltration, which is the most important functional abnormality during the first years of PD. Indeed a relationship has been found between ultrafiltration and D/P creatinine (Davies, 2004). The relationship between creatinine and ultrafiltration is explained by a similar time course of creatinine appearance in the dialysate and the disappearance of glucose from it, both attributed to diffusion to and from the dialysis solution. The time course of D/P creatinine shows a tendency to increase with time on PD.

Late alterations of the peritoneal membrane

The early alterations tend to be progressive. In some patients the peritoneum after 4 years is characterized by partial loss of mesothelial cells, submesothelial and interstitial fibrosis, more extensive accumulation of AGEs, and vasculopathy. A schematic overview of these alteration has been published recently (Williams et al., 2002). The blood vessels may show signs of vasculopathy, defined as an increased wall thickness due to subendothelial hyalinosis causing narrowing of the lumen (Selgas et al., 1994). In general, subendothelial hyalinosis of arterioles is mostly seen in patients with diabetes mellitus. In the peritoneum of non-diabetic PD patients subendothelial hyalinosis can be found in all microvessels and is possibly caused by deposition of AGEs sub-endothelialy. This narrowing can progress to partial or total lumen obliteration.

The fibrotic alterations can progress to encapsulating peritoneal sclerosis (EPS) in some patients. Ultrafiltration failure is the most relevant functional abnormality (Selgas et al., 1994; Coester et al., 2014). Impaired ultrafiltration is more severe than expected on the basis of D/P creatinine (Parikova et al., 2022) and concerns both SPFT and FWT (Coester et al., 2014). The role of the expanded interstitium in fluid and free water transport is discussed below. Vasculopathy is likely the cause of the decrease of SPFT, because this pathway is driven by the hydrostatic pressure gradient, that is influenced by the presence of vascular stenosis, similar to the post-stenotic pressure drop in renal artery stenosis.

Patients with EPS have reduced FWT (Sampimon et al., 2011; Morelle et al., 2015). They have normal expression of AQP-1, meaning that the crystalloid osmotic gradient in the fibrotic interstitium surrounding the microvessels must be reduced. Passive diffusion is generally considered the major pathway of the glucose absorption from the dialysis solution during a dwell. But its disappearance from the dialysis solution was faster than expected in an acute model in rats (Park et al., 1999). This suggests additional uptake of glucose in interstitial cells. A glucose molecule is too large to diffuse directly across the cell membrane, but requires the presence of special channels, so-called glucose transporters in the cell membrane. Two types can be distinguished: facilitative glucose transporters (GLUTs) and those that also transport sodium into cells (SGLTs) (Navale and Parajape, 2016). GLUTs facilitate glucose diffusion through the cell membrane, glucose uptake by SGLTs is driven by that of sodium. The presence of both faciliative and sodium dependent glucose transporters in peritoneal tissue has been reported, especially in the mesothelium of patients in the initial phase of PD. Only one study described the presence of glucose transporters in long-term patients in the peritoneal interstitium in the proximity of blood vessels (Schricker et al., 2022). But, expression only gives no information on functionality. Therefore the present review focusses on GLUT-1, of which experimental evidence for function in PD has been shown (Bergling et al., 2022). GLUT-1 is ubiquitously expressed by most cells, among which red blood cells and endothelial cells and also by fibroblasts at a low level, but this is upregulated in the presence of cellular stress, including hypoxia. Increased expression of GLUT-1 by peritoneal interstitial fibroblasts has been postulated as an additional cause of rapid loss of the crystalloid osmotic gradient in long-term patients with extensive peritoneal fibrosis/sclerosis (Krediet, 2021). The functionality of GLUT-1 has been confirmed in a recent study in an acute rat model showing that GLUT-1 inhibition by phloretin improved ultrafiltration (Bergling et al., 2022), while SGLT-2 inhibition had no effect (Martus et al., 2021), thereby supporting the importance of cellular uptake of glucose on the osmotic gradient, irrespective of sodium handling.

