IJKD KIDNEY DISEASES

Study on the Relationship Between Peritoneal Dialysis Ultrafiltration Failure and Aquaporin 1, Aquaporin 3, and Vascular Endothelial Growth Factor A Expression

Yu Guigui,[1,2] Wang Ying,[1] Ji Lijun,[2] Wang Feng,[2] Li Feifei[2]

[1]Tongde Hospital of Zhejiang Province, Hangzhou 310012, China
[2] Xianju People's Hospital, Zhejiang Province Taizhou 317300, China

Keywords. Aquaporin-1, aquaporin-3, vascular endothelial growth factor, peritoneal dialysis, ultrafiltration failure

Original Paper

Introduction. The aim of this study was to investigate the expression of aquaporin 1 (AQP-1), AQP-3 and vascular endothelial growth factor A (VEGF-A) in peritoneal tissues of patients without kidney disease, chronic kidney disease at stages 5 (CKD 5) and patients on prolonged peritoneal dialysis with ultrafiltration failure (PD-UFF), and elucidate the possible mechanism of peritoneal dialysis ultrafiltration failure.
Methods. Peritoneal specimens were collected from the following patient groups at Xianju People's hospital: CKD 5, PD-UFF and normal control groups. Routine staining and immunohistochemical analyses were performed on samples obtained from the three groups.
Results. The expression of AQP-1 and AQP-3 on peritoneal mesothelial cells, peritoneal vessels and in the interstitium was significantly lower in the PD-UFF group than the CKD 5 and control groups ($P < .01$), while no statistically significant difference was found between the CKD 5 and control groups ($P > .05$). In contrast, VEGF-A expression was significantly higher in peritoneal mesothelial cells, peritoneal vessels and the interstitium in the PD-UFF group than the CKD 5 and control groups ($P < .01$). No statistically significant difference was found between the CKD 5 and control groups ($P > .05$).
Conclusion. AQP-1 and AQP-3 expression levels decrease in peritoneal mesothelial cells and the vascular interstitium of patients with a prolonged peritoneal dialysis course, while VEGF-A expression gradually increases. The formation of peritoneal neovascularization and the decrease in AQP expression may be primarily associated with peritoneal dialysis ultrafiltration failure.

IJKD 2022;16:252-8
www.ijkd.org
DOI: 10.52547/ijkd.6928

INTRODUCTION

Ultrafiltration failure (UFF is one of the most serious complications of peritoneal dialysis (PD) which makes the patients to withdraw from PD treatment. International studies have shown that PD ultrafiltration failure is closely associated with dysfunction of aquaporins on peritoneal mesenchymal cells (PMCs).[1] Aquaporins (AQPs) are a group of membrane proteins that mediate transmembrane water transport, through the expression of AQP-1 and AQP-3 molecules, located on the surfaces of peritoneal mesenchymal cells. The expression of aquaporins are significantly diminished in peritoneal dialysis ultrafiltration

failure samples. In addition, increased peritoneal vascular formation has been reported in peritoneal tissues samples of patients receiving long-term peritoneal dialysis; the process that might be involved in peritoneal fibrosis and UFF. Currently, peritoneal fibrosis is recognized in patients receiving peritoneal dialysis, and many growth factors may be involved in its pathogenesis. Angiogenesis is regulated by many angiogenic factors, such as vascular endothelial growth factor (VEGF-A), basic fibroblast growth factor (bFGF) and transforming growth factor beta 1 (TGF-β1). Of these, VEGF-A is the most important factor, as it promotes angiogenesis and ultimately peritoneal fibrosis.[2] In addition, this molecule is expressed in peritoneal capillary endothelial cells and PMCs.[3,4] The expression of VEGF-A is significantly enhanced in high glucose environment, probably in relation to bFGF,[5] although, the exact mechanism remains unclear.[6] Here, we have examined the relationship between PD related UFF, and AQP-1, AQP-3 and VEGF-A expression by comparing their expression levels in peritoneal tissue of patients who i) had no kidney disease, ii) presented with CKD but did not receive PD treatment or iii) developed UFF after long-term treatment with PD.

