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Original Article

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The Utility of Bone Morphogenetic Protein 7 Levels on Predicting the Alteration of the Peritoneal Membrane Permeability

Cihan Uysal[1], Ali Gundogdu[2], Sumeyra Koyuncu[3], Derya Kocer[4], Funda Ipekten[5], Ismail Kocyigit[1]

[1]Division of Nephrology, Erciyes University School of Medicine, Kayseri, Türkiye
[2]Division of Nephrology, Isparta City Hospital, Isparta, Türkiye
[3]Division of Nephrology, Kayseri City Hospital, Kayseri, Türkiye
[4]Department of Biochemistry, Kayseri City Hospital, Kayseri, Türkiye
[5]Department of Biostatistics, Erciyes University School of Medicine, Kayseri, Türkiye

ABSTRACT

Background: This study aimed to investigate the potential relationship between bone morphogenetic protein 7 (BMP-7) and peritoneal permeability, as well as clinical outcomes.
Methods: We conducted a cross-sectional study involving 67 peritoneal dialysis (PD) patients who had been on PD for at least 1 year. We measured BMP-7 levels in both plasma and PD effluent fluid. Two peritoneal equilibration tests, the first and last ones, were compared to assess alterations in peritoneal membrane permeability. Dialysate to plasma ratio for creatinine (DPRC) was used to define membrane permeability. BMP-7 level was measured concurrently in both plasma and PD effluent.
Results: Among the patients, 81% (n = 51) were on ambulatory PD, while 19% (n = 12) were on automated PD. The average PD duration was 58.9 months. Increased DPRC was determined in 61.9% of the patients. There was a positive correlation between plasma BMP-7 levels and the change in DPRC (r = 0.323, *P* = .004). No correlation was determined between effluent BMP-7 levels and changes in DPRC. A statistically significant negative correlation was determined between plasma BMP-7 levels and serum albumin levels (r = −0.274, *P* = .02). Plasma BMP-7 levels independently predicted changes in DPRC (*P* = .02), while effluent BMP-7 levels did not (*P* = .212).
Conclusion: We identified a correlation between plasma BMP-7 level and changes in peritoneal membrane permeability. However, we did not find any relationship with the PD clinical outcomes. Plasma BMP-7 levels can serve as a parameter for predicting alterations in permeability.
Keywords: Albumin, bone morphogenetic protein-7, membrane permeability, peritoneal dialysis

Corresponding author: Cihan Uysal ✉ drcihanuysal@hotmail.com
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INTRODUCTION

Peritoneal dialysis (PD) is an option for kidney replacement therapy. The peritoneum has been utilized as a semipermeable membrane in PD, allowing for diffusion and ultrafiltration to occur via this membrane. The carriage of water and particles among the dialysate and blood occurs on the peritoneal membrane.[1] The alterations to the peritoneum can result in inadequate dialysis. Inflammation, neoangiogenesis, and fibrosis are among these alterations. Prolonged PD has been shown to lead to histological and functional changes in the peritoneal membrane.[2]

The mesothelium is constituted of single-layer cells, and it has significant roles in the integrity of the serosal membranes and functions. Exposure to PD solutions can cause mesothelial cell (MC) differentiation concerning function and proliferation. The exact biochemical mechanisms of this process have not been definitively determined.[3] Transforming growth factor-beta 1 (TGF-β1)-induced epithelial-to-mesenchymal transition (EMT) plays a crucial role in alterations of the peritoneal membrane. As a consequence, the peritoneal MC misses the epithelial phenotype and attains novel mesenchymal features.[4] This transdifferentiation

to fibroblast can be explained by the fact that MC is primitive mesodermal-originated and has both epithelial and mesenchymal characteristics.[5]

The bone morphogenetic protein 7 (BMP-7) is a cytokine and is listed in a TGF-β superfamily. It has anti-inflammatory properties. The BMPs have a crucial function in organogenesis, cell proliferation, differentiation, and apoptosis. Bone morphogenetic protein 7 is synthesized predominantly in the kidney at the gestational age of 5-14 weeks, and it is frequently detected in the glomerular and tubular cells of the kidney.[6,7] Also, BMP-7 has an antagonistic effect on TGF-β cellular signaling pathway, which is important for the EMT in the peritoneum.[8] Bone morphogenetic protein 7 can reverse TGF-β1-induced EMT through activation of Smad1/5/8 and E-cadherin. Additionally, various antagonistic molecules regulate BMP-7 levels and its effects.[9]