Glucose causes peritoneal damage by pseudohypoxia

Peritoneal micro-inflammation has been considered the cause of the above discussed peritoneal alterations (Lambie et al., 2013). A critical analysis of the available evidence convincingly showed the weakness of this theory (Krediet and Parikova, 2022). Analogously to the genesis of diabetic complications (Williamson et al., 1993), glucose-induced pseudohypoxia is likely to be the driving force of the long-term peritoneal alterations (Krediet and Parikova, 2022). Hypoxia of cells is characterized by an increase in the ratio of reduced/oxidized nicotinamide dinucleotide (NADH/NAD^+) in the cytosol, due to insufficient supply of oxygen. A similar increase of the NADH/NAD^+ ratio can occur in situations with a high glucose load, like diabetes mellitus and peritoneal dialysis. This explains the term pseudohypoxia. High extracellular/dialysate glucose concentrations cause glucose transport to the cytosol by glucose transporters. Intracellular glucose is degraded in the glycolysis to pyruvate. NAD^+ is converted to NADH in this process. The latter can be oxidized to NAD^+ after uptake of pyruvate in the mitochondria, where it is metabolized in the respiratory chain, and by the lactate dehydrogenase reaction in the cytosol in which pyruvate is converted to lactate. These normal compensatory mechanisms can be impaired in the presence of mitochondrial dysfunction and by using lactate buffered dialysate. In case of a high glucose load additional degradation occurs in the sorbitol pathway, in which glucose is degraded to sorbitol. The latter is broken down to glucose along with the formation of NADH from NAD^+. The various reactions are discussed in ref (Combet et al., 2000) and illustrated in Figure 1.