MATERIALS AND METHODS

Clinical Data

Data Source. This study included 103 peritoneal biopsy specimens (50 of which were normal peritoneal specimens) collected between 2014 and 2019. Patients were divided into the following groups: 1) normal control group, which consisted of patients undergoing elective abdominal surgery, who did not have any renal dysfunction or diseases involving the peritoneum; 2) patients with CKD stage 5 (CKD 5), which consisted of CKD patients undergoing PD for the first time, and 3) patients with peritoneal dialysis related ultrafiltration failure (PD-UFF), which consisted of patients receiving long term PD, who developed UFF after catheter removal.

Experimental Methods. Peritoneal specimens were collected from the patients during surgery. Specimens were fixed with 10% formalin, embedded in paraffin, and sectioned appropriately, for immunohistochemical analysis. Mouse anti-human AQP1 and AQP-3 monoclonal antibodies and a rabbit anti-human VEGF-A polyclonal antibody (all 1:100 dilution, Santa Cruz Biotechnology, Shanghai, China) were used. Immunohistochemistry was performed, using the Streptavidin/Peroxidase (SP) method.

Evaluation of Immunohistochemical Staining. Cells stained with brownish yellow particles on the cell membrane were considered positive for AQP-1 and AQP-3. Quantification of AQP-1 and AQP-3 staining was carried out, using the rating standard chart reported by Schoenicke *et al*.[7] Briefly, AQP-1 and AQP-3 expression levels were divided into four groups, with Grade 0, representing cells with no AQP-1 and AQP-3 expression, and Grade 4, representing cells with highest AQP-1 and AQP-3 expression.

Each sample was sub-divided into three sections, and graded according to the number of positively stained cells, as three typical fields, under 400x magnification. Samples which exhibited mesothelial cell shedding or vascular degeneration were not included. The grading was performed by two independent researchers.

Statistical Methods. Experimental data were expressed as mean ± standard deviation (x ± SD). The Q test was used for pairwise comparison among the three groups. SPSS 22.0 software was used for data statistical analysis and $P < .05$ was considered to be statistically significant.

RESULTS

Comparison of Data Among Control Group, CKD 5, and PD-UFF Patient

A total of 103 patients were included in this study, which was carried out between 2014 and 2019. The control group comprised of 50 patients, 23 males and 27 females, with an average age of 50.24 ± 13.5 years old and average body weight of 65.77 ± 13.16 kg. These patients did not have any renal or peritoneal disease. The CKD 5 group comprised of 30 patients, including 9 cases with diabetic nephropathy, 12 cases with primary chronic glomerulonephritis, 6 cases with benign renal arteriole sclerosis, and 3 cases had drug-induced nephropathy. Peritoneal dialysis catheter was inserted and they were undergoing peritoneal dialysis for the first time. Seventeen males and 13 females were included in this group, with an average age of 55.51 ± 12.67 years old and average body weight of 67.88 ± 12.76 kg. The PD-UFF group comprised of 23 cases, including 15 males

and 8 females with an average age of 58.94 ± 15.45 years old, average body weight of 63.95 ± 14.26 kg, and average CAPD duration of 14.8 ± 2.32 years. Of the 23 PD-UFF patients, 14 cases had primary glomerulonephritis, 4 cases had diabetic nephropathy, 3 cases had hypertensive nephropathy, and 2 cases had obstructive nephropathy. There were no significant differences in the age and body weight among the three groups ($P > .05$).

Comparison of AQP-1, AQP-3, and VEGF-A Expression Scores in Human Peritoneal Mesothelial Cells (PMCs)

As shown in Table 1, AQP-1 and AQP-3 expression scores on PMCs from the PD-UFF group were significantly lower than in the groups (q = 17.06, $P < .01$; q = 14.36, $P < .01$). The results were similar when we compared the PD-UFF group and CKD 5 group (q = 14.46, $P < .01$; q = 11.64, $P < .01$), whereas no statistically significant difference was found between the control and CKD 5 groups (q = 1.37, $P > .05$; q = 1.81, $P > .05$). VEGF-A expression in both control group and CKD 5 group were significantly lower than those in PD-UFF group (q = -13.38, $P < .01$; q = -13.01, $P < .01$), while no statistically significant difference was observed between the control and CKD 5 groups (q = 1.13, $P > .05$).

