Peritoneal protein losses depend on more than just peritoneal dialysis modality and peritoneal membrane transporter status

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Abstract	250
Body	2578
References	39
Tables	4
Supplemental table	1

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Abstract

Background

Peritoneal protein clearance (PPCl) depends upon vascular supply and size selective permeability. Some previous reports suggested PPCl can distinguish fast peritoneal membrane transport due to local or systemic inflammation. However, as studies have been discordant, we wished to determine factors associated with an increased PPCl.

Methods

Consecutive patients starting peritoneal dialysis (PD) who were peritonitis free were studied. Data included a baseline peritoneal equilibration test (PET), measurement of dialysis adequacy, 24-hour dialysate PPCl and body composition measured by multifrequency bioimpedance.

Results

411 patients, mean age 57.2±16.6 years, 60.8% male, 39.4% diabetic, 20.2% treated by continuous ambulatory peritoneal dialysis (CAPD) were studied. Mean PET 4-hour Dialysate/Serum creatinine was 0.73 ±0.13, with daily peritoneal protein loss 4.6 (3.3-6.4) g, and median PPCl 69.6 (49.1-99.6) mL/day. On multivariate analysis, PPCl was most strongly associated with CAPD (β 0.25, $p<0.001$), extracellular water (ECW)/total body water (TBW) ratio (β 0.21, $p<0.001$), skeletal muscle mass index (β 0.21, $p<0.001$), log N-terminal brain natriuretic peptide (NT-proBNP) (β 0.17, $p=0.001$), faster PET transport (β 0.15, $p=0.005$), and normalized nitrogen appearance rate (β 0.13, $p=0.008$).

Conclusions

In addition to the longer dwell times of CAPD, greater peritoneal creatinine clearance and faster PET transporter status, we observed an association between increased PPCl and ECW expansion, increased NT-proBNP, estimated dietary protein intake and muscle mass, suggesting a link to sodium intake and sodium balance, increasing both ECW and conduit artery hydrostatic pressure resulting in greater vascular protein permeability. This latter association may explain reports linking PPCl to patient mortality.

Introduction

An increasing number of patients with chronic kidney disease are treated with peritoneal dialysis (PD) world-wide. After peritonitis [1], failure to prevent extracellular volume expansion [2] is a common cause of patients changing dialysis modality to haemodialysis. Earlier observational studies suggested an association between faster peritoneal transporter status and increased risk for both PD treatment failure and patient mortality [3]. However, later observational studies, including patients treated with automated peritoneal dialysis cyclers (APD) and icodextrin, reported no differences in patient outcomes [4] or extracellular water (ECW) hydration [5] with transporter status.

Peritoneal transporter status depends upon the blood supply to the abdominal cavity. Faster peritoneal transport is associated with greater capillary surface area, which can be found physiologically with larger body size, or pathologically due to local or systemic inflammation [6]. Peritoneal protein clearance (PPCl), has been proposed to separate faster transport status due to inflammatory conditions, as protein clearance is a measure of large

pore flow and is predominantly dependent upon large pore numbers, which are reported to increase with inflammation [6]. As such, an increased PPCl has been suggested to be a marker for increased vascular permeability, and several studies reported an association between increased PPCl with hypoalbuminaemia, PD failure and increased mortality in PD patients [7-9]. However, not all studies demonstrated an association of increased PPCl and mortality [10].

In view of the discrepancy of these reports, and differences between studies as to whether PPCl was affected by patient body size, peritoneal transport status, age, various co-morbid conditions, pulse pressure, C-reactive protein (CRP) and urine output [7-12], we reviewed PPCl at the time of first peritoneal membrane assessment in a cohort of patients starting PD.