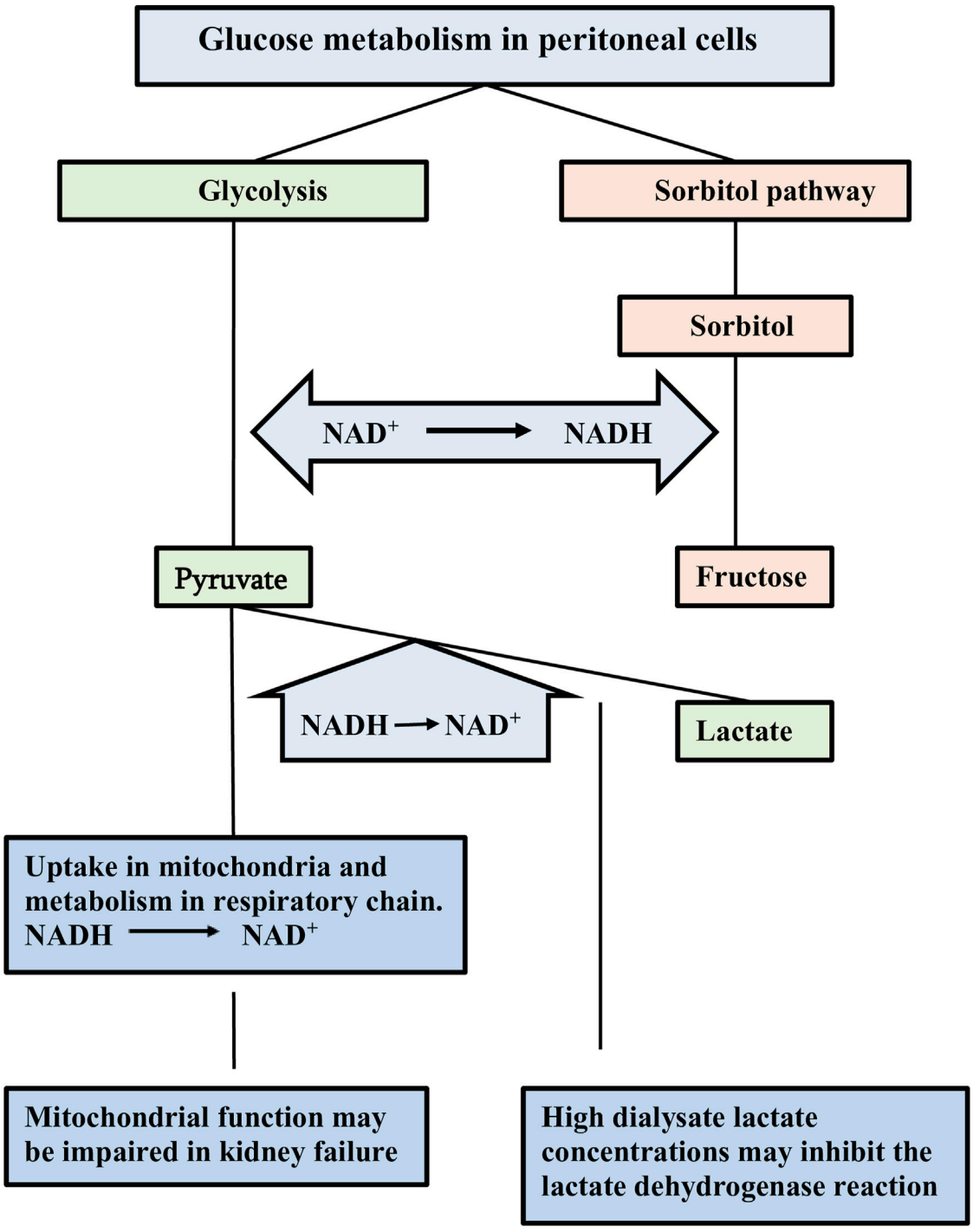


FIGURE 1
Schematic representation of glucose metabolism in peritoneal cells. Intracellular glucose can be degraded in the glycolysis and in the polyol/sorbitol pathway. Nicototinamide dinucleotide (NAD) is involved in by the reduction of NAD^+ to NADH. Pyruvate is the end-product in the glycolysis. Oxidation of the formed NADH occurs by metabolism of pyruvate in the mitochondriae and conversion into lactate. These normal compensatory mechanisms may be impaired due to mitochondrial dysfunction and to the use of lactate as buffer in the dialysis solution. Fructose is the end-product of the sorbitol pathway without any compensatory mechanism to oxidize NADH. The resulting increased NADH/NAD^+ ratio is an indicator of cellular hypoxia. Taken from ref (Krediet, 2022).

Effects of peritoneal (pseudo)hypoxia on the long-term morphologic alterations

Hypoxia activates the hypoxia inducible factor-1(HIF-1) gene, which causes an upregulation of the genes encoding for various proteins, like vascular endothelial growth factor (VEGF), transforming growth factor β (TGF-β), plasminogen activator inhibitor −1 (PAI-1) and connective tissue growth factor (CTGF). All these have profibrotic and angiogenic properties. Gene expression of VEGF has been shown in peritoneal tissue. It increased with PD duration (Zweers et al., 2001). Such increase was also present for peritoneal effluent VEFF protein (Margetts et al., 2001). TGF-β is probably the most important factor for peritoneal fibrosis (Mateijsen et al., 1999). PAI-1 and CTGF probably exert their effects distal from TGF-β. Besides angiogenic and profibrotic factors, HIF-1 also causes upregulation of GLUT-1, which causes a vicious circle in PD patients: more interstitial GLUT-1 will lead to a progressive decrease of FWT and to more extensive pseudohypoxia and upregulation of HIF-1. This will lead to more fibrosis and angiogenesis. The above mechanism explains the findings that have been reported in PD patients with EPS: the interstitium is composed of dense collagen bundles (Park et al., 1999) and myofibroblasts (Zhang et al., 2023). This hypothesis is supported by the finding that microvessel density and HIF abundance decrease after discontinuation of PD following kidney transplantation (Flessner, 2006).

Effects of peritoneal (pseudo)hypoxia on peritoneal transport in long-term patients

Angiogenesis, vasculopathy and interstitial fibrosis all with AGE depositions, are the most important morphologic alterations in long-term PD. Ultrafiltration failure is the main functional abnormality. It concerns both free water transport and small pore fluid transport (Sampimon et al., 2011). Small solute transport is somewhat faster than at the start of PD, but the increase can fully be explained by the vascular density. Various theories have been proposed to elucidate the mechanisms of impaired ultrafiltration in interstitial fibrosis, like binding of filtered plasma water by hyaluronan and/or collagen (Wiedner and Wilhelm, 1974). These binding theories are unlikely, because water binding is a process that will get saturated. As stated above, an effect of progressively increased GLUT-1 in interstitial cells is more plausible. The cause of the decrease in small pore fluid transport is not precisely known, but AGE-induced vasculopathy is a possibility, because this will lower the filtration pressure. Interstitial collagen is unlikely to affect peritoneal transport directly, because experiments with a bio-engineerd native collagen membrane offered no indication of hindrance to small solute transport and a linear increase of ultrafiltration with increasing hydrostatic pressure (Toroian et al., 2007). Also another *in vitro* study with a gel filtration column consisting of bovine collagen-1 showed no effects on glucose transport, because it penetrated in the water shield of the fibers (Toroian et al., 2007). These *in vitro* studies support the contention that collagen itself is not important in the long-term alterations in peritoneal transport, but that glucose-induced pseudohypoxia is the driving force.

