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The calcium concentration of peritoneal dialysis solution modifies levels of key mediators of peritoneal fibrosis

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Abstract

Background: To explore the effects of different calcium concentrations of peritoneal dialysis solution (PDS) on continuous ambulatory peritoneal dialysis (CAPD) and expression of vimentin (VIM), fibroblast-specific protein (FSP1), and E-cadherin.

Materials and Methods: This was a pilot study (#ChiCTR1900021387) conducted from January 2017 to December 2019 at the Hospital. The patients were randomized to undergo CAPD using PDS with a calcium concentration of 1.25 mmol/L (low concentration group) or 1.75 mmol/L (high concentration group). Changes in biochemistry before dialysis and at 6 and 12 months were analyzed.

Results: There were 50 and 52 participants in the low and high calcium groups. The blood biochemical indexes were all different between the two groups (all $P_{time} < .05$, $P_{group} < .05$, $P_{interaction} < .05$), but they remained within their normal ranges. VIM and FSP1 increased over 12 months ($P_{time} < .05$); VIM and FSP1 levels in the high concentration group were higher than in the low concentration group ($P_{group} < .05$, $P_{interaction} < .05$), while E-cadherin showed the inverse association ($P_{time} < .001$, $P_{group} < .001$, $P_{interaction} < .001$). There was no difference in complications ($P = .973$).

Conclusion: The calcium concentration in PDS might be an important factor affecting the progression of peritoneal fibrosis.

1 | INTRODUCTION

The advantages of peritoneal dialysis (PD) include hemodynamic stability during use as well as patient-directed care without the need of a trained healthcare professional.[1-4] Nevertheless, potential complications include peritoneal fibrosis (PF), leading to changes in peritoneal structure and function, increases small-molecule solute transport, and ultrafiltration failure.[5-8] The epithelial-to-mesenchymal transition (EMT) of the cells of the peritoneal membrane and incompatible dialysis solutions are, in part, responsible for PF, but the exact mechanisms remain poorly understood.[9] PF also leads to inflammation that could, in itself, decrease the efficacy of PD and also lead to a further progression of PF.[9] With time, PF will lead to a decrease in PD efficacy, and PD will have to be converted to hemodialysis.[9,10]

Previous studies suggested that calcium in the dialysis fluid could increase the expression levels of vimentin (VIM) and fibroblast-specific protein (FSP1), two markers of mesenchymal cells,

and decrease the expression of E-cadherin (E-CAD), a marker of epithelial cells.[11-13] VIM belongs to the intermediate filament protein family and is the main component of the cytoskeleton structure.[14,15] It is not expressed in normal epithelial cells.[14,15] It can maintain the polarity of epithelial cells in various mesenchymal cells and stabilize the proliferation of epithelial cells.[14,15] It is mainly expressed in fibroblasts, endothelial cells, and leukocytes, among others.[14,15] VIM is a type of intermediate filament protein that is widely expressed in normal mesenchymal cells and is closely related to EMT.[14,15] FSP1, also known as S100A4, is a calcium-binding protein of the S100 supergene family and is mainly expressed in a variety of mesenchymal-derived fibroblasts.[16] FSP1 is a fibroblast (carcinoma-associated fibroblast) specific immunophenotype protein, which is related to peritoneal fibrosis.[8,16]E-CAD is calcium dependent and can maintain the morphological and structural integrity of the epithelial cells and play an important role in maintaining cell-cell adhesion.[17] Decreased expression of E-CAD can lead to an increase of peritoneal mesenchymal cell and fibroblast, which may promote peritoneal fibrosis.[17] Those changes suggest that calcium ions may be an important factor involved in the regulation of EMT in the peritoneum.[11-13] EMT is the main mechanism for peritoneal fibrosis.[17] VIM is expressed by mesenchymal cells and not by epithelial cells, and is a regulator for the maintenance of the mesenchymal phenotype.[14] FSP1 is a fibroblast-specific protein that is associated with mesenchymal cell morphology and motility and is expressed during EMT.[16] E-CAD in an epithelial marker and is decreased in EMT.[17]