Methods

We compared 4-hour peritoneal dialysate effluent creatinine and total protein to corresponding serum samples (S) when PD patients attended for their first routine outpatient peritoneal equilibrium testing (PET) using a standard 22.7 g/L dextrose exchange [13]. All patients using 7.5% icodextrin, had icodextrin drained and a glucose exchange instilled prior to PET. Dialysate (D) creatinine was measured using a kinetic enzymatic method to prevent glucose interference (P module analyzer, Roche Integra, Roche diagnostics, Lewes, UK) [14]. Serum and dialysate total protein were measured by a modified biuret method (colorimetric assay based on divalent copper reacting in alkaline

solution with protein peptide bonds to form a characteristic purple-coloured biuret complex, measuring increased absorbance at 546 nm), and peritoneal dialysate protein using pyrogallol red which complexes with proteins in an acid environment containing molybdate ions, and measuring absorbance at 600nm. This method is linear at lower protein concentrations, but higher concentration samples above 1.25 g/L were diluted to bring them into range [8]. Serum albumin was measured by bromcresol green method, and N terminal brain natriuretic peptide (NT-proBNP) (P module analyzer, Roche Integra, Roche diagnostics, Lewes, UK).C-reactive protein (CRP) was measured using the same assay as the UK National Amlyoid centre, with values reported to < 1 mg/L [15,16], and haemoglobin by an automated counter (Sysmex XN900, Sysmex Corporation, Kobe, Japan) [17]. Multifrequency bioelectrical impedance assessments (MFBIA) were made using a standard protocol (InBody 720 Body Composition Analysis, Biospace, Seoul, South Korea), with the dialysate drained out at the end of the PET [18,19]. Extracellular water volume (ECW) excess was expressed as the ratio of ECW to total body water (TBW).

Data was available from 411 consecutive adult PD patients attending for their first peritoneal membrane assessment [13], with corresponding MFBIA measurements. Patients with pacemakers and amputees were excluded from MFBIA. We also excluded patients who had had a previous episode of peritonitis. These were routine tests performed on stable outpatients, at least six weeks after any hospital admission. Patient co-morbidity was assessed using the Stoke-Davies grade [20], and primary renal disease categorized as diabetic nephropathy, glomerular disease, tubular-interstitial disease, hypertensive

diseases, and unknown. Patient peritoneal transporter status was determined by 4-hour peritoneal to serum creatinine ratios [13]. Normalised nitrogen appearance rate (nPNA) was estimated using the Bergström equation [21], skeletal muscle mass by MFBIA [22] and indexed to height, and peritoneal and urinary clearances estimated by standard equations [13]. Peritoneal protein clearance was calculated as suggested by Haraldsson [23], from 24-hour total peritoneal protein losses and expressed as ml of plasma cleared per day (mL/day). Daily estimated sodium losses were calculated by the difference between peritoneal dialysate effluent and urinary sodium and sodium content of dialysate infilled.

Statistical Analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, or percentage. ANOVA or Kruskal Wallis, with appropriate correction for multiple analyses were used to compare groups. Spearman correlation used for univariate analysis, and all variables with a statistical association of $p<0.1$, and those thought to be of clinical significance (gender, PET transporter, primary renal disease, prescription of 7.5% icodextrin and 22.7 g/L dextrose, and anti-hypertensive medications), were used to create a multivariable model to determine associations with PPCl. Variables which were not significant and did not improve model fit, or demonstrated co-linearity or increased variable inflation factor, were excluded in a step backward model. If required, nonparametric variables were log transformed. Statistical analysis was performed using

Graph Pad Prism (version 6.0, Graph Pad, San Diego, CA, USA, and SPSS version 24.0). Statistical significance was taken at or below the 5% level.

Our retrospective audit complied with NHS guidelines (UK NHS guidelines for clinical audit and service development, available at http://www.hra.nhs.uk/documents/2013/09/defining-research.pdf, and http://www.gov.uk/government/publications/health-research-ethics-committees-governancearrangements). Individual consent was waived as all laboratory tests and MFBIA had been performed as part of the routine clinical care of kidney dialysis patients in keeping with the standard operating policy and no patient identifiable data was used.

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Results

We reviewed the records of 411 consecutive adult patients attending for their first assessment of peritoneal membrane function 2 (2-3) months after PD catheter insertion and training, mean age 57.2±16.6 years, 60.8% male, 39.4% diabetic. Mean body weight 73.8 ±16.3 kg, muscle mass index 9.98±2.18 kg/m^2, percentage body fat 26 (23-30), body surface area 1.86±0.25 m^2, body mass index 26.5 ±5.2 kg/m^2, and percentage ECW/TBW ratio 39.7±1.5 Median Stoke-Davies co-morbidity grade 1 (0-1). Mean haemoglobin was 110±15.1 g/L, serum albumin 36.7±4.8 g/L, total protein 65.3±6.7 g/L, urea 195 ±5.6 mmol/L, median serum creatinine 539 (426-718) umol/L, glucose 5.7 (4.7-9.1) mmol/L, C-reactive protein 4.0 (1.0-9.0) mg/L, NTproBNP 1924 (697-5539) pg/L. Mean arterial blood pressure 100 ±16.7 mmHg, pulse pressure (difference between systolic and diastolic