Experimental studies have revealed that high glucose exposure conspicuously induces a decline in BMP-7 levels in kidney tubular epithelial cells and BMP-7 has been found to prevent EMT and interstitial matrix deposition in kidney tubular cells cultured.[10] Furthermore, exogenous BMP-7 administration hindered EMT via TGF-β inhibition in vitro MCs. However, long-term PD therapy leads to the downregulation of BMP-7 expression in MC.[11]

Peritoneal membrane permeability is critical in PD clinical practice. It is among the high ranks of factors affecting the performance of treatment. Also, long-term PD leads to fibrosis in the peritoneum and increased membrane angiogenesis. The possible role of BMP has not been adequately investigated in clinical studies about PD sufficiency and peritoneal membrane permeability. Thereby, this study has been proposed to focus on the relationship between BMP-7 levels and peritoneal membrane permeability.

MATERIAL AND METHODS

This study was designed as cross-sectional and single-center, the Ethics Committee of Erciyes University approved the study with decision numbered 2019/678, date 09.10.2019. The patients enrolled between January 1, 2020 and January 1, 2021. Written informed consent was obtained from the patients by explaining the procedure of the study. Key inclusion criteria were age ≥18 and a vintage of PD for at least 1 year. Patients with leakage of dialysate, dysfunction of the PD catheter, cirrhosis, ascites, or systemic infection have been excluded. Furthermore, the patient who underwent abdominal surgery during the follow-up period was excluded from the study.

MAIN POINTS

- Plasma bone morphogenetic protein 7 (BMP-7) levels were associated with changes in peritoneal permeability; however, BMP-7 levels in PD effluent did not have any associaton.
- Plasma BMP-7 levels were associated with albumin levels.
- Finally, plasma and effluent fluid BMP-7 were not associated with PD clinical outcomes.

The peritoneal equilibration test (PET) was used to define the transporting properties of the peritoneum. The standard PET was performed in this study as described by Twardowski.[12] The patients were classified by a value of 4-h dialysate to plasma ratio (D/P) for creatinine. Four permeability groups were determined as follows: high, high average, low average, and low. Two PET values were compared for alteration in peritoneal membrane permeability. The first PET was defined as performed at the beginning of PD therapy and we obtained these results from medical record documents. The last PET was defined as being performed concomitantly with BMP-7 sampling. The D/P ratio for creatinine (DPRC) was used to calculate the alteration of peritoneal membrane permeability. *The ratio of the last DPRC to first DPRC*, a percentage value, was defined as the formula for peritoneal permeability alteration. Also, 24-hour urine and dialysate samples were used to calculate creatinine clearance. The obesity is defined as body mass index ≥30 kg/m^2. We used to International Society for Peritoneal Dialysis Guidelines for diagnosis of the peritonitis.[13]

Bone morphogenetic protein 7 level was measured concomitantly in plasma and PD effluent. The effluentwas obtained after a 4-hour dwell period with 2.27% glucose. Venous blood samples were centrifuged for 10 minutes at 5000 rpm (NF 400 centrifuges, Türkiye). The samples were preserved at −80°C until assessment. Bone morphogenetic protein 7 levels were measured by commercially available ELISA kits (Elabscience Biotechnology Inc., Houston, Tex, USA), according to the manufacturer's instruction and expressed as pg/mL. The detection range of the kits for BMP-7 was 31.25-2000 pg/mL. The interassay coefficient of variation for the kits was <10%.

Statistical Analysis

Histogram and q-q plots were examined, and Shapiro–Wilk's test was applied to test the data normality. Numerical variables were summarized with mean and standard deviations or median and quartiles according to the normality of data. Categorical variables were summarized with frequencies and percentages. The Spearman correlation coefficient was used to explore the relationship between numerical variables. Finally, a multiple linear regression analysis was conducted to find independent predictors of alteration of permeability. Analyses were conducted using R 4.2.0 (www.r-project.org). A *P*-value less than $P < .05$ was considered statistically significant.

RESULTS

Totally, 63 (31 male (49.2%) and 32 female (50.8%))PD patients were enrolled in this cross-sectional study. The mean age of patients was 53.1 ± 14.1 years. The average PD duration of patients was 59.8 (minimum: 14, maximum: 216) months.

