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Peritoneal Protein Loss: How Does It Relate to Fluid Overload, Sarcopenia, and Nutrition?

(Perte protéique péritonéale - lien avec surcharge liquidienne, sarcopénie et nutrition)

Inês Alexandre [1], Maria Inês Roxo [2,3], Rita Calça [2,3], Patrícia Matias [2,3,4], Patrícia Branco [2,3,4]

[1]Nephrology Nephrology Department, ULS Amadora Sintra, Lisboa, Portugal

[2]Nephrology Department, ULS Lisboa Ocidental, Lisboa, Portugal

[3]Centro Clínico Académico de Lisboa, Lisboa, Portugal

[4]NOVA Medical School, Faculdade de Ciências Médicas, Universidade NOVA de Lisboa, Lisboa, Portugal

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Summary

Peritoneal protein loss is a well-established complication of peritoneal dialysis (PD) and has been associated with malnutrition and mortality. However, recent studies have challenged this association. More recently, fluid overload has been linked to peritoneal protein loss, highlighting the importance of hydrostatic convection in protein transport. This study aimed to investigate the relationship between peritoneal protein loss and fluid overload, sarcopenia and nutritional markers.

We conducted a single-center, cross-sectional study of prevalent patients on PD who underwent a modified PET. Peritoneal protein concentration was measured in a 24h dialysate collection and in the PET effluent (4h). NTproBNP, CA-125 and extracellular water excess measured by bio-impedance were used as fluid overload markers, and albumin, total proteins, handgrip strength, ultrasound evaluation of the rectus femoris and bio-impedance parameters as nutritional and sarcopenia markers. Sixty-one patients were included (64% male, mean age 59 ± 13 years). The median peritoneal protein concentration was 0.081 g/dL (24h) and 0.046 g/dL (4h). Higher 4h peritoneal protein concentration was positively associated with NT-proBNP (p=0.001), extracellular water excess (p=0.018), and lean tissue mass (p=0.006), and negatively with fat mass (p=0.015). No associations were found between peritoneal protein concentration and albumin, total proteins, handgrip strength, muscle thickness, or other bioimpedance parameters.

Our study shows that peritoneal protein loss is not associated with sarcopenia or malnutrition in PD patients. It also suggests an association between fluid overload and peritoneal protein transport.

Keywords: Fluid overload, nutrition, peritoneal dialysis, peritoneal protein loss, sarcopenia

Résumé

La perte protéique péritonéale est une complication connue de la dialyse péritonéale, longtemps associée à la malnutrition et à la mortalité, mais récemment remise en question. La surcharge hydrosodée a également été liée à cette perte, soulignant le rôle de la convection hydrostatique dans le transport des protéines. Cette étude visait à explorer les liens entre perte protéique péritonéale, surcharge hydrosodée, sarcopénie et nutrition.

Nous avons mené une étude transversale monocentrique incluant des patients sous dialyse péritonéale ayant réalisé un PET modifié. La perte protéique péritonéale a été mesurée sur un recueil de dialysat de 24h et dans l'effluent du PET (4h). Le NT-proBNP, le CA-125 et l'excès d'eau extracellulaire évalué par bio-impédance ont servi de marqueurs de surcharge hydrosodée. Les marqueurs nutritionnels et de sarcopénie comprenaient l'albumine, les protéines totales, la force de préhension, l'échographie du muscle droit fémoral et les paramètres de bio-impédance. Soixante et un patients ont été inclus (64 % d'hommes, âge moyen 59 ± 13 ans). La perte médiane de protéines péritonéales était de 0,081 g/dl (24h) et de 0,046 g/dl (4h). Une perte protéique péritonéale plus élevée sur 4h était associée positivement au NT-proBNP (p=0,001), à l'excès d'eau extracellulaire (p=0,018) et à la masse maigre (p=0,006), et négativement à la masse grasse (p=0,015). Aucune association n'a été retrouvée avec l'albumine, les protéines totales, la force de préhension, l'épaisseur musculaire ou d'autres paramètres de bio-impédance.

Ces résultats suggèrent que la perte protéique péritonéale n'est pas liée à la sarcopénie ni à la malnutrition. Ces résultats suggèrent également un lien entre la surcharge liquidienne et la perte protéique péritonéale.