pressures) 58.9 ±19.7 mmHg, with 336 (81.8%) patients prescribed antihypertensive medications, median number of agents 1 (1-2) (beta blockers 43%, calcium channel blockers 40.1%, angiotensin receptor blockers or angiotensin converting enzyme inhibitors 31.4%) and 85.9% loop diuretics. In addition to standard 13.6 g/L dextrose dialysates, 33% were prescribed 22.7 g/L dextrose (median 0 (0-4) l/day), and 73.1% 7.5% icodextrin (median 1.0 (1.0-1.5) L/day). Median urine output was 1121 (613-1700) mL/day, urinary protein 1.25 (0.59-2.44) g/day, and average of combined urea and creatinine clearance 5.1 (3.1-7.6) mL/min/1.73m^2. Mean peritoneal equilibration test (PET) 4-hour D/S creatinine was 0.73 ±0.13, 4-hour D/S total protein 0.011±0.010, ultrafiltration volume 200 (110-400) mL, PET protein loss 0.57 (0.41-0.84) g. Median weekly peritoneal urea clearance (Kt/Vurea) 1.1 (0.84-1.37), 24-hour peritoneal ultrafiltration386 (116-722) mL/day, protein loss 4.6 (3.3-6.4) g/day, with a median PPCl 69.6 (49.1-99.6) mL/day.

20% were treated by continuous ambulatory peritoneal dialysis (CAPD), the remainder on cyclers with 25.8% on overnight cyclers with no day time exchange (APD) and the remainder utilizing a day time exchange, continuous cycling peritoneal dialysis (CCPD) (table 1). Patients treated by CAPD were older, with higher NT-proBNP, and greater ECW/TBW ratio and lower muscle mass (table 1). Those treated by APD without a day time exchange had greater residual renal function, and urinary protein excretion was greater for those treated by CCPD. Serum total protein was similar between PD modalities. 24-hour PD protein loss and PPCl were greater for the CAPD cohort. Although patients

treated by APD had lower PET 4-hour D/S creatinine ratios, the 4-hour D/S total protein was higher.

We then determined whether primary renal disease had an effect on PPCl. Patients with glomerular disease were generally younger, and those with diabetic nephropathy greater ECW/TBW ratios, and NT-proBNP values were higher in those with diabetic nephropathy and hypertensive nephropathy (table 2). Serum protein and PET results were not different between the groups. Residual renal function was similar, although urinary protein losses were greater for those with diabetic nephropathy and those with glomerular diseases. PPCl was lower in those patients with glomerular disease.

Comparing patients according to PET creatinine transporter status, the fast transporters had lower total serum protein, greater PET and 24-hour protein losses, and greater PPCl (Table 3). More male patients were faster transporters than slow transporters, and faster transporters had greater muscle mass compared to slow transporters. ECW/TBW ratios were greatest for the faster transporters.

On univariate analysis serum total protein, NT-proBNP, ECW/TBW, PET 4-hour D/S creatinine, 24-hour glucose absorption, serum albumin, age, Stoke-Davies co-morbidity and pulse pressure were all highly associated with PPCl ($p<0.001$) (supplemental table). Peritoneal ultrafiltrate, prescription of 22.7% glucose and net daily sodium losses were also associated with PPCl ($p<0.01$). We then chose variables which were associated with PPCl on univariate analysis and constructed a multivariable model to determine which factors were independently associated with PPCl (table 4). As expected faster PET

transporter status, and CAPD modality were associated with greater PPCl, as were skeletal muscle mass index and nPNA, and greater peritoneal creatinine clearance. However, PPCl was also associated with greater ECW/TBW ratios and NT-proBNP concentrations, and negatively with both serum total protein concentration and urinary protein loss.