Nevertheless, to date, no clinically oriented studies investigated the effect of the calcium concentrations of the peritoneal dialysis solution (PDS) on the expression levels of VIM, FSP1, and E-CAD in human peritoneal mesothelial cells (HPMCs) in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). The aim of this study was to explore the effects of different calcium concentrations of PDS on the efficacy of CAPD and expression levels of VIM, FSP1, and E-CAD, as well as adverse patient clinical outcomes.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a pilot study conducted from January 2017 to December 2019 at the Nephrology Department of Rui'an People's Hospital, Zhejiang Province, PR China. This study was approved by the Ethics Committee of Rui'an People's Hospital (approval number: YJ2016011). The trial was registered (#ChiCTR1900021387). Written informed consent was obtained from all patients.

Routinely, we discuss in detail the pros and cons of PD vs HD with each patient before starting any therapy, including the different dialysis methods, at home vs at the hospital, different time freedom, different costs, different protection for residual kidney function, etc. All patients included in this study chose PD, and no patient had received HD before PD.

Participants were included consecutively with the inclusion criteria being: (a) patients undergoing CAPD for the first time; and (b) meeting the diagnostic criteria for stage V CKD, with a glomerular filtration rate (GFR) <15 mL/min.[1]

The exclusion criteria were: (a) allergy to PDS; (b) unable to control blood sugar (fasting plasma glucose > 200 mg/dL, HbA1c > 7.2%); (c) blood urea nitrogen (BUN) > 38 mmol/L, symptoms of uremia, metabolic acidosis, electrolyte disturbance, congenital amino acid metabolism deficiency, severe acute pancreatitis, severe hyperbilirubinemia, or hyperuricemia; (d) hyperthyroidism or patients taking corticosteroids; (e) malignant tumors, blood or immune system diseases, or other severe systemic diseases; (f) history of high fever and acute infection within 12 months; (g) those who might undergo kidney transplantation during the study; (h) expected survival time < 12 months; (i) pregnant or lactating women; (j) patients who participated in other medication clinical trials within 3 months before enrollment; (k) unable to cooperate due to poor mental status; or (l) ineligible patients assessed by clinicians for other reasons. The withdrawal criteria were: (a) referral; (b) loss to follow-up; or (c) incomplete clinical data during the treatment.

2.2 | PD access site and CAPD

The participants were randomized to the low concentration group (calcium concentrations of 1.25 mmol/L) and high concentration group (calcium concentration of 1.75 mmol/L) according to the odd-even method based on admission time. PDSs with different calcium concentrations were used for CAPD. All patients were informed of the PD methods, medication names, precautions, and possible complications.

The PD dialysis catheter site access and CAPD cycles were performed according to guidelines.[1] All treatments were conducted by a chief physician and a nurse in charge. In order to place the PD catheter, a skin incision was made about 3 cm below the umbilicus. A Tenckhoff double-cuff straight or curled tube was used with the outlet of the catheter downward. The deep cuff was placed in the muscle layer of the rectus abdominis, and the shallow cuff was placed in the subcutaneous tissue 2-3 cm away from the outlet. The dialysis catheter was inserted under the abdominal wall to make a subcutaneous tunnel of about 10 cm, and the dialysis catheter was placed into the bladder rectal fossa (male) or uterine rectal fossa (female). A "Y"-shaped connector piece was connected to the dialysis catheter and sealed until further clinical use.

Both groups underwent PD by instillation, and PDS with a calcium concentration of 1.25 or 1.75 mmol/L (Guangzhou Baxter Medical Supplies Co., Ltd.) was administered for PD. The containers for the two solutions were PVC, and the magnesium ion concentration was 0.275 mmol/L in both cases. The connecting tubes and the disinfection caps were the same, without differences in the procedures. Intermittent PD was started for 1-2 weeks at 500-1000 mL/time, followed by a rest of 30 minutes. The total amount of dialysis was controlled at 4000-10 000 mL/d. Once

stable, CAPD was performed at 1500-2000 mL/time, which was maintained for about 4-6 hours, and about 10 hours at night. The PD access site was cleaned with 2% iodine solution for 3-5 minutes each time the PD dialysis catheter site was accessed. Each time PDS was changed, 20 mL of heparin was given as needed to prevent obstruction.

