



ORIGINAL ARTICLE

Characterization of sodium removal to ultrafiltration volume in a peritoneal dialysis outpatient cohort

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ABSTRACT

Background. Failure to control volume is the second most common cause of peritoneal dialysis (PD) technique failure. Sodium is primarily removed by convection, but according to the three-pore model, water and sodium movements are not necessarily concordant. We wished to determine factors increasing sodium to water clearance in clinical practice.

Methods. We reviewed 24-h peritoneal dialytic sodium removal (DSR) and ultrafiltration (UF) volume in consecutive PD patients attending for routine assessment of peritoneal membrane function and adequacy testing. We used a regression model with the DSR/UF ratio as the dependent variable. A second model with DSR as the dependent variable and interaction testing for UF was used as sensitivity analysis.

Results. We included 718 adult PD patients. Mean values were 51.8 ± 64.6 mmol/day and 512 ± 517 mL/day for DSR and UF, respectively. In multivariable analysis, DSR/UF ratio was positively associated with transport type (fast versus slow, $P < 0.001$), serum sodium ($P < 0.001$) and diabetes ($P = 0.026$), and negatively associated with PD mode [automated PD versus continuous ambulatory PD (CAPD), $P < 0.001$] and the use of 2.27% glucose dialysate ($P < 0.001$). Sensitivity analysis showed positive interaction with UF for transport type ($P < 0.001$) and serum sodium ($P = 0.032$) and negative interaction for PD mode ($P < 0.001$) and cycles number ($P < 0.001$).

Conclusions. CAPD, fast transport and high serum sodium allow relatively more sodium to be removed compared with water. Icodextrin has no effect on sodium removal once confounders have been accounted for. Although widely used in the assessment of PD patients, UF should not be considered as a surrogate for DSR in clinical practice.

Keywords: automated peritoneal dialysis, continuous ambulatory peritoneal dialysis, icodextrin, peritoneal dialysis, sodium removal, ultrafiltration volume

INTRODUCTION

For peritoneal dialysis (PD) patients, treatment adequacy has been traditionally estimated by small solute removal using urea kinetic models (K_v/V). Increasing PD urea clearance, however, has not consistently led to improved clinical outcomes [1, 2]. On

the other hand, the volume control is increasingly being recognized as a pivotal determinant of dialysis adequacy as it has been shown to strongly determine patient outcome and was associated with adverse cardiovascular effects, including left ventricular hypertrophy [3–5]. Moreover, ultrafiltration (UF) failure is recognized as the second most common cause of PD

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technique failure and transfer to haemodialysis, and observational studies have suggested that >50% of PD patients are volume overloaded [6, 7].

Volume control in PD can be considered as having two distinct components. First, UF is defined as the difference between filled and drained volume (i.e. fluid weight loss). Secondly, dialytic sodium removal (DSR) is the net amount of sodium removed by PD. Sodium balance is of particular importance beyond fluid overload as it has recently been suggested that sodium accumulation in interstitial tissues could contribute to adverse cardiovascular outcomes by volume-independent effects via local inflammation [8]. This inflammatory process could, in turn, alter peritoneal permeability perpetuating a vicious circle of fluid and sodium overload [8]. According to the three-pore model, the total UF is the sum of free-water transfer via aquaporins and sodium-coupled water removal via small pores [9, 10]. DSR, on the other hand, involves small pores only and is predominantly convective as the effective diffusive sodium gradient between dialysate and blood is usually negligible. DSR is thus highly dependent on UF and in clinical practice, it is usually estimated from the UF volume rather than actually measured [10]. The relationship between DSR and UF is, however, not straightforward, as it could dissociate with a relative decrease of DSR for a given UF volume. This phenomenon has been reported with automated PD (APD), which uses shorter dwell times compared with continuous ambulatory PD (CAPD), favouring sodium sieving and greater free-water transfer through aquaporins [11]. Although less well studied, other clinical factors (e.g. use of icodextrin and serum sodium) have been reported to influence DSR in various settings [11–15]. However, their respective influence on DSR has not been systematically described in a large cohort. More importantly, the complex interplay between DSR and UF has not yet been fully characterized in a clinical perspective.