Comparison of AQP-1, AQP-3, and VEGF-A Expression Scores in Human Peritoneal Blood Vessels and the Interstitium

AQP-1 and AQP-3 expression levels were significantly lower in the peritoneal vessels and interstitium of the PD-UFF group compared to the control and CKD 5 groups (q = 13.65, $P < .01$; q = 11.82, $P < .01$). The results were similar when we compared the PD-UFF group and CKD 5 group (q = 15.28, $P < .01$; q = 11.75, $P < .01$). No statistically significant difference was observed between the control and CKD 5 groups (q = 0.71, $P > .05$; q = 0.12, $P > .05$). VEGF-A expression was significantly higher in the PD-UFF group than the control and CKD 5 groups (q = -9.80, $P < .01$; q = -7.75, $P < .01$). No statistically significant difference was observed between the control and CKD 5 groups (q = -1.39, $P > .05$).

AQP-1, AQP-3, and VEGF-A Expression Patterns in Human Peritoneal Mesothelial Cells

Cells were stained with antibodies against AQP-1, AQP-3, and VEGF-A by immunohistochemistry, and observed by light microscopy at a magnification of 400× (Figure 1). As shown in Figure 1, PMCs in the control group samples showed strong staining for AQP-1 and AQP-3, with almost no VEGF-A expression. PMCs in the CKD 5 group also stained strongly for AQP-1 and AQP-3, while VEGF-A was only slightly expressed. AQP-1 and AQP-3 expression in the PD-UFF group was significantly reduced compared to the CKD 5 and control groups, whereas VEGF-A levels were significantly higher.

AQP-1, AQP-3, and VEGF-A Expression Patterns in Human Peritoneal Vessels and the Interstitium

Cells were stained with antibodies against AQP-1, AQP-3, and VEGF-A using the immunohistochemistry, and observed by light microscopy at a magnification of 400× (Figure 2). As shown in Figure 2, strong AQP-1 and AQP-3 staining was observed in the peritoneal vessels and interstitium of the control group, whereas virtually no VEGF-A staining was seen. In the CKD 5 group, strong AQP-1 and AQP-3 staining were also observed, with weak VEGF-A expression. Finally, in the PD-UFF group, AQP-1

Table 1. Comparison Between AQP1, AQP3, and VEGF-A Expression Scores on Human Peritoneal Mesothelial Cells

Group	n	AQP1 (X ± S)	AQP3 (X ± S)	VEGF-A (X ± S)
Ctrl	50	3.52 ± 0.65	3.40 ± 0.64	1.32 ± 0.65
CKD 5	30	3.37 ± 0.76	3.20 ± 0.66	1.20 ± 0.66
PD-UFF	23	1.44 ± 0.66	1.65 ± 0.78	2.87 ± 0.63

Table 2. Comparison Between AQP1, AQP3, and VEGF-A Expression Scores in Human Peritoneal Blood Vessels and the Interstitium

Group	n	AQP1 (X ± S)	AQP3 (X ± S)	VEGF-A (X ± S)
Ctrl	50	3.26 ± 0.75	3.08 ± 0.69	0.78 ± 0.68
CKD 5	30	3.17 ± 0.75	2.77 ± 0.78	0.93 ± 0.58
PD-UFF	23	1.30 ± 0.97	1.04 ± 0.83	1.96 ± 0.77