Mots-clés : Surcharge liquidienne, nutrition, dialyse péritonéale, perte protéique péritonéale, sarcopénie

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Introduction

Peritoneal protein loss via peritoneal effluent is a well-established consequence of peritoneal dialysis (PD) and has long been considered a drawback [1]. Patients typically lose 5-15 g of protein daily into the dialysate effluent, with more recent studies reporting lower values, with a median of 4.8-6.7 g/day, possibly reflecting the use of more biocompatible solutions, optimized prescriptions, and better volume management [2-4]. Peritoneal protein loss was considered a significant limitation of PD because it was associated with malnutrition and increased mortality [5,6]. However, more recent studies have challenged this long-held assumption [3,7]. Recent evidence suggests that fluid overload and venous congestion may be the main determinants of increased peritoneal protein loss, emphasizing the role of hydrostatic convection in protein transport across the peritoneal membrane [3,8].

Nutritional status and sarcopenia are important concerns in this population. Individuals receiving dialysis are at higher risk of sarcopenia, with a reported prevalence of 20.5% in PD in the study by Stockings et al. [9]. Sarcopenia, in turn, is associated with increased frailty, functional decline, and mortality [10]. Given the non-negligible daily protein losses, it was previously hypothesized that peritoneal protein loss could contribute to malnutrition, thereby promoting sarcopenia. However, recent evidence has contradicted this hypothesis, showing that peritoneal protein loss is not associated with muscle mass, strength, or sarcopenia in PD patients [11].

The association between peritoneal protein loss and fluid overload marks a significant recent conceptual advance. A growing body of evidence indicates that fluid overload and excess extracellular water are strong, independent predictors of increased peritoneal protein loss [8,12]. Peritoneal protein transport is predominantly driven by hydrostatic convection across large pores. In states of fluid overload, increased systemic venous pressure directly increases the hydrostatic pressure gradient across the peritoneal capillary wall, thereby augmenting protein escape [8]. Fluid overload is a well-recognized predictor of cardiovascular events and mortality in PD patients, which might explain the association between peritoneal protein loss and mortality reported in previous studies [12].

This study aimed to investigate the relationship between peritoneal protein loss and fluid overload, sarcopenia, and nutritional markers in prevalent PD patients.

Methods

We conducted a single-center, cross-sectional study of all prevalent patients on PD in our unit who underwent a modified peritoneal equilibration test (PET) in 2024. One patient with bilateral lower-limb amputation was excluded.

Demographic and clinical data, including age, gender, body mass index (BMI), body surface area, etiology of chronic kidney disease (CKD), and comorbidities, namely diabetes mellitus, coronary artery disease, cerebrovascular disease, and peripheral artery disease, were obtained from clinical records. All patients received normal-pH dialysis solutions with reduced glucose degradation products, either Vantive or Fresenius. Dialysis-related variables were recorded, including PD modality, icodextrin use, and total daily dialysate volume (L/day).

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A modified PET was performed using 3.86% or 4.25% glucose solution. A 24-h spent dialysate collection and a 24-h urine collection were also obtained. Peritoneal protein concentration was measured in the 4-h PET effluent and in the 24-h spent dialysate collection and expressed as g/dL. These measurements were used as markers of peritoneal protein transport.

Biochemical parameters, sarcopenia assessment, and bioelectrical impedance analysis (BIA) were evaluated at the same time as PET. Biochemical evaluation included albumin (g/dL), total proteins (g/dL), NT-proBNP (pg/mL), CA-125 (U/mL), and proteinuria measured in a 24-h urine collection and expressed in grams per 24 hours. NT-proBNP and CA-125 were considered markers of fluid status, while extracellular water excess measured by BIA was used as an objective measure of extracellular volume status. Sarcopenia was assessed using handgrip strength and ultrasound evaluation of the rectus femoris muscle. Body composition was evaluated using BIA and included the following parameters: extracellular water excess (L), lean tissue index (kg/m2), lean tissue mass (kg), fat tissue index (kg/m2), fat mass (kg), and adipose tissue mass (kg).
Statistical analysis was conducted using IBM SPSS version 28. Categorical variables were summarized as frequencies and percentages, and continuous variables as mean ± standard deviation for normally distributed data and as median (interquartile range) for skewed distributions. Univariable analysis was performed using linear regression models, and $p \leq 0.05$ was considered statistically significant.

Results

A total of 61 patients were included, of whom 39 (64%) were male, with a mean age of 59 ± 13 years. *Table I* presents demographic and clinical characteristics. The most frequent causes of CKD were diabetes in 15 patients (24.6%), glomerular diseases in 10 (16.4%), autosomal dominant polycystic kidney disease in 7 (11.5%), and hypertension in 6 (9.8%). The etiology was unknown in 12 patients (19.6%), while cardiorenal syndrome, multifactorial disease, systemic diseases with renal involvement, tubulointerstitial disease, and post-renal disease accounted for the remaining cases.