The mean plasma BMP-7 level of the patients was 74.01 ± 15.46 pg/mL, and the mean effluent BMP-7 level of the patients was 464.27 ± 85.32 pg/mL. The analysis of the patients according to the residual kidney functions: 30.2% (n = 32) of the patients had anuria, 11.1% (n = 7) of the patients had oliguria, and 58.7% (n = 37) of the patients had >400 mL urine volume. The frequency of hypoalbuminemia was 9.5% (n = 6). The frequency of obesity was 19.0% (n = 20). Demographic features and laboratory results of patients are summarized in Table 1.

81% (n = 51) of the patients were on ambulatory PD, and 19% (n = 12) of the patients were on automated PD. The frequency of individuals who underwent at least 1 peritonitis attack during the follow-up period was 31.7% (n = 20). The overall peritonitis rate was 0.13 episodes per year per individual. The parameters related to PD are summarized in Table 2.

High-average permeability was the most frequently subgroup, with 36% (n = 23) in the first PET and 47.6% (n = 30) in last PET. The results were summarized in Table 3.

Table 1. Demographic Features and Laboratory Results of Patients

Clinical Features	
Male n, (%)	31 (49.2%)
Female n, (%)	32 (50.8%)
Age (years)	53.08 ± 14.09
Body mass index (kg/m^2)	27.19 ± 5.46
Plasma BMP-7 (pg/mL)	74.01 ± 15.46
Effluent BMP-7 (pg/mL)	464.27 ± 85.32
BUN (mg/dL)	52.90 ± 12.44
Creatinine (mg/dL)	8.58 ± 2.95
Uric acid (mg/dL)	5.59 ± 1.25
Calcium (mg/dL)	9.11 ± 0.86
Phosphorus (mg/dL)	4.70 ± 1.05
PTH (pg/dL)	421.0 (261.0-556.0)
Sodium (mEq/L)	137.56 ± 4.48
Potassium (mEq/L)	4.55 ± 0.69
Albumin (g/dL)	3.87 ± 0.35
Glucose (mg/dL)	121.63 ± 42.66
Hemoglobin (g/dL)	11.63 ± 1.84
Leukocytes (10^3/μL)	7.37 ± 2.58
Platelet (10^3/μL)	246.59 ± 69.28

Values are expressed as n (%) mean ± standard deviation, median (first-third quartiles).
BMP, bone morphogenetic protein; BUN, blood urea nitrogen; PTH, parathyroid hormone.

Table 2. The Clinical Features of Peritoneal Dialysis Patients

Parameters	**Values**
PD duration (months)	42.0 (24.0-88.0)
Kt/V	2.14 ± 0.49
Ultrafiltration volume (mL)	1100.0 (850.0-1700.0)
Creatinine clearence (mL/min)	62.2 (51.3-79.9)

Values are expressed as mean ± standard deviation, median (first-third quartiles).
PD, peritoneal dialysis.

Table 3. The Features of Patients According to Peritoneal Equilibration Test Results

Parameters	**First PET**	**Last PET**
DPRC	0.65 ± 0.14	0.68 ± 0.11
Classification		
High	9 (14.3)	7 (11.1)
High average	23 (36.5)	30 (47.6)
Low average	21 (33.3)	25 (39.7)
Low	10 (15.9)	1 (1.6)

Values are expressed as n (%) mean ± standard deviation, median (first-third quartiles).
DPRC, dialysate to plasma ratio for creatinine; PET, Peritoneal Equilibration Test.

The mean change in DPRC was a 4.6% increment in this cohort during the follow-up period. In the comparison of DPRC in the first and last PET, it increased in 39 (61.9%) patients, decreased in 22 (34.9%) patients, and was stable in 2 (3.2%) patients.

There was a positive correlation between plasma BMP-7 levels with the DPRC values only in the first PET (r = 0.293, P = .05). However, no correlation was found between effluent BMP-7 levels and DPRC values in the first or last PET. There was a positive correlation between plasma BMP-7 levels and the change in DPRC over time (r = 0.323, P = .004). There was no correlation between effluent BMP-7 levels and the change in DPRC over time. There was a statistically significant negative correlation with serum albumin level (r = −0.274, P = .02). Furthermore, there was no correlation between plasma BMP-7 levels and effluent fluid BMP-7 levels. The results of the correlation analysis are shown in Figures 1-4.

Multiple linear regression analyses were performed to determine independent variables to predict the alteration of peritoneal permeability. The original model included changes in DPRC, plasma BMP-7 level, effluent BMP-7 level, ultrafiltration volume, albumin, and Kt/V. The change in DPRC was independently predicted by plasma BMP-7 levels (P = .005) but not by effluent BMP-7 levels (P = .212). The results of the analysis are summarized in Table 4.