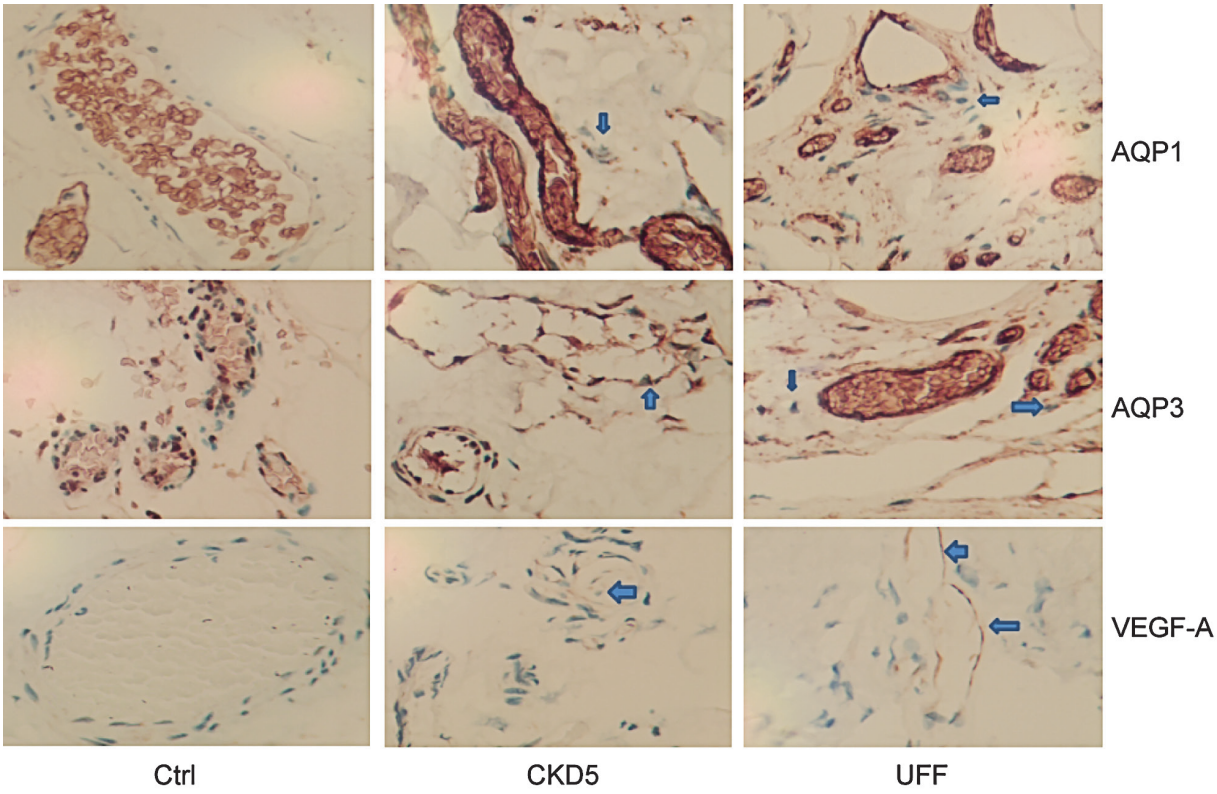

Figure 1. AQP-1, AQP-3, and VEGF-A Staining on Human Peritoneal Mesothelial Cells in the Control, CKD 5, and PD-UFF Groups

