Protein losses and urea nitrogen underestimate total nitrogen losses in peritoneal dialysis and haemodialysis patients

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Abstract

Background

Muscle wasting is associated with increased mortality and is common in dialysis patients. Haemodialysis (HD) and peritoneal dialysis (PD) treatments lead to protein losses in effluent dialysate. As haemodiafiltration (HDF) protein losses may be of nutritional significance, we compared losses between dialysis modalities.

Methods

We measured total protein, urea and total nitrogen in effluent dialysate from 24-hour collections from PD patients, and during HDF and HD sessions, and determined urea and protein nitrogen.

Results

Dialysate protein losses were measured in 68 PD and 40 HD patients. Sessional losses of urea (13.9 (9.2-21.1) vs. 4.8 (2.8-7.8) g); protein (8.6 (7.2-11.1) vs. 6.7 (3.9-11.1) g) and nitrogen 11.5 (8.7-17.7) vs. 4.9 (2.6-9.5) g), were all greater for HD than PD, $p<0.001$. Protein-derived nitrogen was 71.9 (54.4-110.4) g for HD and 30.8 (16.1-59.6) g for PD. Weekly protein losses were lower with HD 25.9 (21.5-33.4) vs. 46.6 (27.-77.6) eek, but nitrogen losses were similar. We found no difference between high-flux HD and HDF: urea (13.5 (8.8-20.6) vs. 15.3 (10.5-25.5) g); protein (8.8 (7.3-12.2) vs. 7.6 (5.8-9.0) g) and total nitrogen 11.6 (8.3-17.3) vs. 10.8 (8.9-22.5) g). Urea nitrogen (UN) only accounted for 45.1 (38.3-51.0)% PD and 63.0 (55.3-62.4)% HD of total nitrogen losses.

Conclusion

Although sessional losses of protein and UN were greater with HD, weekly losses were similar between modalities. We found no differences between HD and HDF. However, total nitrogen losses were much greater than the combination of protein and UN, suggesting greater nutritional losses with dialysis than previously reported.

Introduction

Muscle wasting is associated with an increased risk of morbidity and mortality [1]. Patients with chronic kidney diseases are potentially at increased risk of muscle loss, due to combinations of dietary restrictions, vitamin deficiencies, changes in anabolic hormones and insulin resistance, metabolic acidosis and the effects of uraemic toxins [2], along with physical inactivity [3]. In addition, although dialysis treatments clear retained waste products of metabolism, dialysis is non-selective, and so can potentially clear useful nutrients, including glucose and proteins. As such, clinical guidelines have recommended greater dietary protein intakes than for the general population to compensate for protein losses during dialysis [4-6].

Older studies have reported removal of amino acids (varying between 6 to 12 g per haemodialysis session), some peptides, and small amounts of protein (≤ 1 to 3 g per dialysis session) [4-7]. However, the practice of haemodialysis (HD) has changed over time, and previous reports of higher protein losses were associate with dialyzer re-use [7], and reprocessing dialyzers with bleach [8]. Most centres now use dialyzers with larger pore sizes designed to deliver high flux dialysis, and in Europe the introduction of haemodiafiltration (HDF), adding convective transport which increases middle molecule clearances compared to diffusional clearance with haemodialysis, has the potential to increase nutritional losses [5].

Similarly, older studies in peritoneal dialysis (PD) patients have suggested daily peritoneal dialysate losses of 5-15 g of protein and around 2-4 g of amino acids [10]. Again, peritoneal dialysis has changed from intermittent PD with the introduction of continuous ambulatory peritoneal dialysis (CAPD), automated cycler peritoneal dialysis (APD), and changes in dialysates and connectology. The older studies have comprised small series, typically less than 30 patients, and with measurements of either protein, or peptides or amino-acids, but not total nitrogen losses. We therefore wished to measure total nitrogen losses in a contemporary cohort of dialysis patients, including patients treated by HDF, to determine whether nitrogen losses were different between modalities, and were greater than in earlier studies.