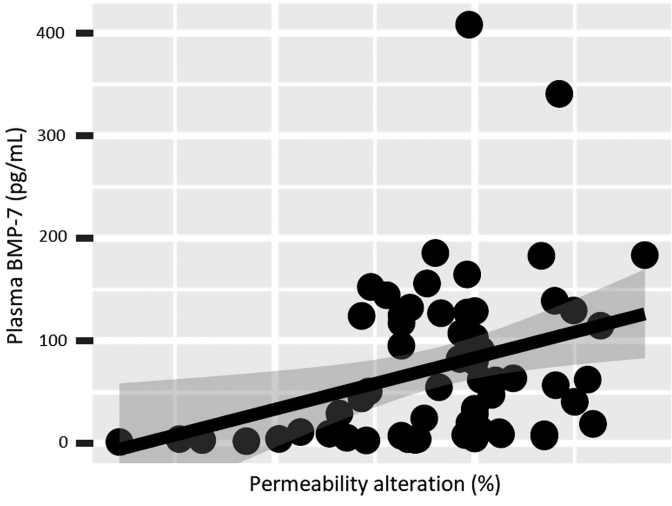

Figure 1. The correlation analysis of the alteration of peritoneal membrane and plasma bone morphogenetic protein 7 levels. BMP-7, bone morphogenetic protein 7.

DISCUSSION

In this article, we focused on the BMP-7 levels and peritoneal membrane transport features. The primary outcome of this study is to determine a statistically significant correlation between plasma BMP-7 levels and alterations in peritoneal membrane permeability. The results revealed higher plasma BMP-7 levels in patients with increasing peritoneal permeability during the follow-up period. Also, plasma BMP-7 levels had an inverse correlation with serum albumin levels. However, we did not determine any correlation between effluent BMP-7 levels and alteration of the peritoneal membrane permeability. Moreover, one of the interesting results of this study was that plasma and effluent fluid BMP-7 levels are not correlated.

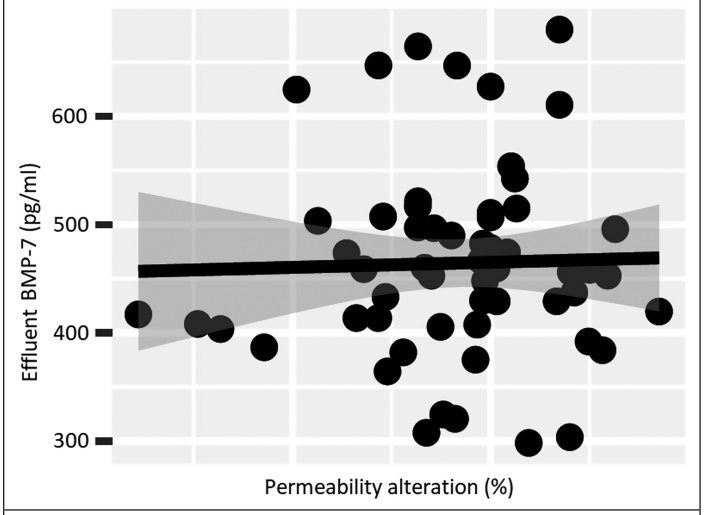

Figure 2. The correlation analysis of the alteration of peritoneal membrane and effluent fluid bone morphogenetic protein 7 levels. BMP-7, bone morphogenetic protein 7.markers very large

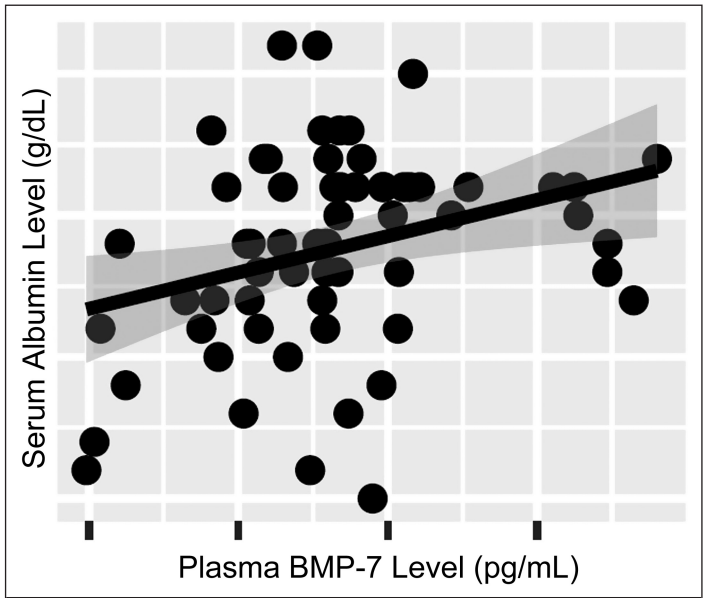

Figure 3. The correlation analysis of the plasma bone morphogenetic protein 7 levels and serum albumin levels. BMP-7, bone morphogenetic protein 7.