Discussion

Peritoneal protein transport is much slower than that of creatinine, and as such the 4-hour D/S total protein to creatinine ratios were around one hundred times lower. Peritoneal protein losses were greater with the longer CAPD dwell exchanges compared to APD cyclers without a day time exchange, and PPCl was greater for those treated by CAPD compared to both APD and CCPD. Similarly, 4-hour-PET protein losses and 24-hour peritoneal protein losses and PPCl were greater for those patients classified as fast transporters. In addition, PCCL was greater for those with greater peritoneal creatinine clearance.

Previous reports have differed as to whether primary renal diseases have an effect on peritoneal protein excretion, with some suggesting increased protein excretion in those with diabetic nephropathy and diabetes [12,24,25]. We were unable to confirm this suggestion made in much smaller cohorts of patients. However, we did find that PPCl was lower in patients classified as having glomerular diseases as the primary cause of renal disease. These patients, and those with diabetic nephropathy, had the greatest urinary

protein losses, and, on multivariable testing, greater urinary protein loss was associated with lower PPCl.

Reports suggested increased PPCl in older patients [7,25], although several other observational studies reported no effect of age [9,26]. We noted a univariate association with patient age, but in our cohort more older patents were treated by CAPD, whereas younger and more active patients were treated by APD and CCPD. However, on multivariable testing, patient age was no longer a significant factor. PPCl could also be affected by the intra-abdominal capillary surface area available for transport, and several studies have reported greater PPCl in male patients [9,25,27], although others found no effect with gender [10,26]. We did not note an effect of gender, but noted that patient size, as expressed by ICW, ECW, skeletal muscle mass and height, were all associated with PPCl on univariate analysis, but not weight, body mass index or body surface area. Previous authors have commented that although the intra-abdominal capillary surface area increases with body size, there is no simple relationship to weight, body mass index or body surface area [7].

Previous reports have reported various associations between hypertension [25], and pulse pressure [9], and PPCl, and in theory raised intravascular hydrostatic pressure could increase PPCl. On the other hand, others found no effect of blood pressure [27]. We noted a univariate association with pulse pressure, and systolic pressure, but not mean arterial blood pressure, or anti-hypertensive medications prescribed. There was also an association with sodium losses, and assuming patients were in a steady state, then this may be an

estimate of sodium intake. Dietary sodium intake is often linked to protein intake [28], and accumulation of sodium in tissues can lead to an increase in vascular stiffness [29], and pulse wave velocity [30]. A positive sodium balance would be expected to expand the ECW and increase cardiac natriuretic peptides. On multivariable analysis, PPCl was greater in those patients with greater dietary protein intake, muscle mass, and higher serum NT-proBNP and ECW/TBW ratios, which may suggest an association with greater sodium intake.

Many previous observational studies have noted a relationship between PCCL and increasing co-morbidity [9,10,12]. Although there was a strong univariate association between PPCl and Stoke-Davies co-morbidity grading, this was lost on multivariable analysis. However, we report an independent association between PPCl and both ECW/TBW and NTproBNP. Increased ECW and NT-proBNP are increased in cases of volume overload in peritoneal dialysis patients [31,32], but ECW/TBW and NT-proBNP can also be increased in inflammatory states [15], which also can increase capillary protein leakage [6,33]. In keeping with previous reports, we noted that faster peritoneal transport and diabetes were associated with greater ECW/TBW ratios and NT-proBNP [34]. As increased NT-proBNP and ECW/TBW are associated with an increased risk for mortality [35]. This may well explain the previously reported link between PPCl and increasing co-morbidity, particularly cardiovascular and mortality [9, 12, 25,26]. However, the ability to alter peritoneal dialysis prescriptions to adjust for volume status [35], to transfer

patients to haemodialysis with ultrafiltration failure and achieving target weights may partially explain the differences in mortality reported between studies [10,27].

We found no effect of residual renal function on PPCl, although residual renal protein losses appeared to be associated with a reduction in PPCL. Previous studies in PD patients have not demonstrated a strong association between ECW and residual renal function [36,37], although generally patients with residual renal function are less likely to be volume overloaded [38].