Patients and Methods

Aliquots of PD dialysate effluents were obtained from adult PD patients attending for peritoneal membrane testing [9]. Pooled samples from 24-hour PD effluents were obtained from patients treated by automated peritoneal dialysis (APD) with and without a daytime exchange, and from individual dialysate effluents for those patients treated by continuous ambulatory peritoneal dialysis (CAPD). Aliquots of haemodialysis effluents were sampled at 5, 30, 60 minutes, and then at the end of the dialysis session in patients attending out-patient dialysis sessions, and losses calculated by area under the curve. Dialysate effluent measurements were then adjusted for dialysate volumes to determine total sessional/daily losses.

Serum total protein, and HD dialysate effluent protein were measured by colorimetric assays. PD dialysate protein was measured using pyrogallol red-molybdate (PRM) (Hitachi 726 auto analyser, Maidenhead UK). This method is linear up to 2.14 g/L, and higher concentration samples were diluted to bring them into range [10]. Protein was also measured using a modified Lowry method (BioRad DC protein assay, BioRad, Hemel Hempstead, UK). We also tested to ensure that urea did not interfere with the BioRad protein assay. The commonly used conversion factor of 6.25 was used to determine the protein equivalent of nitrogen (i.e 6.25g protein is equivalent to 1g nitrogen).

Effluent dialysate urea concentration was determined by the diacetyl monoxime colorimetric assay, using appropriate standards [11]. This test was specifically chosen as most 'urea' assays (glutamate dehydrogenase based) used by chemical pathology laboratories actually assay urea plus ammonia. Testing confirmed that exogenous ammonia did not interfere with the assay. Dialysate urea was also measured using the Cobas UREAL assay (Roche Diagnostics, West Sussex, UK), which assays urea plus ammonia. Dialysate urea nitrogen was determined by adjusting for the nitrogen content of urea; 1 mole urea is equivalent to 28g nitrogen.

Total nitrogen concentration was determined using an Antek MultiTek® nitrogen analyser (MultiTek, Houston, USA) and Antek MultiTek Software (version 2.0.0.0) by PAC. The mean of three measurements was recorded, and if the relative standard deviation of the three measurements was > 5%, then sample measurements were repeated. Coefficient of variation of the assay ranged from 0.7-1.0%.

All haemodialysis patients were dialyzed using high-flux polysulfone haemodialyzers (Elisio-H™, Nipro Europe, Zaventem, Belgium) [13], dialyzer surface area 1.5-2.1 m^2, and BBraun Dialog+ machines (B.Braun, Melsungen, Germany). Patients were either treated by haemodialysis or on-line haemodiafiltration (HDF). Low-molecular weight heparin was used for dialysis circuit anticoagulation [14]. Dialysate water quality met current national bacteriological and chemical standards for ultra-pure water. All peritoneal dialysis patients used lactate based peritoneal dialysis fluids, and 7.5% icodextrin for overnight exchange with CAPD and day time exchange with APD (Baxter Health Care, Deerfield, USA).

Statistical Analysis

Results are expressed as mean ± standard deviation, or median and interquartile range, or percentage. Students' t test was used for parametric and the Mann Whitney U test for nonparametric data, with appropriate correction for multiple analyses where appropriate, and Spearman correlation used for non-parametric data. Statistical analysis was performed using Graph Pad Prism (version 7.0, Graph Pad, San Diego, CA, USA) and Statistical Package for Social Science version 24.0 (IBM Corporation, Armonk, New York, USA) and Analyse-It (Analyse IT 4.0, Leeds, UK). Statistical significance was taken at or below the 5% level.

This project was registered Integrated Research Application System (IRAS) reference number 191812/893749/14/564 was approved by the National Research Ethics (Manchester) and the Royal Free Hospital Research and Development Service and complied with NHS guidelines (UK NHS guidelines for clinical audit and service development). Individual consent was waived as we only analysed waste samples. In keeping with the Royal Free Hospital Trust policy no patient identifiable data was used.