In the literature review, we found that BMP-7 has been investigated for membrane permeability in previous studies. However, an evaluation has often been based on the last PET assessment of these patients.[14] We used the overall alteration in peritoneal membrane permeability during PD treatment as a parameter and analyzed it with BMP-7 levels in this study. Moreover, binary sampling of BMP-7 was performed in this study for the evaluation of plasma and effluent fluid. Consequently, an increased DPRC was detected in 61.9% of the patients during an average of 42.0 months of PD treatment.

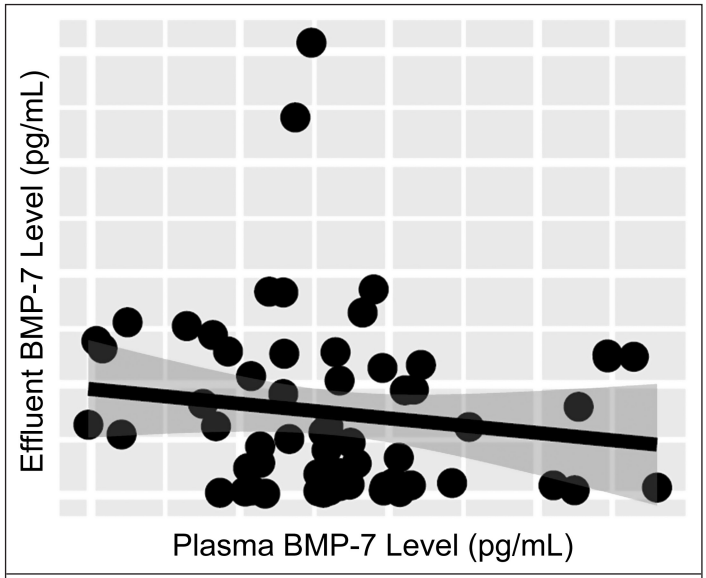

Figure 4. The correlation analysis of the plasma bone morphogenetic protein 7 levels and effluent fluid bone morphogenetic protein 7 levels. BMP-7, bone morphogenetic protein 7.

Table 4. Multiple Linear Regression Analysis Indicating the Alteration of Peritoneal Permeability

Variables	Estimate (SE)	*P*
Plasma BMP-7	0.12 (0.04)	**.005**
Effluent BMP-7	4.23 (3.32)	.212
Albumin	14.63 (9.29)	.121
Ultrafiltration volume	0.01 (0.01)	.441
Kt/V	7.67 (6.67)	.255

BMP-7, bone morphogenetic protein 7; SE, standard error.

Peritoneal membrane permeability is essential in PD practice. It is among the high ranks of factors affecting the performance of treatment. Membrane permeability should be considered when determining the appropriate solutions and dwell durations for the patient. Also, adequate clearance of the uremic toxins and ultrafiltration volume are directly affected by membrane permeability.[15] Therefore, the identification of molecules associated with peritoneal permeability is important for novel therapies and prevention approaches.

A preservative impact of BMP-7 on peritoneal fibrosis has been revealed in several experimental studies. The blockage of the TGF-ß pathway by BMP-7 results in anti-fibrotic processes.[16] Recent studies demonstrate that BMP-7 improved tubulointerstitial fibrosis in experimental kidney injury models. These damage models include ureteral obstruction, ischemic damage, IgA nephropathy, lupus nephritis, and diabetic kidney disease.[17]

Epithelial-to-mesenchymal transition of peritoneal MC is an undesired outcome during PD. Particularly, advanced glycation end products have contributed to the development of EMT in the peritoneum. The constitutive expression of the BMP-7 by MC has been downregulated throughout EMT. The effect of BMP-7 has been investigated in rat models, and EMT was decreased by recombinant BMP-7.[18] The amelioration of the peritoneal thickness by BMP-7 was shown in animal PD models. Min-A Yu et al[19] also observed that high-glucose exposure by dialysate declined the expression of BMP-7 protein.[19] (If this is the case then the amount of glucose load should also be discussed in the text) These results emphasized the significance of BMP-7 on the fibrosis of the peritoneum in long-term PD. As a result, the findings have led us to hypothesize the protective effect of BMP-7 on peritoneal fibrosis.