There have been numerous reports linking PPCl to mortality. In some studies, this has been reported only to be with PPCl measured during the 4-hour PET, others only found an association with 24-hour dialysate collections, and other studies reporting no increased risk with PPCl. In view of the differences between reports we reviewed the results of PPCl obtained in a larger cohort of PD patients initiating dialysis, compared to previous studies. As expected we found that that PPCl was dependent upon dwell time and peritoneal transport status, with greater clearances with longer dwell times and faster peritoneal transporter status, and similarly greater peritoneal protein clearance was linked to greater peritoneal creatinine clearance. However, PPCl was not associated with gender, or body mass index, or primary renal disease, but was greater for those patients with increased ECW/TBW ratios and NT-proBNP, suggesting an association with ECW expansion. As PPCl was also increased in those patients with greater estimated dietary protein intake and skeletal muscle mass, this would suggest a possible association with

greater energy expenditure [39], with greater sodium intake. Increased sodium balance would link ECW expansion, increased NT-proBNP and increased conduit arterial stiffness and transcapillary protein transport by hydrostatic pressure [29,33]. As such our findings show that choice of peritoneal dialysis modality, peritoneal dialysis creatinine clearance and peritoneal transporter status determine peritoneal protein losses. In addition, PPCL is greater in patients with ECW expansion, and increased NT-proBNP accounting for previous reports linking PPCL to patient mortality.

The authors have no conflict of interest
The data contained in this paper have not been previously published in whole or part, except in abstract format.

Table 1. Patient demographics according to peritoneal dialysis modality.
Patients treated by peritoneal dialysis (PD) with continuous ambulatory peritoneal dialysis (CAPD, automated peritoneal dialysis cycler with no day time fill (APD), and automated peritoneal dialysis cycler with a day time exchange (CCPD) at the time of their first peritoneal membrane assessment. 4 hourly peritoneal equilibration test (PET) dialysate to serum ratio (4-hour D/S). Prescription of angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB). N terminal brain natriuretic peptide (NT-proBNP), extracellular water/total body water ratio (ECW/TBW), skeletal muscle mass (SMM). Results expressed as integer, percentage, mean ±standard deviation, median (interquartile range). * p <0.05, ** p<0.01, ***p <0.001 vs CAPD.

variable	CAPD	APD	CCPD
Male (%)	46 (55.4%)	57 (55.3%)	147 (65.3%)
Age years	65.8±15.8	57.1±16.1**	54.1±16.1***
Diabetic (%)	41 (10)	31 (7.5)	90 (21.9)
Dialysis duration months	2.3±1.1	2.2±1.1	2.3±1.1
Weekly urinary Kt/Vurea	1.45(0.95-2.08)	1.59(1.04-2.31)	1.13(0.71-1.85)***
Weekly peritoneal Kt/Vurea	0.84(0.44-1.34)	1.0 (0.75-1.24)	1.21(0.98-1.44)***
Total weekly Kt/Vurea	2.45(1.94-3.09)	2.61(2.05-3.32)	2.38(1.91-3.08)
4hour D/Screatinine	0.79±0.13	0.62±0.13***	0.75±0.11*
4hour D/Sprotein x 100	1.25 (0.84-1.94)	1.51 (0.74-1.52)*	0.73(0.55-1.0)***
PET protein loss g	0.84 (1.53-1.19)	0.67 (0.51-0.93)*	0.47(0.37-0.62)***
Serum total protein g/L	64.4 ±6.3	66.2 ±6.1	65.2 ±7.1
24 hr PD protein loss g/day	6.3 (3.9-8.5)	4.0 (3.0-5.8)***	4.3 (3.3-5.9)**
Peritoneal protein clearance mL/day	95.8(59.8-126.1)	63.4(49.2-87.6)***	67.3(49.7-89.5)***
Urinary creatinine clearance mL/min/1.73m^2	6.8 (4.2-11.5)	7.6 (4.9-10.9)	5.9 (3.6-9.8)
urinary protein loss g/day	0.8 (0.2-1.9)	1.3 (0.6-2.4)	1.4 (0.7-2.9)*
Prescribed ACEI/ARB (%)	26 (6.3)	32 (7.8)	71 (17.3)
NT-proBNP pg/mL	2613 (1074-11323)	1400 (592-3996)**	2017 (693-5649)*
Percentage ECW/TBW ratio	40.3 ±1.3	39.4 ±1.3***	39.6 ±1.5**
SMM kg	25.2 ±6.5	27.6 ±7.5**	29.7 +8.9***

Table 2. Protein losses according to primary renal disease.
4 hourly peritoneal equilibration test (PET) dialysate to serum ratio (4hour D/S), skeletal muscle mass (SMM), percentage ratio extracellular to total body water (%ECW/TBW), n terminal probrain natriuretic peptide (NT-proBNP). Results expressed as integer, percentage, mean ±standard deviation, median (interquartile range) or percentage. * p <0.05, ** p<0.01, ***p <0.001 vs Diabetic nephropathy.