2.3 | Isolation and culture of HPMCs in PDS

About 2000 mL of sterile peritoneal effluent was collected at the initial PD visit, at the 6 months visit, and at the 12 months visit. Collect effluent was centrifuged at 9.8 *g* for 5 minutes at 4°C, and the supernatant was removed. Precipitated cells were washed twice with D-Hank's balanced salt solution (Wuhan Biofavor Biotechnology Service Co., Ltd.), and 15% fetal calf serum DMEM/F12 medium (Shanghai Yuchun Biotechnology Co., Ltd.) was added to resuspend the cells. The cell count was adjusted to 1×10^6/mL, and the cells were inoculated in a gelatin-coated 25 mm^2 culture flask. They were cultured at 37°C in a 5% carbon dioxide incubator, and the medium was changed every 72 hours. The morphology (polygonal, paving stone-like, and cobblestone-like) of the HPMCs was observed using an inverted phase-contrast microscope.

2.4 | Detection of VIM, FSP1, and E-CAD

Western blot was performed to determine the protein contents of VIM, FSP1, and E-CAD. HPMC culture medium (30 μL) was extracted, and 300 μL of radio immunoprecipitation assay strong lysis buffer was added (Beijing Applygen Technologies Inc.); 30 μg of the buffer after lysis was collected and submitted to SDS-PAGE gel electrophoresis. The membrane transfer occurred over 1.5-2 hours at constant pressure, and the proteins were transferred to a 0.22-μm polyvinylidene fluoride membrane. Staining was performed to observe the transfer effect, and 4% bovine serum albumin (Shanghai Yubo Biotechnology Co., Ltd.) was used for blocking at 4°C for 2 hours, and the membrane was washed. Mouse anti-human VIM (Shanghai KMin Biotechnology Co., Ltd.) (1:800), FSP1 (1:100), and E-CAD (1:100) were added for hybridization for 24 hours. Secondary hybridization was performed with goat anti-mouse immunoglobulin G (Shanghai Morey Biosciences, Inc.) followed by the reaction on the ECI membrane for 5 minutes, then fixation and staining. Mounting was made with a mounting solution containing an anti-fluorescence quencher (Beijing Biolab Technology Co., Ltd.), and photography was performed under a fluorescence microscope. The protein content was detected by UV spectrophotometry, and the result was read at 562 nm.

2.5 | Outcomes and follow-up

The patients were followed every month. Serum albumin, BUN, calcium, serum creatinine, phosphorus, and intact parathyroid hormone (iPTH) levels were collected before the initial PD visit, at 6, and at 12 months for all participants (Olympus AU-400 automatic biochemical analyzer; OLYMPUS Optical Co., Ltd.). iPTH was detected using luminescent immunoassay, and the other biochemical indexes were detected by colorimetric methods.

The morphology of HPMCs and protein contents of VIM, FSP1, E-CAD of culture media in the PDS were collected at the initial PD visit and at the 6- and 12-month visits.

2.6 | Statistical analysis

SPSS 19.0 (IBM Corp.) was used for statistical analysis. Data were analyzed in the per-protocol setting (PPS). Categorical data were presented as frequencies and percentages and were analyzed using the chi-square test. The continuous data were presented as means ± SDs and compared using Student's *t* test or non-parametric tests, as appropriate. Repeated measurement data were analyzed by repeated measure ANOVA. $P < .05$ were considered statistically significant.