Summary and conclusions

The physiology of peritoneal transport in the initial phase of PD is only different from general microvascular filtration of plasma with respect of two conditions: (1) the presence of dialysis fluid in the peritoneal cavity and interstitial tissue allowing diffusion of solutes from the circulation to the dialysate through inter-endothelial pores, and (2) the presence of glucose in high concentrations, that induces free water transport through the intra-endothelial water channel AQP-1, and thereby removal of excess water from the body. Ultrafiltration is determined by the crystalloid osmotic pressure gradient, which decreases during a dialysis dwell due to absorption of the instilled glucose. Impaired ultrafiltration in the initial phase of PD is mainly due to fast transport of small solutes, including a fast glucose absorption rate. Long-term PD affects peritoneal morphology and function. Loss of mesothelial cells, interstitial fibrosis and vasculopathy may develop. Ultrafiltration failure is the most important functional abnormality, not necessarily associated with fast small solute transport rates. It can be caused by an impaired hydrostatic pressure gradient due to vasculopathy, but is often due to high uptake of glucose in interstitial fibroblasts by the glucose transporter GLUT-1. Glucose-induced pseudohypoxia is probably the cause of the increased GLUT-1 expression by HIF-1, that also increases the expression of various other factors involved in angiogenesis and fibrosis. These include VEGF, TGF-β, PAI-1 and CTGF. Glucose exposure in PD increases the cytosolic NADH/NAD^+ ratio in peritoneal cells. The resulting pseudohypoxia is the driving force for the long-term morphologic and functional alterations.

Author contributions

RK: Writing–original draft.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

Bergling, K., Martus, G., and Oberg, C. (2022). Phloretin improves ultrafiltration and reduces glucose absorption during peritoneal dialysis in rats. *J. Am. Soc. Nephrol.* 33, 1857–1863. doi:10.1681/ASN.2022040474

Coester, A. M., Smit, W., Struijk, D. G., Parikova, A., and Krediet, R. T. (2014). Longitudinal analysis of peritoneal fluid transport and its determinants in a cohort of incident peritoneal dialysis patients. *Perit. Dial. Int.* 34, 195–203. doi:10.3747/pdi.2012.00189

Combet, S., Miyata, T., Moulin, P., Pouthier, D., Goffin, E., and Devuyst, O. (2000). Vascular endothelial growth factor in peritoneal dialysis: a longitudinal follow-up. *J. Lab. Clin. Med.* 137, 125–132. doi:10.1067/mlc.2001.112235

Davies, S. J. (2004). Longitudinal relationship between solute transport and ultrafiltration capacity in peritoneal dialysis patients. *Kidney Int.* 66, 2437–2445. doi:10.1111/j.1523-1755.2004.66021.x

Del, P. G., Jimenz-Heffernan, J. A., Bajo, M. A., Aroeira, L. S., Fernandez-Perpen, A., Cirugeda, A., et al. (2008). Epithelial-to-mesenchymal transition of mesothelial cells is an early event during peritoneal dialysis and is associated with high peritoneal transport. *Kidney Int.* 73, S26–S33. doi:10.1038/sj.ki.5002598

Flessner, M. F. (2006). The effect of fibrosis on peritoneal transport. *Contrib. Nephrol.* 150, 174–180. doi:10.1159/000093518

Flessner, M. J. (1994). Osmotic barrier of the peritoneum. *Am. J. Physiol.* 207, F861–F870.

Hall, J. E. (2016). *Textbook of physiology*. 13 ed. Philadelphia: Elsevier, 189–197.