We therefore designed this study to analyse DSR determinants and describe their interaction with UF in a large PD outpatient cohort.

MATERIALS AND METHODS

Participant selection

We consecutively included PD outpatients treated with CAPD, APD (night time cycler-assisted therapy with a dry day) or APD with a daytime exchange [continuous cycling PD (CCPD)] attending for their routine clinical follow-up at a single tertiary hospital. Exclusion criteria were: (i) peritonitis or emergency admission to hospital in the previous 8 weeks; (ii) implantable cardiac device; (iii) limb amputation; and (iv) inability to stand. No patient was prescribed a glucose dialysate concentration >2.27%.

Variables collection

Blood pressure was recorded in the supine position after the patient had drained out dialysate and rested for a minimum of 30 min and abstained from any stimulants (Dinamap, Critikon Corporation, Tampa, FL, USA). Creatinine was enzymatically measured and serum albumin was measured by bromocresol green method (Roche Modular P[®] analyser, Roche Diagnostics Limited, Burgess Hill, UK). Sodium in urine and dialysate was measured using an indirect ion electrode [16]. Serum sodium values were corrected if serum glucose was elevated [17]. Solute removal was calculated by standard methods from 24-h urinary

collections and samples from spent dialysates [18]. Peritoneal membrane transport was evaluated from plasma creatinine concentration and a 4-h dwell using 2 L of 2.27% dialysate [4]. UF and DSR were corrected for flush before fill technique in CAPD patients [19]. Thus, for each exchange, 60 mL of UF and 7.9 mmol of DSR were deducted from 24-h measured values. Multifrequency bioelectrical impedance (MFBI) was measured using a standardized protocol (InBody 720, Seoul, South Korea), with dialysate drained out and after voiding [20]. All patients were provided with dietary advice from a renally trained dietician to limit dietary sodium around 100 mmol/day. Loop diuretics (250 mg/day furosemide) were prescribed as the standard treatment for patients with urinary output \geq 200 mL/day.

Statistical analysis

Continuous variables are expressed as mean \pm standard deviation and categorical variables as number and relative frequencies. The normality of distribution was assessed graphically. No outliers were specified. Variables were compared between groups using Student's *t*-test and Chi-square for continuous and categorical variables, respectively.

In order to characterize the relative efficiency of UF and DSR, absolute values were rescaled into a relative score ranging from 1 to 1000 while keeping the same statistical distribution. The ratio of these values (DSR/UF) was then used to express the relative efficiency of DSR compared with UF. Outliers were defined as patients with DSR/UF >99th percentile of below first percentile. DSR/UF was divided into two quantiles using the median to assess associations with baseline characteristics.

Two conceptually and statistically distinct approaches were used to characterize the relationship between DSR and UF. In the first model, a multivariable linear regression with DSR/UF as the dependent variable was computed using a backward stepwise method keeping in the final model only variables with $P < 0.05$. In the second model, as a sensitivity analysis, another multivariable linear regression was built with DSR as the dependent variable. The same backward stepwise procedure was applied. Interaction terms (UF \times) were then sequentially added to detect modification effects on the relationship between DSR and UF. Modification effect of the selected variable (x) was considered significant if P -value for interaction term (UF \times) was <0.05 . Likelihood ratio test (LRT) was then used to compare models with and without interaction terms (UF \times). Interaction was confirmed if P -value for LRT was <0.05 . A subgroup analysis was then performed if the interaction was significant.

In all multivariable models, independent variables considered were: UF, age, gender, body mass index (BMI), diabetes, extracellular water to total body water ratio (ECW/TBW) measured by MFBI, serum sodium, C-reactive protein (CRP), albumin, PD mode (CAPD, CCPD and APD), transport type according to European guidelines (slow, average and fast), dwell volume divided by body surface area, number of cycles, use of icodextrin solution, use of 2.27% glucose solution and PD urea K_t/V [21].