3 | RESULTS

3.1 | Baseline clinical characteristics

A total of 120 participants were enrolled, including 60 in the low concentration group and 60 in the high concentration group. During treatment, in the low concentration group, there were two referrals,

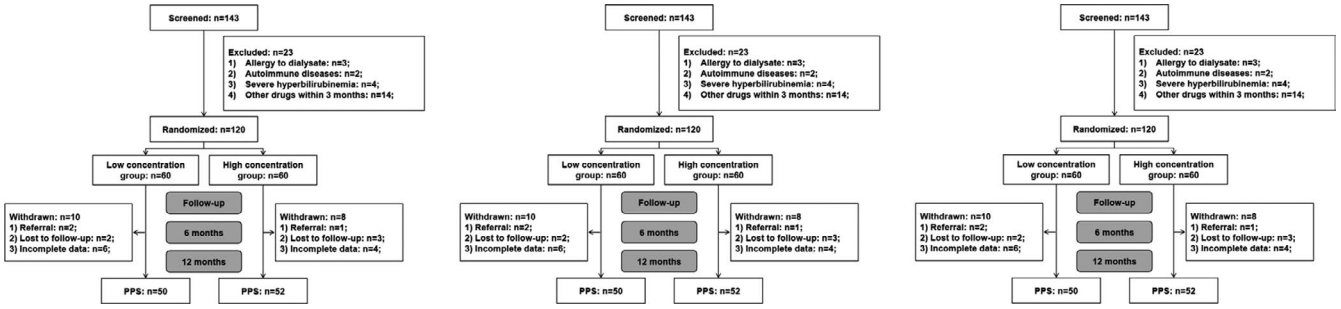

FIGURE 1 Participant flowchart. PPS, per-protocol setting

TABLE 1 Baseline characteristics of the participants

Characteristics	Low concentration group (n = 50)	High concentration group (n = 52)	*P*
Sex (male), n (%)	32 (64.0)	33 (63.5)	.881
Age (y), mean ± SD	48.3 ± 5.8	48.5 ± 5.9	.863
Disease course (mo), mean ± SD	21.3 ± 10.8	22.7 ± 11.3	.524
Basic renal diseases, n (%)			.849
CGN	24 (48.0)	25 (48.1)	
DN	12 (24.0)	12 (23.1)	
HP	13 (26.0)	14 (26.9)	
PKD	1 (2.0))	1 (1.9)	

Abbreviations: CGN, chronic glomerulonephritis; DN, diabetic nephropathy; HN, hypertensive nephropathy; PKD, polycystic kidney disease.

TABLE 2 Changes in blood biochemical indexes before PD and at 6 and 12 mo

Characteristics	Groups	Before PD	6 mo after PD	12 mo after PD	*P* (time)	*P* (group)	*P* (interaction)
Albumin (g/L)	Low	34.35 ± 2.08	37.44 ± 2.25	37.68 ± 2.31	.021	.010	.023
	High	34.81 ± 2.02	37.94 ± 2.56	37.54 ± 2.68	.016	.008	.021
Blood urea nitrogen (mmol/L)	Low	30.35 ± 3.35	17.58 ± 1.75	17.25 ± 1.81	<.001	<.001	<.001
	High	30.94 ± 3.03	17.67 ± 1.17	17.65 ± 1.24	<.001	<.001	<.001
Calcium (mmol/L)	Low	2.19 ± 0.08	2.18 ± 0.07	2.19 ± 0.08	.006	.010	.013
	High	2.18 ± 0.07	2.19 ± 0.08	2.20 ± 0.06	.005	.011	.012
Serum creatinine (μmol)	Low	820.21 ± 96.24	689.25 ± 33.86	684.68 ± 34.64	<.001	<.001	<.001
	High	817.28 ± 95.29	692.37 ± 34.82	681.35 ± 35.25	<.001	<.001	<.001
Phosphorus (mmol/L)	Low	1.27 ± 0.11	1.26 ± 0.10	1.27 ± 0.12	.003	.014	.011
	High	1.26 ± 0.12	1.25 ± 0.13	1.24 ± 0.14	.002	.015	.012
Intact parathyroid hormone (pg/mL)	Low	220.1 ± 34.2	226.6 ± 36.8	227.4 ± 38.5	<.001	<.001	<.001
	High	220.8 ± 34.6	226.5 ± 36.9	227.7 ± 38.5	<.001	<.001	<.001

Abbreviations: Alb, albumin; BUN, blood urea nitrogen; Ca, calcium; iPTH, intact parathyroid hormone; P, phosphate; PD, peritoneal dialysis; Scr, serum creatinine.

two lost to follow-up, and six not completing the measurements of all outcomes. In the high concentration group, there was one referral, three lost to follow-up, and four not completing the measurements of all outcomes. Therefore, 50 participants in the low concentration group and 52 in the high concentration group were included in the final analysis (shown in Figure 1).