Results

We measured dialysate protein losses in 68 PD and 40 HD patients (Table 1). The majority of patients were treated by APD and HDF. Pre-dialysis serum urea and haemoglobin were significantly greater in the HDF cohort (Table 2), and urea greater in patients treated by CAPD compared to APD, who used more dialysate per day (Table 3). Using the PRM method, the amount of protein in effluent dialysate was below the limit of detection (0.4 mg/L) for haemodialysis patients, compared to a mean of 0.09 mg/L (range 0.005 to 1.5 mg/L) with the BioRad DC assay. Daily protein dialysate losses in the PD patients were 4.86 ±4.09 g/day using the PRM method, and 7.79 ±4.96 with the BioRad DC assay. Correlation between assays, r^2=0.35, p<0.001, although the mean Bland Altman bias 3.3 (95% limits of agreement -4.2 to 10.8 g), there was a systematic bias with the PRM method giving higher results when protein concentrations were low, and the BioRad DC giving higher results at higher concentrations.

Urea concentrations were also measured by two different methods. The correlation between methods was r^2=0.24, p;<0.001. On Bland Altman analysis, the mean bias for the UREAL method over the colorimetric method was 4.65 (-0.7 to 10) g of urea. There was no systematic bias between methods.

Protein loss during haemodialysis session was greatest at 5 minutes; 0.19±0.11 g/L, compared to 30 minutes; 0.12 ±0.06 g/L, and 0.09 ±0.04 g/L after 60 minutes (all p<0.001 vs. 5 minutes), there after there was no significant difference in protein losses during the dialysis session, with an ending dialysate protein concentration 0.07 ±0.04 g/L.

The amount of urea, protein and total nitrogen lost during dialysis was significantly greater during a single haemodialysis session compared to the 24- hour losses with peritoneal dialysis (Table 4). There were no significant differences in total losses between HD and HDF sessions, although after 5- minutes protein losses were greater with HDF (0.18 [0.15-0.25] vs. 0.13 [0.09-0.16] g/L, p=0.03). We compared protein losses with dialyzer sizes, but did not find a difference between 1.7 and 2.1 m^2 dialyzers (8.74 [7.36-13.89] vs. 8.77 [7.01-10.15] g/session). There was no relationship between serum albumin or total protein loss and dialysate protein losses. Urea removal was greater for APD compared to CAPD, and although not significant, protein losses were marginally greater for CAPD (Table 4). There was no association between the length of time patients had been on dialysis therapy (in months) and dialysate protein losses. However, protein losses were less for PD faster transporters (r^2=0.44, p<0.01).

Whereas haemodialysis is a thrice weekly treatment, PD is a daily treatment. As such, we examined weekly losses between dialysis modalities, and weekly protein losses were greater for PD patients (Figure 1), whereas there was no difference in weekly total nitrogen losses (PD 34.5 [18.0-66.8] vs. 34.5 [26.1-53.0] g/week).

We then compared urea nitrogen and protein equivalent nitrogen to total nitrogen losses (Table 4). Urea nitrogen losses accounted for only around 50% of total nitrogen losses for both PD and HD treatments, with protein-derived nitrogen losses being relatively greater for HD session losses compared to daily PD losses. However, overall for both modalities total nitrogen loss was around 30% greater than that attributable to urea and protein losses. The weekly median difference between total nitrogen losses and that from urea and protein was similar for HD and PD (11.0 and 11.5 g nitrogen/week). Although not statistically different the median difference was marginally greater for HDF compared to HD, 11.7 vs 7.3 g/week (33.7 vs 25.2%).

Discussion

This study demonstrates that although the losses of nitrogen, protein and urea were higher during sessions of haemodialysis than during peritoneal dialysis, the greater length of time that patients experienced peritoneal dialysis led to an equalisation of these losses. This is an important finding because it implies that need to correct this loss of nutritional nitrogen is the same for patients receiving either therapy. We did not compare net glucose loss or gain during either type of dialysis, and as such cannot comment on net glucose balance during dialysis, which can be substantial [15]. A second finding was that we were unable to balance the nitrogen accountancy. Total nitrogen losses were much greater than the combination of protein and urea nitrogen and suggests a "missing" nitrogen fraction. Nutritional losses of nitrogen during dialysis may be greater than previously reported [4].

Previous investigations of "protein losses" during dialysis treatments measured amino acids, specific peptides, albumin, selected proteins or total protein, or used urea losses to estimate protein losses [7,8, 16-19]. However, many of these studies are more than 30 years old, when dialysis practices differed. Historically, direct measurement of total nitrogen in body fluids using the Kjeldahl method was cumbersome and time consuming [20]. However, automated chemiluminescence measurements of total nitrogen are easier and faster [21,22]. We therefore used this methodology to measure nitrogen losses in dialysate effluents, and to compare losses with those of traditional measurements of total protein and estimates of nitrogen in urea.