Ho-dac-Pannekeet, S. N., Langedijk, M., Hiralall, J. K., de Waart, D. R., Struijk, D. G., Krediet, R. T., et al. (1996). Peritoneal transport characteristics with glucose polymer based dialysate. *Kidney Int.* 50, 979–986. doi:10.1038/ki.1996.399

Imholz, A. L. T., Koomen, G. C. M., Voorn, W. J., Struijk, D. G., Arisz, L., and Krediet, R. T. (1998). Day-to-day variability of fluid and solute transport in upright and recumbent positions during CAPD. *Nephrol. Dial. Transpl.* 13, 146–153. doi:10.1093/ndt/13.1.146

Krediet, R. T. (2018). Ultrafiltration failure is a reflection of peritoneal alterations in patients treated with peritoneal dialysis. *Front. Physiol.* 9, 1815. doi:10.3389/fphys.2018.01815

Krediet, R. T. (2021). Acquired decline in ultrafiltration in peritoneal dialysis: the role of glucose. *J. Am. Soc. Nephrol.* 32, 2408–2415. doi:10.1681/ASN.2021010080

Krediet, R. T. (2022). Aging of the peritoneal dialysis membrane. *Front. Physiol.* 13, 885802. doi:10.3389/fphys.2022.885802

Krediet, R. T., Lopes Barreto, D., and van Diepen, A. T. N. (2022). Assessment of the size selectivity of peritoneal permeability by the restriction coefficient to protein transport. *Perit. Dial. Int.* 42, 335–343. doi:10.1177/08968608221075102

Krediet, R. T., and Parikova, A. (2022). Relative contributions of pseudohypoxia and inflammation to peritoneal alterations with long-term peritoneal dialysis patients. *Clin. J. Am. Soc. Nephrol.* 17, 1259–1266. doi:10.2215/CJN.15371121

Lambie, M., Chess, J., Donovan, K. L., Kim, Y. L., Do, Y. J., Lee, H. B., et al. (2013). Independent effects of systemic and peritoneal inflammation on peritoneal dialysis survival. *J. Am. Soc. Nephrol.* 24, 2071–2080. doi:10.1681/ASN.2013030314

La Milia, V., Di Fillippo, S., Crepaldi, M., Del Vecchio, L., Dell Óro, C., Andrulli, S., et al. (2005). Mini-peritoneal equilibration test: a simple and fast method to assess free water and small solute transport across the peritoneal membrane. *Kidney Int.* 68, 840–846. doi:10.1111/j.1523-1755.2005.00465.x

Margetts, P. J., Kolb, M., Galt, T., Hoff, C. M., Shockley, T. R., and Gauldie, M. (2001). Gene transfer of transforming growth factor-beta1 to the rat peritoneum: effects on membrane function. *J. Am. Soc. Nephrol.* 12, 2029–2039. doi:10.1681/ASN.V12102029

Martus, G., Bergling, K., de Arteaga, J., and Oberg, C. M. (2021). Sglt2 inhibition does not reduce glucose absorption during experimental peritoneal dialysis. *Perit. Dial. Int.* 41, 373–380. doi:10.1177/08968608211008095

Mateijsen, M. A. M., van der Wal, A. C., Hendriks, PMEM, Zweers, M. M., Mulder, J. B., Struijk, D. G., et al. (1999). Vascular and interstitial changes in the peritoneum of CAPD patients with peritoneal sclerosis. *Perit. Dial. Int.* 19, 517–525. doi:10.1177/089686089901900605

Morelle, J., Marechall, C., Yu, Z., Debaix, H., Corre, T., Lambie, M., et al. (2021). AQP-1 promoter variant, water transport and outcomes in peritoneal dialysis. *N. Engl. J. Med.* 385, 1570–1580. doi:10.1056/NEJMoa2034279

Morelle, J., Sow, A., Hautem, N., Bouzin, C., Crott, R., Devuyst, O., et al. (2015). Interstitial fibrosis restricts osmotic water transport in encapsulating peritoneal sclerosis. *J. Am. Soc. Nephrol.* 26, 2521–2533. doi:10.1681/ASN.2014090939

Nakano, T., Mizumassa, T., Kuroki, Y., Eriguchi, M., Yoshida, H., Taniguchi, M., et al. (2020). Advanced glycation end products are associated with immature angiogenesis and peritoneal dysfunction in patients on peritoneal dialysis. *Perit. Dial. Int.* 40, 67–75. doi:10.1177/0896860819878344

Navale, A. M., and Parajape, A. N. (2016). Glucose transporters: physiological and pathological roles. *Biophys. Res.* 8, 5–9. doi:10.1007/s12551-015-0186-2

Parikova, A., Michalickova, K., van Diepen, A. T. N., Voska, L., Viklicky, O., and Krediet, R. T. (2022). Do low GDP neutral pH solutions prevent or retard peritoneal membrane alterations in long-term peritoneal dialysis? *Perit. Dial. Int.* 42, 236–245. doi:10.1177/08968608211027008

Parikova, A., Smit, W., Struijk, D. G., Zweers, M. M., and Krediet, R. T. (2005). The contribution of free water transport and small pore fluid transport to the total fluid removal in peritoneal dialysis. *Kidney Int.* 68, 1849–1865.