⬇ *Table I. Population characteristics: demographics, comorbidities, and dialysis parameters (n = 61)*

Demographics and comorbidities		
Age (years)		59 ± 13
Gender, male (%)		39 (64%)
BMI (kg/m^2)		26 ± 4
Body surface area (m^2)		1.8 ± 0.8
Diabetes mellitus		20 (33%)
Coronary artery disease		8 (13%)
Cerebral artery disease		5 (8%)
Peripheral artery disease		7 (12%)
Dialysis parameters		
CAPD (vs. cycler)		45 (73%)
Vantive (vs. Fresenius)		35 (57%)
Dialysate volume (L/day)		6 (6-8)
Icodextrin use		35 (57%)
	1 exchange/day	21 (34%)
	2 exchanges/day	14 (23%)

BMI: body mass index; CAPD: continuous ambulatory peritoneal dialysis.

Dialysis characteristics are shown in *Table I*. Most patients (73%) were on continuous ambulatory peritoneal dialysis (CAPD), with the choice largely based on patient preference. Approximately half of the patients (57%) used icodextrin once or twice daily. Median protein concentration was 0.081 g/dL (0.055-0.099) in the 24-h dialysate and 0.046 g/dL (0.039-0.063) in the 4-h

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dialysate. Regarding fluid overload, the median NT-proBNP was 1260 pg/mL (517-3702), the median CA-125 was 13 U/mL (9-23), and the mean extracellular water excess was 1.5 ± 1.6 L. Average handgrip strength was 28 kg and 26 kg in the right and left arms, respectively, with a mean rectus femoris muscle thickness of 13.7 ± 4.4 mm.

Table II. Biochemical, PET, sarcopenia, and BIA parameters (n = 61)

Biochemical evaluation	
Albumin (g/dL)	3.8 (3.5-4.0)
Total proteins (g/dL)	6 ± 0.7
NT-proBNP (pg/mL)	1260 (517-3702)
CA-125 (U/mL)	13 (9-23)
Proteinuria (mg/24 h)	263 (67-744)
Peritoneal equilibration test (PET)	
Kt/V urea	2.19 (1.82-2.74)
Ultrafiltration volume (mL/4 h)	462 ± 236
Urine volume (mL/day)	1557 ± 968
Total volume of water removed (mL/day)	2160 (1770-2600)
eGFR (mL/min/1.73 m^2)	4.1 (2.2-8.1)
Creatinine clearance (L/1.73 m^2/week)	82 (61.3-108)
nPCR (g/kg/day)	0.95 (0.85-1.12)
D/P creatinine	0.72 ± 0.10
CA-125, 4 h (U/mL)	23 ± 10
CA-125, 24 h (U/mL)	24 (17-33)
Peritoneal protein loss, 4 h (g/dL)	0.046 (0.039-0.063)
Peritoneal protein loss, 24 h (g/dL)	0.081 (0.055-0.099)
Sarcopenia evaluation	
Handgrip strength (kg)	
Right arm	28 (22-38)
Left arm	26 (20-38)
Ultrasound evaluation of the rectus femoris (mm)	13.7 ± 4.4
Bioelectrical impedance analysis (BIA)	
Extracellular water excess (L)	1.5 ± 1.6
Lean tissue index (kg/m^2)	11.2 ± 4.5
Lean tissue mass (kg)	32 ± 12.1
Fat tissue index (kg/m^2)	12.4 ± 5.8
Fat mass (kg)	26.3 ± 10.1
Adipose tissue mass (kg)	33.2 ± 15.6

PET: peritoneal equilibration test; BIA: bioelectrical impedance analysis; Kt/V urea: urea clearance index; eGFR: estimated glomerular filtration rate; nPCR: normalized protein catabolic rate; D/P creatinine: dialysate-to-plasma creatinine ratio.

The remaining data, including biochemical evaluation, PET parameters, and BIA results, are detailed in *Table II*. Univariate analysis showed positive associations between protein concentration in the 4-h PET effluent and NT-proBNP (p = 0.001), extracellular water excess (p = 0.018), and lean tissue mass (p = 0.006). A negative association was found between protein concentration in the 4-h PET effluent and fat mass measured by BIA (p = 0.015). The

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results of the univariate regression analyses, including regression coefficients, 95% confidence intervals, and R^2 values, are presented in *Table III*. Albumin, total proteins, handgrip strength, muscle thickness, and other BIA parameters were not associated with protein concentration in either the 4-h PET effluent or the 24-h spent dialysate.

Table III. Univariate linear regression analysis of variables significantly associated with protein concentration in the 4-h PET effluent

Variable	B	95% CI	p-value	R^2
NT-proBNP	3.55×10^{-6}	1.60×10^{-6} to 5.49×10^{-6}	0.001	0.192
Extracellular water excess	0.004	0.001 to 0.007	0.018	0.101
Lean tissue mass	0.001	0.0003 to 0.0017	0.006	0.127
Fat mass	–0.001	–0.0018 to –0.0002	0.015	0.101

B: unstandardized regression coefficient; CI: confidence interval; PET: peritoneal equilibration test; R^2: coefficient of determination.