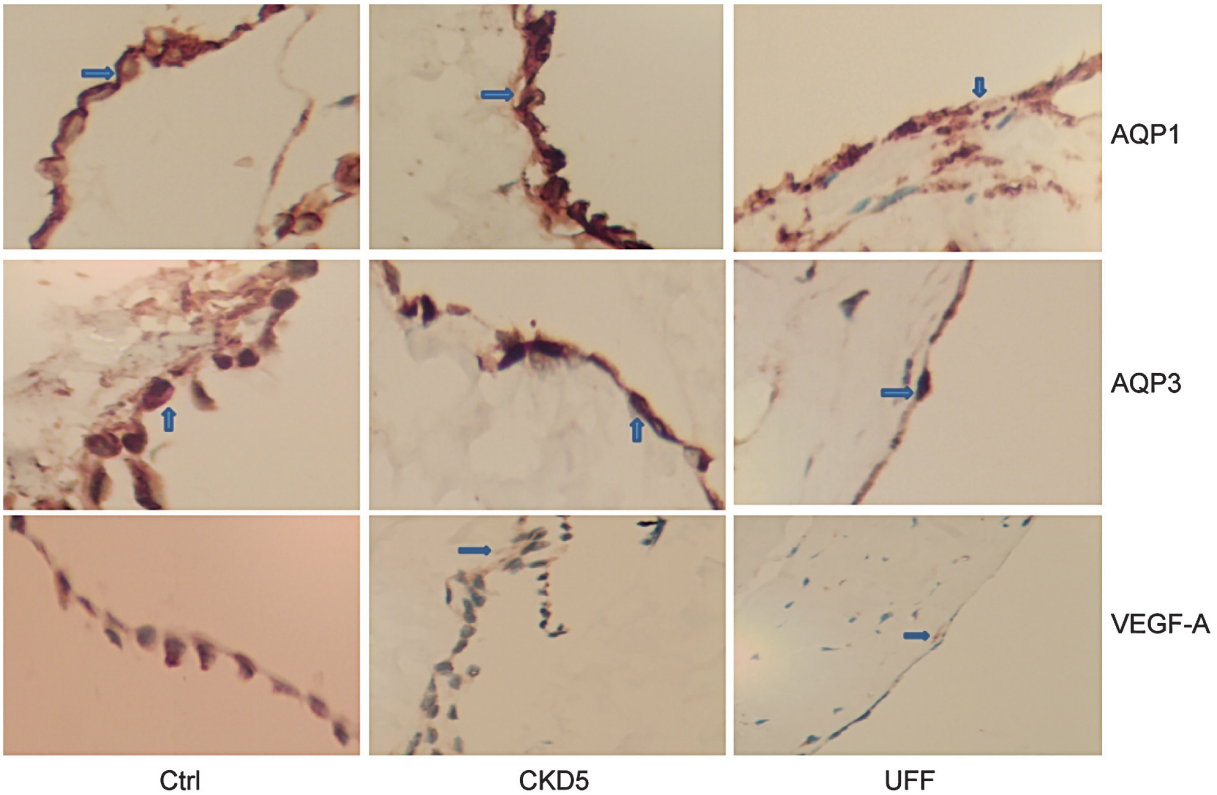

Figure 2. AQP-1, AQP-3, and VEGF-A Staining in Human Peritoneal Vessels and the Interstitium in the Control, CKD 5, and PD-UFF Groups

and AQP-3 expression were significantly reduced compared to the CKD 5 and control groups, while VEGF-A levels were significantly higher.

DISCUSSION

Peritoneal dialysis (PD) is one of the main alternative treatment methods for end-stage kidney disease (ESKD), which has been established and applied for more than 90 years.[8] Ultrafiltration failure (UFF) is the most serious complication of PD, which deprives the patients of this treatment modality. UFF can be divided into membrane and non-membrane types, with membrane UFF being further subdivided into three types. However, recently a fourth category has been proposed, which involves a decrease in AQP expression, as well as structural changes in PMCs .[9] In addition, in patients with PD, VEGF-A on PMCs is continually enhanced, leading to the formation of new vessels[10-12] and ultimately peritoneal interstitial fibrosis.[13] The aim of this study was to examine the changes in expression levels of AQP-1, AQP-3 and VEGF-A in peritoneal tissue. obtained from different patient groups, and to infer the possible mechanism of AQP in UFF.

AQPs belong to a class of integrative membrane proteins, which are mainly responsible for cellular water transport, into and out of the cells. Verkman *et al.* proposed the "three-hole model theory" to explain peritoneal permeability, for the first time.[14] Functionally, AQPs can be characterized based on their selectivity either to water transport (AQP-1, AQP-2, AQP-4, AQP-5, and AQP-8) or glycerol, some small molecules and water (AQP-3, AQP-7, AQP-9, and AQP-10).[15-16] Maria S. Stoenoiu *et al.*[17] have showed that, AQP-1 is abundant on PMCs, and its transcription and expression are induced by high osmotic agents such as glucose. In addition, several studies have confirmed that, AQP-1 expression on PMCs is closely related to water transport.[18-20] Similar findings were reported in both in vitro cell culture and clinical studies. Here, we found that AQP-1 was expressed on the PMCs of both normal control and CKD 5 groups, and there was no significant difference between these two groups (Figure 1).

Multiple studies have found that AQP-3 is expressed in peritoneal tissue. Lai *et al.*[21] showed that, unlike AQP-1, AQP-3 was only expressed on PMCs and not in peritoneal capillary and venule epithelial cells. The localization of AQP-1 and AQP-3 on PMCs suggests that AQP-3 may have a pivotal and independent role in these tissues. Peritoneal effusion is mainly derived from mesothelial cells. Studies on peritoneal effusion in PD patients have detected AQP-3 expression rather than AQP-1, suggesting a vital role for AQP-3 in peritoneal transport by mesothelial cells.[22] Cheuk-chun Szeto[23] *et al,* have explained the functional role of mesothelial AQP-3 in peritoneal transport. They also showed that, expression of AQP-3 is affected by glucose exposure, peritonitis, and VEGF-A. In agreement with these studies, we found a strong AQP-1 and AQP-3 expression on PMCs, with lower levels of expression in peritoneal capillary and small venule epithelial cells, especially in patients with kidney failure who had not received PD treatment yet. Moreover, the expression of AQP-1 and AQP-3 on PMCs, and in peritoneal blood vessels and the interstitium were significantly reduced or negligible in the PD-UFF group (Figure 1, 2) compared with the normal control and CKD 5 groups. Similarly, AQP-3 expression was significantly lower in PD-UFF patients than CKD 5 and control patients ($P < .01$). These findings suggest that, decreased expression of AQP-1 and AQP-3 on human PMCs plays an important role in UFF.