Park, M. S., Lee, E. J., Suh, G. I. L., Suh, G. I., Waniewski, J., Werynski, A., et al. (1999). Peritoneal transport of glucose in rat. *Perit. Dial. Int.* 19, 442–450. doi:10.1177/089686089901900507

Rippe, B. (1993). A three-pore model of peritoneal transport. *Perit. Dial. Int.* 13 (Suppl. 2), S35–S38. doi:10.1177/089686089301302s09

Sampimon, D. E., Coester, A. M., Struijk, D. G., and Krediet, R. T. (2011). The time course of peritoneal transport parameters in peritoneal dialysis patients who develop encapsulating peritoneal sclerosis. *Nephrol. Dial. Transpl.* 26, 291–298. doi:10.1093/ndt/gfq343

Schaefer, B., Bartosova, M., Mecher-Groepinger, S., Sallay, P., Voros, P., Ranchin, B., et al. (2018). Neutral pH and low-glucose degradation product dialysis fluids induce major early alterations of the peritoneal membrane in children on peritoneal dialysis. *Kidney Int.* 94, 419–429. doi:10.1016/j.kint.2018.02.022

Schricker, S., Oberachecker, T., Fritz, P., Ketteler, M., Alscher, M. D., and Schanz, M. (2022). Peritoneal expression of,SGLT 2, Glut 1 and GLUT 3 in peritoneal dialysis patients. *Kidney Blood Press Res.* 47, 125–134. doi:10.1159/000520894

Selgas, R., Fernandez-Reyez, M. J., Bosque, E., Bajo, M. A., Borrego, E., Jimenez, C., et al. (1994). Functional longevity of the human peritoneum: how long is continuous peritoneal dialysis possible? Results of a prospective medium long-term study. *Am. J. Kidney Dis.* 23, 64–73. doi:10.1016/s0272-6386(12)80814-6

Sherif, A. M., Nakayama, M., Maruyama, Y., Yoshida, H., Yamamoto, H., Yokayama, K., et al. (2006). Quantitative assessment of the peritoneal vessel density and vasculopathy in CAPD patients. *Nephrol. Dial. Transpl.* 21, 1675–1681. doi:10.1093/ndt/gfl054

Smit, W., Dijk, V., Schouten, N., Langedijk, M., van den Berg, N., Struijk, D. G., et al. (2003). Peritoneal function and assessment of reference values using a 3.86% glucose solution. *Perit. Dial. Int.* 23, 440–449. doi:10.1177/089686080302300507

Smit, W., Struijk, D. G., Ho-dac-Pannekeet, M. M., and Krediet, R. T. (2004). Quantification of free water transport in peritoneal dialysis. *Kidney Int.* 66, 849–854. doi:10.1111/j.1523-1755.2004.00815.x

Struijk, D. G., Krediet, R. T., Imholz, A. L. T., Koomen, G. C. M., and Arisz, L. (1996). Fluid kinetics in CAPD patients during dialysis with a bicarbonate-based hypoosmolar solution. *Blood Purif.* 14, 217–226. doi:10.1159/000170264

Toroian, D., Lim, J. E., and Price, P. A. (2007). The size exclusion characteristics of type I collagen: implications for the role of noncollagenous bone constituents in mineralization. *J. Biol. Chem.* 282, 22437–22447. doi:10.1074/jbc.M700591200

Twardowski, Z. J., Nolph, K. D., Khanna, R., Prowant, B. F., Ryan, L., Moore, H., et al. (1987). Peritoneal equilibration test. *Perit. Dial. Bull.* 7, 138–147.