Table 1 presents the baseline characteristics of the participants. In the low concentration group, there were 32 men and 18 women. The age range was 38-56 (mean, 48.3 ± 5.8) years. The history of chronic kidney disease was 6-36 (mean, 21.3 ± 10.8) months. The primary renal diseases included chronic glomerulonephritis (CGN, n = 24), diabetic nephropathy (DN, n = 12), hypertensive nephropathy (HP, n = 13), and polycystic kidney disease (PKD, n = 1). In the high concentration group, there were 33 men and 19 women. The age range was 37-59 (mean, 48.5 ± 5.9) years. The history of chronic kidney disease was 5-39 (mean, 22.7 ± 11.3) months. The primary renal diseases included CGN (n = 25), DN (n = 12), HP (n = 14), and PKD (n = 1).

3.2 | Changes in blood biochemical indexes

As shown in Table 2, the blood biochemical indexes were all significantly different between the two groups as the time went by (all $P_{time} < .05$, $P_{group} < .05$, $P_{interaction} < .05$), but they all remained within their respective normal ranges.

3.3 | VIM, FSP1, and E-CAD

As shown in Table 3, as the time went by, VIM and FSP1 increased significantly over 12 months(both $P_{time} < .05$); VIM and FSP1 levels in the high concentration group were significantly higher than in the low concentration group (both $P_{group} < .05$, both $P_{interaction} < .05$). E-CAD decreased significantly with time ($P_{time} < .001$), and the decrease was more significant in the high concentration group than in the low concentration group ($P_{group} < .001$, $P_{interaction} < .001$).

TABLE 3 Changes in VIM, FSP1, and E-CAD of HPMC culture medium before PD

Characteristics	Groups	Before PD	6 mo after PD	12 mo after PD	*P* (time)	*P* (group)	*P* (interaction)
VIM (ng/mL)	Low	4.03 ± 0.16	4.83 ± 0.18	6.01 ± 0.27	.022	.014	.011
	High	3.98 ± 0.22	5.34 ± 0.15	6.98 ± 0.34	.004	.016	.002
FSP1 (ng/mL)	Low	1.77 ± 0.11	2.40 ± 0.16	3.16 ± 0.27	.026	.031	.003
	High	1.79 ± 0.12	2.99 ± 0.18	3.75 ± 0.23	.028	.019	.010
E-CAD (ng/mL)	Low	76.82 ± 7.15	60.13 ± 4.69	46.86 ± 3.20	.001	<.001	<.001
	High	75.89 ± 7.12	52.47 ± 2.45	35.71 ± 2.70	<.001	<.001	<.001

Abbreviations: E-CAD, E-cadherin; FSP1, fibroblast-specific protein 1; HPMC, human peritoneal mesothelial cells; PD, peritoneal dialysis; VIM, vimentin.

3.4 | Complications

During treatment, there was one participant with PD-related peritonitis in the low concentration group. There was one participant with congestive heart failure and one with a transient ischemic attack in the high concentration group. These treatment-related adverse events in the three participants were effectively controlled using symptomatic treatments, and CAPD could continue. There was no significant difference in the total complication rate (2.0% vs 3.8%) between the two groups ($P = .973$).

4 | DISCUSSION

This study aimed to explore the effects of different calcium concentrations of PDS on CAPD and expression of VIM, FSP1, and E-CAD. The main takeaway observations of this pilot study were: (a) PDS calcium concentrations led to changes in VIM, FSP1, and E-CAD levels in HPMC culture media; and (b) different PDS calcium concentrations showed no significant differences in clinical outcomes.