	Diabetic nephropathy	Glomerulo-nephritis	Interstitial disease	hypertension	unknown
Number	123	110	64	65	44
Male (%)	78 (62.9%)	59 (56.2%)	41 (56.2%)	45 (69.2%)	27 (61.4%)
Age years	60.5±13.9	48.1±16.1***	54.7±16.4	64.1±15.9	63.9±16.4
Serum total protein g/L	66.6±6.3	64.4±6.8	66.3±7.6	65.6±6.3	67.4±6.4
PET protein loss g	0.57(0.43-0.82)	0.45(0.35-0.71)	0.65(0.46-1.0)	0.61(0.45-0.89)	0.58(0.44-0.9)
4hour D/Sprotein x 100	0.84(0.65-1.25)	0.74(0.53-1.09)	0.97(0.71-1.59)	0.91(0.69-1.36)	0.85(0.66-1.51)
4hour D/Screatinine	0.74±0.12	0.70±0.13	0.74±0.15	0.73±0.13	0.73±0.13
24 hour PD protein loss g/day	4.94(3.49-6.97)	3.6(2.5-5.6)	5.3(3.6-6.7)	5.1(3.8-6.4)	4.9(3.8-6.5)
Peritoneal protein clearance mL/day	76.9(52.1-112.7)	55.5(38.0-84.0)**	74(52.2-105.8)	77.3(55.0-97.6)	73.8(53.0-98.7)
urinary protein loss g/day	1.7(0.8-3.8)	1.8(0.9-2.8)	1.0(0.6-2.2)**	0.6(0.3-1.5)***	0.9(0.4-1.4)***
Urinary creatinine clearance mL/min/1.73m^2	6.5(3.9-10.1)	7.1(4.2-10.7)	6.6(4.1-10.2)	6.9(4.2-11.7)	5.8(3.8-8.8)
NTproBNP pmol/L	2605 (1216-6808)	1218 (592-4220)	1378 (564-4068)	3645 (1252-11603)	2309 (626-5402)
%ECW/TBW	40.4±1.2	39.0±1.2***	39.4±1.4***	39.7±1.6**	39.6±1.6*
SMM kg	28.0±6.5	27.6+7.5	28.2+6.1	28.4±9.7	28.6±12.8

Table 3. Patient demographics in patients treated by peritoneal dialysis (PD) transporter status based on 4-hour peritoneal equilibration test (PET).

Dialysate to serum creatinine ratio (4hour Dialysate/Serum creatinine) [14].). N terminal brain natriuretic peptide (NT-proBNP), extracellular water/total body water ratio (ECW/TBW), skeletal muscle mass (SMM). Results expressed as integer, percentage, mean ±standard deviation, median (interquartile range) or percentage. * p <0.05, ** p<0.01, ***p <0.001 vs Fast transporter.

	Slow	Slow average	Fast average	Fast
Number (%)	27 (6.6)	108 (26.5)	166 (40.7)	107 (26.2)
Male (%)	6 (22.2%)*	64 (59.3%))	106 (63.9%))	74 (71.2%)
Age years	56.2 ±17.7	53.3 ±17.8*	57.8 ±14.8	60.3 ±17.4
Diabetic (%)	6 (1.5)	36 (8.8)	71 (17.4)	47 (11.5)
Serum total protein g/L	68.7±5.0***	67.0±6.2***	65.1±6.6	63.1±7.1
PET protein loss g	0.54(0.41-0.64)***	0.49(0.38-0.67)***	0.53(0.4-0.71)***	0.83((0.51-1.28)
4hour D/Sprotein x 100	0.75(0.61-0.9)**	0.74(0.53-1.0)***	0.84(0.61-1.15)***	1.26(0.79-2.05)
24 hr PD protein loss g/day	3.7(3.0-5.3)**	3.8(2.7-5.5)****	4.6(3.5-6.2)***	6.0(3.9-9.1)
Peritoneal protein clearance mL/day	54.0(43.5-80)***	55.6(39.2-82.9)***	71.6(52.1-94.1)***	90.4(60.7-148.7)
urinary protein loss g/day	0.5(0.3-1.2)*	1.7(0.7-2.5)	1.3(0.6-2.5)	1.1(0.4-2.7)
Urinary creatinine clearance mL/min/1.73m^2	7.9(6.3-10.6)	6.9(4.3-11.3)	6.7(4.1-10.5)	6.0(3.3-10)
NTproBNP pmol/L	1370 (746-3417)	1387 (491-3315)	1894 (693-5193)	3582 (1269-13780)
%ECW/TBW	39.3 ±1.1**	39.1 ±1.5***	39.7 ±1.3***	40.3 ±1.5
SMM kg	22.8 ±5.1*	28.0 ±9.3	29.1 ±8.4	28.0 ±5.9