For every model, linearity of relationship, normality of residuals and homoscedasticity of residuals have been assessed graphically. Huber–White heteroscedasticity-consistent standard errors were also been implemented as confirmatory procedure. Collinearity was assessed using the variance inflation factors method.

Data were considered to be missing completely at random and therefore patients with any missing variables were excluded from the multivariable analyses. For every model, results are presented as β coefficients and associated 95% confidence

Table 1. Patients characteristics according to median value of DSR/UF ratio (n = 718)

Characteristics	Overall	Low DSR/UF, n = 359	High DSR/UF, n = 359	P-value
DSR/UF ratio	1.04 ± 0.21	0.9 ± 0.11	1.19 ± 0.17	<0.001
DSR, mmol/day	51.8 ± 64.55	43.58 ± 57.41	60.03 ± 70.1	<0.001
UF, mL/day	511.69 ± 516.6	704.02 ± 494.9	319.36 ± 464.1	<0.001
Age, years	57.28 ± 15.9	56.57 ± 15.32	58 ± 16.46	0.23
MAP, mmHg	101.1 ± 16.3	111.8 ± 16.9	101.4 ± 15.7	0.632
BMI, kg/m ²	26.28 ± 5.09	25.88 ± 4.78	26.68 ± 5.35	0.03
ECW/TBW	0.4 ± 0.01	0.4 ± 0.01	0.4 ± 0.01	0.19
Hb, g/L	111.8 ± 15.7	112.3 ± 15.7	111.2 ± 15.7	0.334
Serum sodium, mmol/L	137.93 ± 4.47	136.75 ± 4.87	139.11 ± 3.68	<0.001
CRP, mg/L	10.41 ± 23.09	11.13 ± 24.6	9.68 ± 21.49	0.4
Albumin, g/L	37.37 ± 4.73	37.62 ± 4.88	37.13 ± 4.58	0.16
Dwell volume, L/m ^{2a}	1 ± 0.18	1.02 ± 0.19	0.99 ± 0.17	0.03
Number of cycles	5.25 ± 1.78	5.57 ± 1.47	4.94 ± 2	<0.001
K _t /V	1.2 ± 0.51	1.28 ± 0.53	1.12 ± 0.47	<0.001
Men, %	407 (56.7)	197 (54.9)	210 (58.5)	0.33
Diabetes, %	272 (37.9)	130 (36.2)	142 (39.6)	0.36
Mode, %				<0.001
CAPD	171 (23.8)	58 (16.2)	113 (31.5)	
CCPD	349 (48.6)	174 (48.5)	175 (48.8)	
APD	198 (27.6)	127 (35.4)	71 (19.8)	
Transport type, %				<0.001
Slow	129 (18)	85 (23.7)	44 (12.2)	
Average	383 (53.3)	202 (56.3)	181 (50.4)	
Fast	206 (28.7)	72 (20.1)	134 (37.3)	
Use of icodextrin dialysate, %	500 (69.6)	225 (62.7)	275 (76.6)	<0.001
Use of 2.27% dialysate	227 (31.6)	137 (38.2)	90 (25.1)	<0.001

^aNormalized to BSA.

MAP, mean arterial pressure; Hb, haemoglobin.

Data are presented as mean ± standard deviation or n (%). Bold values indicate P < 0.05.

intervals (CIs) as well as P-values. P < 0.05 were considered significant. Statistical analyses were conducted using STATA version 15 (StataCorp, College Station, TX, USA).

Ethics

Our retrospective audit was checked with, and complied with the UK National Health Service Health Research Authority guidelines for clinical audit and service development (<https://www.hra.nhs.uk>), and registered with the UCL Department of Nephrology Royal Free Hospital. All patient data were anonymized.