We used two methods to measure total protein in dialysates, the pyrogallol red-molybdate (PRM) and modified Lowry methods. In many of the haemodialysis samples the amount of protein was below the detection limit of the PRM method, however when measuring effluent peritoneal dialysates, the Lowry method gave higher estimates than the PRM method. The difference between the two methods may reside in their basis. The Lowry method combines the Biuret reaction of copper (CuII) with the peptide bonds under alkaline conditions with reduction of the Folin–Ciocalteu reagent included

in the reagent and the consequent oxidation of aromatic amino acid residues in protein. The reaction mechanism is not well understood. In contrast, pyrogallol red binds basic amino acid groups in proteins and the addition of molybdenum (VI) improves the sensitivity of the difference spectrum generated on addition of the sample to the reagent. Thus, the protein results depend on the type of protein in the sample which may have a different responsiveness to that of the protein standard used for calibration. As such, it is important that studies reporting protein losses in dialysis patients specify methods. In addition, the conversion factor of 6.25g protein = 1g nitrogen was used to convert protein estimates into nitrogen equivalence. This widely-used conversion factor is for an 'average' protein and varies according to the actual amino acid composition of the protein. It is correct when applied to isolated milk proteins, for example, but less so for foodstuffs which contain nitrogen which is not protein [23,24]. As we used this conversion the factor to convert protein to nitrogen equivalent, then this provides reasonable approximation, subject to the limitations of the protein assays.

Total protein and urea losses were greater during a HD session compared to PD. Our results are comparable to previous reports of losses of protein in haemodialysis and peritoneal dialysis effluents [17,25]. Previous reports have suggested that protein losses may be greater with HDF [5], but we did not find any significantly increased total protein loss with HDF sessions. Similarly, we were unable to demonstrate a difference in losses with dialyzers of different surface area. We did find that protein losses were highest during the first 5 minutes of the dialysis session, and then rapidly fell, presumably as proteins were deposited on the dialyzer surface area, so restricting pore size and reducing protein losses [26]. In keeping with previous reports of greater urea and protein losses with intermittent cycler peritoneal dialysis, we found greater losses with APD compared to CAPD [17]. Although not significantly different the protein losses were slightly greater with CAPD, reflecting the longer dwell times, as protein transport is much slower than that of urea [27].

When comparing weekly losses, PD was associated with greater total protein losses than HD. Although not significant, urea nitrogen losses tended to be greater with HD, although this have been due to the lower urea losses with CAPD compared to APD.

There have been very few reports of attempts to measure total nitrogen losses in dialysate [20]. One previous report, based on a smaller cohort of patients using low flux haemodialyzers, which were re-used, reported a much greater sessional total nitrogen loss of around 16g/session, equivalent to around 100g protein [20]. Whether such greater losses are due to methodology used to measure total nitrogen, or due to dialyzer re-use is unclear, as other studies have reported that using bleaches to re-use polysulphone dialyzers increases protein losses [8].

Nitrogen losses were greater during a single HD session compared to PD. Similarly, urea and protein losses were greater during a single dialysis session. However, when adjusted to a weekly basis although there were no differences between

the different dialysis modalities for total nitrogen losses, PD patients had greater protein losses. Urea nitrogen losses were marginally greater with HD, but around 50% of all nitrogen losses in the dialysates could be attributed to urea losses. Adding nitrogen losses due to protein loss, then we could account for around 70% of dialysate nitrogen losses. Total nitrogen measurement would include not only proteins and urea, but also small peptides, nucleotides, amino acids, organic acids, uric acid, nitrates and nitrites. However, even making allowance for some of these compounds which will be increased in the dialysis patient, and therefore cleared in dialysate, our study suggests that total nitrogen losses are much greater than previously reported by studies based on measuring proteins or amino acids.