Table 4. Peritoneal protein clearance multivariable model.

Extracellular water (ECW) and Total Body water (TBW) peritoneal dialysis (PD) mode (automated peritoneal dialysis vs continuous ambulatory peritoneal dialysis), skeletal muscle mass (SMM), N terminal probrain natriuretic peptide (NTproBNP), normalised nitrogen appearance rate (nPNA), peritoneal dialysis equilibrium test creatinine (4hour Dialysate/Serum creatinine). Standard error of β (StE β), standardised β (St β), 95% confidence interval (95% CI). Multivariable model r=0.61, r^2=0.38, adjusted r^2=0.36.

Variable	β	StE β	St β	t	95% CI	p
PD mode (APD vs other modes)	-14.6	3.0	-0.25	-4.9	-20.5 to -8.7	<0.001
ECW/TBW ratio	631	176	0.21	3.6	285 to 977	<0.001
SMM Index kg/m^2	4.2	0.4	0.21	4.4	2.4 to 6.0	<0.001
Log NT-proBNP pg/L	11.6	0.2	0.17	3.4	4.9 to 18.4	0.001
4 hourD/Screatinine)	51.4	18.2	0.15	2.8	15.5 to 87.3	0.005
24 hour urine protein g/day	-2.9	1.0	-0.13	-2.8	-4.9 to -0.8	0.006
nPNA g/kg/day	23.8	8.9	0.13	2.7	6.3 to 41.2	0.008
Serum total protein g/L	-0.81	0.3	-0.12	-2.5	-1.5 to -0.2	0.015
peritoneal creatinine clearance L/wk/1.73m^2	0.57	0.2	0.18	3.5	0.3 to 0.7	0.016

Supplemental Table. Univariate association with peritoneal protein clearance.

Spearman correlation. Peritoneal equilibrium test (PET). Variables in descending order of association.

Variable	r	p
24hour protein loss g	0.98	<0.0001
4 hour PET Dialysate/serum protein ratio	0.62	<0.0001
4 hour PET protein loss g	0.57	<0.0001
Serum N terminal brain natriuretic protein pg/L	0.42	<0.0001
Extracellular Water/total body water ratio	0.39	<0.0001
Serum total protein g/L	-0.38	<0.0001
4 hour PET Dialysate/Serum creatinine ratio	0.38	<0.0001
Peritoneal creatinine clearance L/week	0.38	<0.0001
Glucose absorption mmol/day	0.28	<0.0001
Serum albumin g/L	-0.28	<0.0001
Age year	0.24	<0.0001
Stoke-Davies comorbidity grade	0.23	<0.0001
Extracellular Water L	0.21	<0.0001
Volume 22.7% glucose dialysate L/day	0.18	0.0003
Pulse pressure mmHg	0.19	0.0002
Weekly Urinary Kt/V urea	-0.15	0.0029
Weekly Peritoneal Kt/Vurea	0.16	0.0013
Serum C reactive protein mg/L	0.16	0.0020
Daily Sodium loss (urine and peritoneal) mmol	0.15	0.0045
Haemoglobin g/L	-0.15	0.0043
Peritoneal Ultrafiltration volume mL/day	-0.14	0.0072
Intracellular water L	0.13	0.0120
Skeletal muscle mass kg	0.13	0.0107
Litres peritoneal dialysate prescribed/day	0.17	0.008
Urinary Creatinine clearance ml/min/1.73m2	-0.13	0.012
Blood glucose mmol/L	0.11	0.036
Height m	0.12	0.021
Systolic blood pressure mmHg	0.12	0.017

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