RESULTS

The complete cohort included 800 patients. Fourteen patients were considered as outliers, and 68 had missing values on considered variables. Present analyses thus included 718 patients in total.

Mean values of DSR and UF were 51.8 ± 64.6 mmol and 512 ± 517 mL, respectively. Median value of DSR/UF was 1.03. Patients' characteristics are described according to below and above the median DSR/UF in Table 1. Absolute DSR and UF were increased and decreased, respectively, in the high DSR/UF group compared with the low DSR/UF group. Serum sodium concentration was higher in the high DSR/UF compared with the low DSR/UF group (P < 0.001), whereas dwell volume, number of cycles and K_t/V were all lower in the high DSR/UF group (P = 0.03, <0.001 and <0.001, respectively). Compared with the low DSR/UF group, patients in the high DSR/UF group were more frequently treated with CAPD, classified as faster peritoneal transporters and users

of icodextrin, whereas the low DSR/UF group used more 2.27% glucose dialysates (all P < 0.001).

Characterization of DSR/UF ratio

In multivariable analysis, factors positively associated with DSR/UF were (Table 2 and Figure 1a–c: transport type (P < 0.001), serum sodium (P < 0.001) and diabetes (P = 0.026). Factors negatively associated with DSR/UF were: PD mode (P < 0.001) and the use of 2.27% glucose solution (P < 0.001). During the backward stepwise procedure, non-significant variables were discarded in the following order: CRP, number of cycles, gender, BMI, K_t/V, age, ECW/TBW, albumin, dwell volume and use of icodextrin.

Characterization of DSR and UF relationship

In multivariable analysis, factors positively associated with DSR were (Table 3) UF (P < 0.001), diabetes (P < 0.040), transport type (P < 0.001) and serum sodium (P < 0.001). Factors negatively associated with DSR included PD mode (P < 0.001). In the final model, every additional litre of UF was associated with a 98 mmol increase in DSR. In the backward stepwise multivariable model, non-significant variables were discarded in the following sequential order: gender, BMI, use of icodextrin, number of cycles, CRP, ECW/TBW, age, dwell volume, albumin, use of 2.27% glucose dialysate and K_t/V.

In this second model, factors demonstrating a positive interaction with UF for DSR were (Supplementary data, Table S1) transport type (P < 0.001) and serum sodium (P = 0.032). Factors with a negative association with UF for DSR included PD mode (P < 0.001) and number of cycles (P < 0.001). No significant

interaction was present for the following variables: age, diabetes, use of icodextrin, use of 2.27% glucose dialysates, dwell volume, CRP, albumin, ECW/TBW and K_t/V . The multivariable association between DSR and UF according to sub-groups showing significant interaction is presented in Table 4 and Figure 2a–c.

Table 2. Factors associated with DSR/UF ratio in multivariable linear regression (n = 718)

Independent variables	Final model	
	β (95% CI)	P-value
Transport type ^a		
Average	0.038 (−0.001 to 0.077)	0.059
Fast	0.092 (0.046 to 0.137)	<0.001
Serum sodium (mmol/L)	0.019 (0.016 to 0.022)	<0.001
Use of 2.27% dialysate	−0.07 (−0.102 to −0.041)	<0.001
Diabetes	0.032 (0.003 to 0.061)	0.026
PD mode ^b		
CCPD	−0.038 (−0.073 to −0.003)	0.033
APD	−0.130 (−0.174 to −0.086)	<0.001

^aSlow as reference category.

^bCAPD as reference category.

Bold values indicate P < 0.05.

DISCUSSION

In this cross-sectional observational study, we characterized clinical determinants of DSR as well as its relationship with UF in a large adult PD outpatient population. In order to characterize the interaction between sodium removal and volume control, we used two conceptually and statistically distinct approaches. Both models allowed us to describe the relative efficiency of DSR compared with UF and led to similar results. PD mode, transport type and serum sodium were the main factors influencing the relative efficiency of peritoneal sodium to fluid removal.