As far as peritoneal angiogenesis is involved in the pathogenesis of UFF, VGEF plays a critical role in both physiologic and pathologic angiogenesis in peritoneal vessels.[22,25] Kariya *et al.*[11] demonstrated that, angiogenesis is associated with fibrosis, and mediated by TGF-β1/VEGF-A-A pathway in mesothelial cells and fibroblasts. Furthermore, TGF-β1 plays an important role in peritoneal fibrosis,[25-26] which eventually leads to UFF. Combet *et al.*[27] showed that VEGF-A expression is upregulated in PMCs of patients with a prolonged course of PD treatment, indicating that VEGF-A may be involved in the development of UFF. Increased VEGF-A expression on the PMCs of uremic patients has also been reported in China.[10] In this study, the average CAPD duration was more than 14 years in patients with UUF, all patients were treated with hypertonic grape peritoneal dialysis solution, and the peritoneum was stimulated by hypertonic glucose for a long time period. Therefore, they concluded that, high glucose concentration has significant influence on peritoneal AQP, and promotes the formation of new blood vessels,

ultimately leading to peritoneal fibrosis. Similarly, we found that VEGF-A expression was significantly higher in PD-UFF patients than the control and CKD 5 patients, regardless of the expression of VEGF-A, either on human PMCs or in the human peritoneal blood vessels and interstitium (Figure 1, 2). Increased expression of VEGF-A in the peritoneal interstitium and tissues of UFF patients is thought to have an important role in the pathogenesis of UFF, as the formation of new blood vessels in the peritoneal tissues results in peritoneal fibrosis,[28] which ultimately leads to peritoneal UFF.

Most of the studies regarding the correlation between peritoneal ultrafiltration failure and aquaporin 1, 3, and vascular endothelial growth factor have basically used in vitro cell cultures, but there are large differences between in vitro cell culture models and the human environment, suggesting that human based clinical research is necessary in this field. The current clinical study obtained valuable human pathological tissue, although the numbers of pathologic findings are still insufficient. Due to the lack of gene monitoring equipment in our center, we were not able to test the gene level of aquaporin 1, 3, and VEGF-A in peritoneal pathological tissues, and we are hopeful that the gene monitoring equipment will be provided in the future studies.

In summary, many of the earlier studies regarding the relationship between AQP-1, AQP-3, VEGF-A, and UFF, were restricted to animal studies.[11-12, 20-21] Previous in vitro studies have suggested that the possible causes of PD-UFF may include peritoneal interstitial neovascularization,[11] increased advanced glycosylation products of peritoneal fluid,[29-30] decreased quantity and quality of AQP[20] and advent of new targets for peritoneal fibrosis.[31] However, the pathogenesis of UFF is still not fully understood. Here, we examined peritoneal tissues from normal individuals, non-dialysis uremic patients and those on long-term peritoneal dialysis with ultrafiltration failure, by using immunohistochemistry staining, to determine the relationship between AQP-1, AQP-3 and VEGF-A, and peritoneal dialysis ultrafiltration failure. We found that AQP-1 and AQP-3 were decreased in PMCs and the vasculature of the interstitium of patients with prolonged PD treatment, while VEGF-A was gradually increased and new blood vessels were formed, eventually leading to peritoneal fibrosis and UFF.

CONCLUSION

Our findings suggest that peritoneal neovascularization, peritoneal fibrosis and decreased AQP expression could contribute to peritoneal dialysis ultrafiltration failure. Although our study was composed of valuable human pathological tissues, it was limited by its small sample size. Future studies should include larger sample size and genomic detection of AQP-1, AQP-3, and VEGF-A.