HDF adds convective transport to standard diffusional losses with HD, so potentially increasing losses of larger solutes. We used the same dialyzers for both HD and HDF treatments. Urea nitrogen losses were marginally greater for HD treatments, whereas total nitrogen and protein losses were marginally greater for HDF. This would suggest that HDF treatments may increase nitrogen losses other than urea compared to HD. However, with the small number of patients we studied we were unable to demonstrate a significant difference. Although sessional losses were greater for HD and HDF, when comparing weekly losses, then PD patients had both a greater total dialysate protein loss, and protein accounted for a greater proportion of total nitrogen losses.

Measurements of muscle mass in dialysis patients can be over-estimated due to hydration status [28,29], so leading to an under-estimate of the prevalence of sarcopenia in the dialysis population [30,31]. Dialysis modalities provide an unselective clearance of compounds from plasma water, and higher urea clearance targets designed to increase clearance of azotaemic solutes, and the introduction of dialyzers with larger pore sizes will potentially lead to greater nutritional losses. Our study is a timely reminder as to the importance of nutritional intake to compensate for dialysate nitrogen losses.

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Figure 1. Weekly dialysate protein losses in all peritoneal dialysis (PD) and haemodialysis (HD) patients and those treated by automated peritoneal dialysis cycler (APD), continuous ambulatory peritoneal dialysis (CAPD), haemodiafiltration (HDF), high-flux haemodialysis (HD).

Table 1. Patient demographics. Automated peritoneal dialysis cycler (APD), continuous ambulatory peritoneal dialysis (CAPD), haemodiafiltration (HDF), high-flux haemodialysis (HD). Mean ± standard deviation, or percentage ().

	Peritoneal dialysis			Haemodialysis		
	all	APD	CAPD	all	HDF	HD
number	68	45	23	40	30	10
male	42 (61.8)	26 (57.8)	16 (69.6)	25 (62.5)	19(63.3)	6 (60)
female	26 (38.2)	19 (42.2)	7 (30.4)	15 (37.5)	11 (36.7)	4 (40)
Age years	64.7 ±16.0	60.7±15.9	72.5±13.5	64.3 ±16.6	66.1±15.5	59.1±20
Weight kg	74.0 ±15.5	75.4±16.4	71.2±14.6	66.9 ±8.1	67.1±12.5	66.5±21.6
Height m	1.67 ±0.1	1.66±0.1	1.67±0.1	1.64 ±0.1	1.65±.0.1	1.63±0.1
ethnicity						
White	21 (30.9)	16 (35.6)	10 (43.5)	13 (32.5)	8 (26.7)	5 (50)
Asian	26 (38.2)	15 (33.3)	6 (26.1)	15 (37.5)	13 (43.3)	2 (20)
African-Afro-Caribbean	11 (16.2)	9 (20)	2 (8.7)	5 (12.5)	3 (10)	2 (20)
Other/mixed race	8 (11.2)	5 (11.1)	5 (21.6)	5 (12.5)	6 (21)	1 (10)

Table 2. Treatment parameters of patients treated by haemodiafiltration and haemodialysis. Dialysate flow was set at 500 mL/min for haemodialysis treatments. Mean ± standard deviation, or median (interquartile range), percentage (). Single pool urea kinetic clearance (SpKt/Vurea). * p<0.05, ** p<0.01, *** p<0.001 vs haemodiafiltration

variable	haemodiafiltration	haemodialysis
Session time minutes	211 ±24	198 ±24
Dialysate flow mL/min	471 ±15	500 ***
Substitution flow mL/min	69.2 ±5.2	-
Substitution volume L/session	13.7 (10.8-15.1)	-
Ultrafiltration rate mL/min	637 (527-787)	571 (454-870)
Dialyzer surface area m^2	2.1 (1.7-2.1)	2.1 (1.7-2.1)
Length of time on dialysis therapy (months)	3.1 (1.1-5.3)	1.4 (0.5-3.3)
Blood flow mL/min	300 (330-350)	300 (280-303)
SpKt/Vurea	1.44 (1.17-1.65)	1.21 (1.05-1.63)
On-line urea clearance	1.40 (1.30-1.59)	1.45 (1.13-1.94)
Weight pre-dialysis kg	69.3 (63.1-75.7)	61.4 (54.6-83.0)
Weight post-dialysis kg	67.8 (60.8-73.7)	60.5 (52.8-81.4)
Pre-dialysis serum creatinine μmol/L	635 (500-721)	651 (606-940)
Pre-dialysis serum urea mmol/L	16.7 (14.5-21.2)	23.1 (17.8-28.6)*
Pre-dialysis serum albumin g/L	38.5 (37.0-40.3)	38.5 (36.8-42.3)
Pre-dialysis Haemoglobin g/L	107.0 (93.0-115.3)	116.5 (103.8-128.3)*