PD mode

The influence of PD mode on DSR remains controversial with some studies reporting a difference between APD and CAPD on sodium control while others did not [11, 22–28]. In a recent meta-analysis including 683 patients by Borrelli et al., CAPD allowed a higher DSR than ADP even though UF was not different [14]. However, the majority of studies had not taken into account the confounding effect of the flush before fill technique used in CAPD. Whereas in our study, accounting for the flush before fill, we confirmed the dissociation between peritoneal sodium and fluid removal according to PD mode, as DSR was more efficient relative to UF with CAPD compared with APD. This

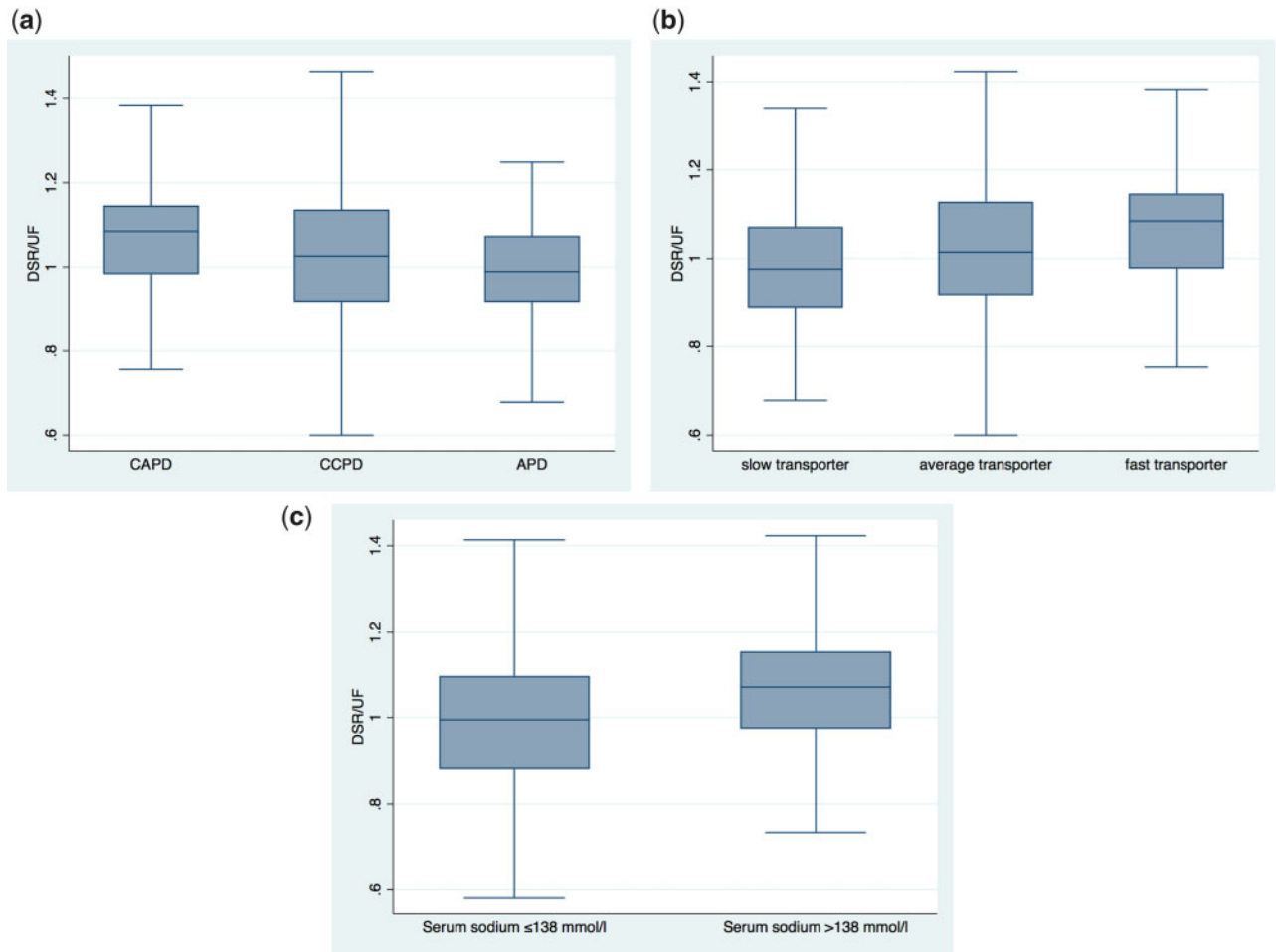


FIGURE 1: Boxplot of DSR/UF ratio values according to significant variables in multivariable linear regression (first model, see text) (n = 718). (a) According to PD mode. (b) According to transport type. (c) According to serum sodium.

Table 3. Factors associated with DSR in multivariable linear regression (n = 718)

Independent variables	Final model	
	β (95% CI)	P-value
UF, mL	0.098 (0.089 to 0.106)	<0.001
PD mode ^a		<0.001
CCPD	-14.041 (-21.406 to -6.675)	
APD	-33.182 (-41.982 to -24.383)	<0.001
Diabetes	6.554 (0.303 to 12.805)	0.040
Transport type ^b		
Average	3.329 (-4.387 to 11.046)	0.397
Fast	18.918 (9.963 to 27.873)	<0.001
Serum sodium, mmol	3.743 (2.827 to 4.658)	<0.001

^aCAPD as baseline category.^bSlow as baseline category.

Bold values indicate P < 0.05.

Table 4. Association between DSR and UF according to subgroups showing significant interaction in multivariable linear regression (n = 718)

Subgroups	β (95% CI)	P-value
Transport type		
Slow	0.076 (0.060–0.092)	<0.001
Average	0.092 (0.081–0.103)	<0.001
Fast	0.118 (0.103–0.132)	<0.001
Serum sodium, mmol/L		
<138	0.092 (0.079–0.105)	<0.001
≥138	0.103 (0.093–0.114)	<0.001
PD mode		
CAPD	0.120 (0.108–0.132)	<0.001
CCPD	0.095 (0.082–0.107)	<0.001
APD	0.079 (0.063–0.094)	<0.001
Number of cycles		