COMPLIANCE WITH ETHICAL STANDARDS

Funding

None.

Conflicts of Interest

All authors had no conflicts of interest.

Ethical Approval

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. No animals were involved in this study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was obtained from all individual participants included in the study.

REFERENCES

1. Johann Morelle, Amadou Sow, Nicolas Hautem, et al. Ultrafiltration Failure and Impaired Sodium Sieving During Long-Term Peritoneal Dialysis: More Than Aquaporin Dysfunction? Perit Dial Int. Mar-Apr 2016;36(2):227-31.
2. María Luisa Pérez-Lozano, Pilar Sandoval, Angela Rynne-Vidal, et al. Functional Relevance of the Switch of VEGF-A Receptors/Co-Receptors during Peritoneal Dialysis-Induced Mesothelial to Mesenchymal Transition PLoS One. 2013; 8(4): e60776.
3. Yu-Pei Fan, Ching-Chih Hsia, Kuang-Wen Tseng, et al.The Therapeutic Potential of Human Umbilical Mesenchymal Stem Cells From Wharton's Jelly in the Treatment of Rat Peritoneal Dialysis-Induced Fibrosis Stem Cells Transl Med. 2016; 5(2): 235–247.
4. Alferso C. Abrahams, Sayed M. Habib, Amélie Dendooven, et al. Patients with Encapsulating Peritoneal Sclerosis Have Increased Peritoneal Expression of Connective Tissue Growth Factor (CCN2), Transforming Growth Factor-β1, and Vascular endothelial growth factor

A PLoS One. 2014; 9(11): e112050.