Vlahu, C. A., Lopes Barreto, D., Struijk, D. G., Vink, H., and Krediet, R. T. (2014). Is the systemic microvascular endothelial gycocalyx in peritoneal dialysis patients related to peritoneal transport? *Nephron Clin. Pract.* 128, 159–165. doi:10.1159/000368081

Wiedner, G., and Wilhelm, G. (1974). Water and ion permeability of a native collagen membrane. *Biochem. Biophys. Acta* 367, 349–360. doi:10.1016/0005-2736(74)90091-1

Williams, J. D., Craig, K. J., Topley, N., Von Ruhland, C., Fallon, M., Newman, G. R., et al. (2002). Morphologic changes in the peritoneal membrane of patients with renal disease. *J. Am. Soc. Nephrol.* 13, 470–479. doi:10.1681/ASN.V132470

Williamson, J. R., Chang, K., Frangos, M., Hassan, K. S., Ido, Y., Kawamura, T., et al. (1993). Hyperglycemic pseudohypoxia and diabetic complications. *Diabetes* 42, 801–813. doi:10.2337/diab.42.6.801

Yamada, K., Miyahara, Y., Hamaguchi, K., Nakayama, M., Nakano, H., Nozaki, O., et al. (1994). Immunohistochemical study of human advanced glycosylation end-products (AGE) in chronic renal failure. *Clin. Nephrol.* 42, 354–361.

Yanez-Mo, M., Lara-Pezzi, E., Selgas, R., Ramirez-Huesca, M., Dominiguez-Jimenez, C., Jimenez-Heffernan, J. A., et al. (2003). Peritoneal dialysis and epithelial-to-mesenchymal transition of mesothelial cells. *New Engl. J. Med.* 348, 403–413. doi:10.1056/NEJMoa020809

Zhang, C., Bartosova, M., Marinovic, I., Schab, C., Schaefer, B., Vondrak, K., et al. (2023). Peritoneal transformation shortly after kidney transplantation in pediatric patients with preceding chronic peritoneal dialysis. *Nephrol. Dial. Transpl.* 38, 2170–2181. doi:10.1093/ndt/gfad031

Zweers, M. M., Struijk, D. G., Smit, W., and Krediet, R. T. (2001). Vascular endothelial growth factor in peritoneal dialysis, a longitudinal follow-up. *J. Lab. Clin. Med.* 137, 125–132. doi:10.1067/mlc.2001.112235

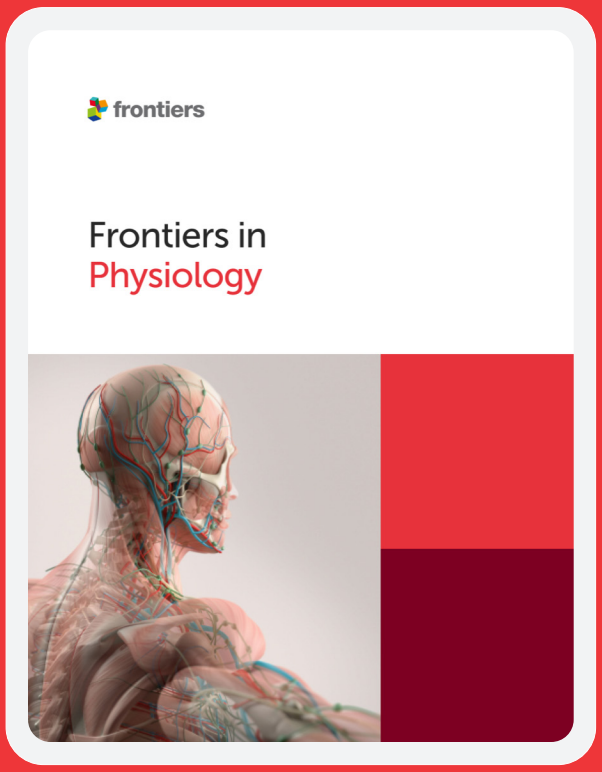
Frontiers in Physiology

Understanding how an organism's components work together to maintain a healthy state

The second most-cited physiology journal, promoting a multidisciplinary approach to the physiology of living systems - from the subcellular and molecular domains to the intact organism and its interaction with the environment.

Discover the latest Research Topics

See more →



Frontiers

Avenue du Tribunal-Fédéral 34
1005 Lausanne, Switzerland
frontiersin.org

Contact us

+41 (0)21 510 17 00
frontiersin.org/about/contact