The peritoneal area is large and rich in capillaries, and PD will efficiently remove the toxic metabolites and correct the disorders in water-electrolyte and acid-base balance.[1,2] Since no extracorporeal circulation is created during PD, PD has a small effect on blood volume and hemodynamics, leading to a reduced incidence of heart failure.[1-4] In addition, PD has small impacts on the internal environment and protects the residual renal function.[1,2] PD uses the peritoneum as a semi-permeable membrane to remove toxins through diffusion and osmosis.[1,2] The main advantages are simpler operation, a better quality of life, and lower cost.[1,2,18,19] Nevertheless, the daily protein loss when undergoing PD will lead to malnutrition, decreased immune function, peritoneal infection, damage to digestive function, glucose and fat metabolic disorders, hypertension, and other complications.[1,2,18,19] Ultimately, these changes will lead to peritoneal fibrosis and reduce the efficacy of PD.[17]

The results of the present study showed that PDS with calcium concentrations of 1.25 and 1.75 mmol/L both achieve significant effects, with some differences regarding the biochemical indexes, but all indexes remained within their respective normal ranges and could be considered clinically non-significant. In clinical practice, the calcium concentration of PDS can be adjusted according to the needs of the patient. The complication rate of the two groups was 2.0% and 3.8%, respectively, without significant difference, suggesting that PDS with calcium concentrations of 1.25 and 1.75 mmol/L did not affect the incidence of short-term (12 months) PD-related complications, as supported by previous studies.[20-23] Nevertheless, those results should be validated in the longer term (>12 months).

In the present study, the precipitated cells from the PDS were cultured with an HPMC culture media. The results showed an association between PDS with higher calcium concentrations with increased expressions of VIM and FSP1 and decreased expression of E-CAD over the 12-month study period. Increased expressions of VIM and FSP1 can induce the proliferation of peritoneal epithelial cells and fibroblasts, and leading to a progression of peritoneal fibrosis.[8,17] E-CAD can promote the breakdown of intercellular components and activation of matrix metalloproteinase, thereby reducing cell-cell adhesion.[24] E-CAD can affect the EMT process to reduce the fibrous tissues and promote the degradation of cytoskeletal components.[24] Decreased expression of E-CAD can lead to an increase of peritoneal mesenchymal cell and fibroblast, which may promote peritoneal fibrosis.[17] Nevertheless, peritoneal fibrosis is a complex process. Higher PDS calcium concentration can affect the expression levels of VIM, FSP1, and E-CAD in HPMCs, but the exact mechanisms remain poorly understood. Future studies will have to examine the exact mechanisms and whether treatments could be given to slow down peritoneal fibrosis and improve patient prognosis.

The study limitations include a small sample size at a single-center institution. Patients received only CAPD, and the other forms of PD were not examined. In addition, the transporter status was not examined over the course of the study. Per protocol analysis was specified in the original study design and protocol, although dropouts were higher than expected. An ITT analysis was not done and could potentially yield different results. The results of the present study might not be generalizable to a larger ESRD patient population. Aside from treatment-related adverse clinical events that were recorded, additional clinical hard endpoints were not included in this study.

5 | CONCLUSION

Patients receiving CAPD show higher levels of VIM and FSP1 and lower E-CAD in HPMC culture media, suggesting higher EMT and

progression toward peritoneal fibrosis. Further prospective studies are needed to validate these results. The inclusion of these biomarkers in future clinical trials must be strongly considered.

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None.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

Chusheng Miao, Shanshan Li, and Zhangjian Zhao were involved in **conceptualization**. Ruiyu Zhao, Li Dai, and Zengqi Xue were involved in **formal analysis**. Hanlei Song and Zengqi Xue were involved in **resources**. Shanshan Li, Huanlin Jin, and Xiangliang Xue were involved in **investigation**. Xiangliang Xue, Hanlei Song, and Zengqi Xue were involved in **methodology**. Huanlin Jin and Zengqi Xue were involved in **Project administration**. Chusheng Miao was involved in **funding acquisition**. Li Dai, Zhangjian Zhao, and Zengqi Xue were involved in **supervision**. Chusheng Miao and Ruiyu Zhao were involved in **visualization**. Chusheng Miao and Li Dai were involved in **writing—original draft**. Chusheng Miao and Xiangliang Xue were involved in **writing—review and editing**.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Rui'an People's Hospital (approval number: YJ2016011). The trial was registered (#ChiCTR1900021387). Written informed consent was obtained from all patients.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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