The association between the BMP-7 levels in PD effluent and peritoneal transport characteristics was demonstrated in several studies. Szeto et al[20] reported that high BMP-7 level in PD effluent was correlated with a gradual increase in peritoneal permeability parameters, such as DPRC and mass transfer area coefficient of creatinine. In fact, this result is confusing and unclear when considered in conjunction with the physiological effects of BMP-7. Furthermore, the authors considered the presence of BMP-7 in PD as locally produced in the peritoneum. Because of this, the large molecular weight (30 000 kDa) of BMP-7 results in slow transport from the plasma to the peritoneum. In contrast to this study, the BMP-7 levels of effluent did not have any association with peritoneal permeability in our study.

Long-term PD can lead to peritoneal membrane deterioration, such as increased membrane transporting rate. Moreover, an increased membrane permeability results in fibrosis in the peritoneum over time.[21] Likewise, we observed that the average of DPRC has increased over the follow-up period in this cohort. Also, according to the regression model, BMP-7 could predict an increment in the peritoneal membrane permeability. However, we did not perform histological examinations on the patients to assess peritoneal fibrosis. We have interpreted these results, high plasma BMP-7 levels, as a response to the peritoneal alterations. This increment might be a marker of the compensatory mechanism of membrane impairment.

Any correlation was not observed between plasma BMP-7 levels and ultrafiltration volume or Kt/V in our results. Actually, the ultrafiltration volume of PD is affected by multiple clinical parameters. Residual kidney functions, PD solutions, volume status, adherence to treatment, catheter malpositions, diuretic therapy, and lymphatic absorption are among these factors. Also, we did not determine any correlation between effluent BMP-7 and ultrafiltration volume or Kt/V. In this study, we considered that Kt/V was a marker of PD competence. Consequently, a regression analysis model including these detailed parameters may yield different results.

Plasma BMP-7 levels had a negative correlation with serum albumin levels. This correlation reflects a similar result with DPRC. We consider this a consistent clinical outcome. The leakage of albumin into the peritoneal cavity is an undesired consequence of PD. Therefore, increased peritoneal permeability results in more albumin wasting. The frequency of hypoalbuminemia was 9.5% in this cohort, and all of these hypoalbuminemic individuals had high-averaged classification in the last PET. Numerous factors affect albumin levels in PD patients. The contributing factors include inflammation, hypervolemia, peritoneal and urinary protein wasting, malnutrition, and impaired compensatory albumin production.[22] Daily protein wasting through PD effluent fluid is approximately 5-15 g, and urinary protein loss is also possible. Daily liver albumin synthesis markedly increases for replacement of this decrement. The essential pathway of protein loss to PD effluent fluid is the large-pore flux across the peritoneal capillary lumen.[23]

Several limitations could have influenced the results of this study. First, the number of participants may be insufficient because this study was conducted at a single center. Since the study was cross-sectional, a cause-effect relationship could not be determined. Some of the patients underwent a peritonitis

episode during the follow-up period, and peritonitis is a factor affecting peritoneal permeability. Therefore, a design could be made by excluding peritonitis patients. We did not assess ultrafiltration failure status in this cohort. Subgroup analysis could be conducted in patients with UF failure. If the initial BMP-7 levels of the patients had been measured, the relationship between changes in BMP-7 levels relative to the baseline and alterations in peritoneal permeability could have been examined. Finally, the assessment of TGF-β may have contributed accuracy to the results.

In conclusion, we found a positive correlation between plasma BMP-7 levels and changes in peritoneal permeability. We interpreted this relationship as a compensatory response to the alterations in permeability via the TGF-β pathway. In contrast to previous studies, no correlation was found between PD effluent BMP-7 levels and permeability alterations in the outcomes of this study. Nonetheless, plasma BMP-7 levels can be used as a parameter to predict alteration permeability.

Ethics Committee Approval: The Ethics Committee of Erciyes University approved the decision numbered 2019/678, date 09.10.2019.

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.U.; Design – A.G.; Supervision – I.K.; Resources – A.G.; Materials – C.U.; Data Collection and/or Processing – F.I.; Analysis and/or Interpretation – F.I.; Literature Search – S.K.; Writing Manuscript – C.U.; Critical Review – D.K., I.K.; Other – S.K.

Declaration of Interests: The authors have no conflict of interest to declare.

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