5. De Vriese AS, Mortier S, N H Lameire. Glueotoxieity of the Peritoneal membrane: the case for VEGF-A.Nephrol Dial Transplant. 2001 Dec;16(12):2299-302.
6. Devuyst O, Rippe B. Water transport across the peritoneal membrane. Kidney Int. 2014;85(4):750-758.
7. Schoenicke G,Diamant R, Donner A,et al.Histochemocal distribution and expression of aquaporin 1 in the peritoneum of patients undergoing peritoneal dialusis: relation to peritoneal transport.Am J Kidney Dis,2004 Jul;44(1):146-154.
8. Maria Claudia Cruz Andreoli, Claudia Totoli. Peritoneal Dialysis Rev Assoc Med Bras. 2020 Jan 13;66Suppl 1(Suppl 1): s37-s44.
9. Yi Wang, Yingfeng Shi, Min Tao, et al. Peritoneal fibrosis and epigenetic modulation. Perit Dial Int. 2021 Mar;41(2):168-178.
10. Zhenyuan Li, Hao Yan, Jiangzi Yuan, et al. Pharmacological inhibition of heparin-binding EGF-like growth factor promotes peritoneal angiogenesis in a peritoneal dialysis rat model. Clin Exp Nephrol. 2018 Apr;22(2):257-265.
11. Tetsuyoshi Kariya, Hayato Nishimura, Masashi Mizuno, et al. TGF-β1-VEGF-A-A pathway induces neoangiogenesis with peritoneal fibrosis in patients undergoing peritoneal dialysis.Am J Physiol Renal Physiol. 2018 Feb 1;314(2):F167-F180.
12. Qianxin He, Lu Wen, Luyao Wang, et al. miR-15a-5p suppresses peritoneal fibrosis induced by peritoneal dialysis viatargeting VEGF-A in rats. Ren Fail.2020 Nov;42(1):932-943.
13. Joanna Stachowska-Pietka, Jan Poleszczuk, Michael F Flessner, et al. Alterations of peritoneal transport characteristics in dialysis patients with ultrafiltration failure: tissue and capillary components Nephrol Dial Transplant. 2019 May 1;34(5):864-870.
14. Baoxue Yang, A.S. Verkman. Water and Glycerol Permeabilities of Aquaporins 1-5 and MIP Determined Quantitatively by Expression of Epitope- tagged Constructs in Xenopus Oocytes.J. Biol. Chem.Jun 1997; 272: 16140-16146.
15. Mariko Hara-Chikuma, A S Verkman. Aquaporin -1 facilitates epithelial cell migration in kidney proximal tubule. J Am Soc Nephro, 2006, 17: 39-45.
16. Kuniaki Takata, Toshiyuki Matsuzaki, Yuki Tajika. Aquaporins: water channel proteins of the cell membrane. Prog Histochem Cytochem 2004;39: 1-83.
17. S Tang, J C Leung, C W Lam, et al: Invitrostudies of aquaporins 1 and 3 expression in cultured human proximal tubular cells: Upregulation by transferring but not albumin. Am J Kidney Dis, 2001,38:317-330.
18. Ramesh Khanna. Solute and Water Transport in Peritoneal Dialysis: A Case-Based Primer. Am J Kidney Dis. 2017 Mar;69(3):461-472.
19. Raymond T Krediet.Ultrafiltration Failure Is a Reflection of Peritoneal Alterations in Patients Treated With Peritoneal Dialysis. Front Physiol. 2018 Dec 20;9:1815.
20. Simone Corciulo, Maria Celeste Nicoletti, Lisa Mastrofrancesco, et al. AQP1-Containing Exosomes in Peritoneal Dialysis Effluent As Biomarker of Dialysis Efficiency Cells. 2019 Apr 9;8(4):330.
21. Kabanda A, Goffin E, Bernard A, e t al: Fact ors influencing serum levels and peritoneal clearances of low molecular weight proteins in CAPD. Kidney In t, 1995,48:1946-1952.
22. Boulanger E, Grossin N, Wautier MP, et al. Mesothelial RAGE activation by AGEs enhances VEGF-A release and potentiates capillary tube formation [J].Kidney Int,2007,71(2):126-133.
23. Cheuk-Chun Szeto, Ka-Bik Lai, Kai-Ming Chow, et al. The relationship between peritoneal transport characteristics and messenger RNA expression of aquaporin in the peritoneal dialysis effluent of CAPD patients. J Nephrol. Mar-Apr 2005;18(2):197-203.
24. Wang ZK, Wang ZX, Liu ZY, et al. Effects of RNA interference-mediated gene silencing of VEGF-A on the ultrafiltration failure in a rat model of peritoneal dialysis. Biosci Rep. 2020 May 29;40(5):20170342_COR.
25. Longkai Li, Nan Shen, Nan Wang, et al. Inhibiting core fucosylation attenuates glucose-induced peritoneal fibrosis in rats. Kidney Int. 2018 Jun;93(6):1384-1396.
26. Jingjing Wu,Changying Xing, Li Zhang, et al. Autophagy promotes fibrosis and apoptosis in the peritoneum during long-term peritoneal dialysis.J Cell Mol Med. 2018 Feb;22(2):1190-1201.
27. Combet S, Miyata I, Moulin P, et al. Vascular proliferation and enhanced expression of endothelial nitric oxide synthase in human peritoneum exposed to long-term periotoneal dialysis [J].J Am Soc Nephrol,2000,11(4):717-728.
28. Toshiaki Nakano, Torisu Kumiko, Tohru Mizumasa, et al. heglucose degradation product methylglyoxal induces immature angiogenesis in patients undergoing peritoneal dialysis.Biochem Biophys Res Commun. 2020 May 7;525(3):767-772.
29. Michael S Balzer, Song Rong, Johannes Nordlohne, et al. SGLT2 Inhibition by Intraperitoneal Dapagliflozin Mitigates Peritoneal Fibrosis and Ultrafiltration Failure in a Mouse Model of Chronic Peritoneal Exposure to High-Glucose Dialysate. Biomolecules. 2020 Nov 19;10(11):1573.
30. Raymond T Krediet, Anouk T N van Diepen, Annemieke M Coester, et al. Peritoneal vasculopathy in the pathophysiology of long-term ultrafiltration failure: A hypothesis based on clinical observations.Clin Nephrol. 2019 Jan;91(1):1-8.
31. Xiejia Li, Hong Liu, Lin Sun, et al. MicroRNA-302c modulates peritoneal dialysis-associated fibrosis by targeting connective tissue growth factor. J Cell Mol Med. 2019 Apr;23(4):2372-2383.

Correspondence to:
Wang Ying, BM
NO. 234 Gucui Road, Hangzhou, Zhejiang Province, PRC, 310012, China
Tel: 0086 136 5655 5776
E-mail: 598137926@qq.com

Received March 2022
Revised May 2022
Accepted June 2022