Table 3. Treatment parameters of patients treated by Automated peritoneal dialysis cycler (APD), continuous ambulatory peritoneal dialysis (CAPD). Peritoneal transport status according to NKF-K/DOQI Clinical practice guidelines [ref]. Number, mean ± standard deviation, or median (interquartile range), and percentage (%). *p<0.05,*** p<0.001 vs APD.

	APD	CAPD
Length of time on dialysis therapy (months)	2.6 (0.6-3.4)	1.64 (0.7-2.7)
Fast transporters	5 (20.8)	10 (66.7)
Fast-average transporters	12 (50.0)	5 (33.3)
Slow average transporters	4 (16.0)	-
Slow transporters	3 (12.5)	-
Volume dialysate used/day L	12.4 (9.5-15.5)	6.3 (2.5-8.1)***
Weekly Kt/Vurea	2.09 (1.74-2.8)	2.1 (1.79-2.44)
L creatinine cleared/wk.1.73m^2	69.2 (55.8-99.7)	76.4 (63.0-92.3)
Serum urea mmol/L	17.8 ±4.5	23.0 ±8.2*
Serum creatinine μmol/L	550 (468-871)	574 (402-704)
Serum albumin g/L	39.5 (36.0-42.0)	35.5 (34.0-40.0)
Serum total protein g/L	68.4 ±5.6	66.0 ±8.6
Haemoglobin g/L	111.1 ±12.3	108.2 ±15.3

Table 4. Comparison of urea, urea nitrogen, protein, protein nitrogen and total nitrogen between different dialysis modalities. Results expressed as g/session for haemodialysis and g/day for peritoneal dialysis. Results expressed as median (interquartile ranges). Automated peritoneal dialysis cycle (APD), continuous peritoneal dialysis (CAPD), on-line haemodiafiltration (HDF) and high flux haemodialysis (HD). # p< 0.05 APD vs CAPD and * p<0.05 and *** p<0.001 all peritoneal dialysis vs all haemodialysis, there were no significant differences between HDF and HD.

	Peritoneal dialysis			Haemodialysis		
	all	APD	CAPD	all	HDF	HD
number	68	45	23	40	30	10
Urea	4.8 (2.8-7.8)	5.7 (3.4-8.6)	3.5 (2.4-5.7) #	13.9*** (9.2-21.1)	13.5 (8.8-20.6)	15.3 (10.5-25.5)
Urea Nitrogen	2.2 (1.3-3.7)	2.7 (1.6-7.4)	1.8 (1.1-2.6) #	6.5 *** (4.3-9.8)	6.3 (4.1-9.6)	7.1 (4.9-11.9)
Protein	6.7 (3.9-11.1)	6.4 (4.0-10.7)	7.5 (3.8-12.0)	8.6 * (7.2-11.1)	8.8 (7.3-12.2)	7.6 (5.8-9.0)
Total Nitrogen	4.9 (2.6-9.5)	5.2 (2.7-9.9)	3.6 (2.2-6.6)	11.5*** (8.7-17.7)	11.6 (8.3-17.3)	10.8 (8.9-22.5)
Protein nitrogen	1.1 (0.6-1.8)	1.0 (0.7-1.7)	1.2(0.5-1.9)	1.4(1.2-1.8) *	1.5(1.2-2.0)	1.2(0.9-1.5)
% urea nitrogen/total nitrogen	48.4 (34.4-62.3)	49.8 (34.1-69.2)	48.4 (36.3-58.0)	57.6 (33.0-69.1)	57.6 (29.4-68.0)	56.2 (48.5-72.5)
% protein nitrogen/total nitrogen	20.6 (12.0-35.2)	17.3 (11.6-35.5)	29 (16.7-35.2)	11.6 (7.5-18.8) *	12.1 (7.5-22.2)	10.5 (7.0-13.8)