Discussion

Peritoneal protein loss is a clinically relevant consequence of PD; however, its relationship with key clinical domains such as fluid overload, sarcopenia, and nutritional status remains a subject of debate.

Our study is consistent with recent data reinforcing the absence of a relationship between peritoneal protein loss and sarcopenia, as well as markers of malnutrition [11,12]. This is supported by the lack of association between protein concentration in either the 4-h PET effluent or the 24-h spent dialysate and handgrip strength, muscle thickness, albumin, and total serum proteins. Do et al. evaluated sarcopenia using appendicular lean mass and handgrip strength, finding that peritoneal protein loss is not independently associated with muscle mass or strength in PD patients [11]. Regarding BIA parameters, we found a positive association between lean tissue mass and protein concentration in the 4-h PET effluent. This finding is consistent with previous observations showing an association between higher lean body mass index and greater peritoneal protein clearance in patients on PD [13]. One possible explanation is that greater lean tissue mass may reflect better nutritional status and may be associated with differences in protein metabolism that influence peritoneal protein transport. However, the mechanisms underlying this association remain uncertain and were not directly assessed in our study. A similar rationale may explain the negative association observed between fat mass and protein concentration in the 4-h PET effluent, as greater fat mass may be associated with lower protein turnover. These results challenge the conventional view that higher peritoneal protein loss may lead to hypoalbuminemia and malnutrition.

On the other hand, our study suggests an association between fluid overload and peritoneal protein transport, as evidenced by the statistically significant associations between protein concentration in the 4-h PET effluent and both NT-proBNP and extracellular water excess. These findings are consistent with those reported by other authors [8,12]. Krediet et al. demonstrated in a cohort of 316 incident PD patients that NT-proBNP and right atrial area were significant independent predictors of peritoneal protein clearance [8]. Later, Malho Guedes et al. corroborated this mechanism using BIA, showing that extracellular water excess was a strong independent predictor of peritoneal protein clearance [12].

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Our study has several inherent limitations that must be considered. First, it was a single-center cross-sectional study with a limited number of patients. Second, because the analyses were restricted to univariate methods, the study was unable to account for potential confounding variables. Third, regarding fluid overload, NT-proBNP and extracellular water excess were significantly associated with protein concentration in the 4-h PET effluent, but not in the 24-h spent dialysate. Although the standardized 4-h PET provides a controlled assessment of peritoneal protein transport, the inconsistent findings from the 24-h collection warrant further studies to validate this association and clarify its clinical relevance. Fourth, some additional factors that may influence peritoneal protein transport, such as PD vintage, previous peritonitis episodes, and inflammatory status, were not evaluated in our study. These variables may have influenced the observed associations and should be considered in future studies. Fifth, the lack of a standardized sarcopenia classification according to the EWGSOP2 criteria is another limitation of our study. Finally, lung ultrasound may provide an additional, noninvasive assessment of pulmonary congestion and volume overload in patients undergoing PD and could be incorporated into future studies to provide a more comprehensive evaluation of fluid status and its relationship with peritoneal protein transport.

Conclusion

In conclusion, our study shows that peritoneal protein loss is not associated with sarcopenia or malnutrition in PD patients. Moreover, it highlights an association between fluid overload and peritoneal protein transport. These results emphasize the importance of maintaining euvolemia and appropriate fluid management in these patients. Considering this study's limitations, further prospective longitudinal studies are needed to validate these findings.

Statements

Authors' Contributions

Patrícia Branco conceived and designed the study. Inês Alexandre and Maria Inês Roxo collected and analysed the data. Inês Alexandre drafted the manuscript. All authors contributed to the interpretation of the results, critically revised the manuscript, and approved the final version.

Ethical Considerations

This was an observational, single-center cross-sectional study. Data were collected from routinely available clinical records and were anonymized prior to analysis. No identifiable patient information is reported.

Patient Consent

Individual informed consent was not obtained, as the study involved the analysis of anonymized routinely collected clinical data without any additional intervention.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request, subject to applicable data protection and confidentiality restrictions.

ORCID iDs

Inês Alexandre: https://orcid.org/0009-0004-9482-3055

Maria Inês Roxo: https://orcid.org/0000-0003-1512-8077

Patrícia Matias: https://orcid.org/0000-0003-4344-5555

Rita Calça: https://orcid.org/0000-0001-8960-2363

Patrícia Branco : https://orcid.org/0000-0002-8563-834X

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