<6	0.107 (0.094–0.119)	<0.001
≥6	0.090 (0.079–0.102)	<0.001

Bold values indicate P < 0.05.

supports that the shorter dwell times used in APD promote sodium sieving and greater water removal through aquaporins that cannot be compensated by the later convective transfer of sodium. In addition to CAPD and APD, a significant proportion of patients were on CCPD in our study. As a hybrid modality between CAPD and APD, CCPD showed an intermediate pattern of DSR to UF efficiency, consistent with this hypothesis.

Transport type

The interplay between DSR, UF and transport type is a complex one as net peritoneal sodium removal is the sum of convective transport, diffusive transport and peritoneal absorption [13]. Wang *et al.* [13] observed that fast transporters had decreased UF as well as DSR compared with slow transporters when using extended dwell times. Subsequent studies, however, have not been able to confirm these findings [11, 15]. Interestingly, in their meta-analysis, Borrelli *et al.* [14] showed that the difference in DSR between CAPD and APD decreased as transport type [dialysate/plasma (D/P) creatinine] increased. However, none of these studies considered the relative removal of sodium

to UF. In our study, fast transporters had an increased efficiency to remove sodium with respect to water compared with slow transporters. Theoretically, this could either correspond to a relative increased DSR for a given UF or to a relative decreased UF for a given DSR. However, we were also able to show that fast transporters had increased DSR absolute values in our secondary multivariable model. Globally, these findings likely underline the importance of adapted prescription and suggest that, although usually considered well suited for volume control, slow peritoneal transport can hamper sodium removal by magnifying sodium sieving when too short dwells are prescribed [23]. Observational studies have thus shown that fluid overload was the highest in patients with unknown transport status in whom PD prescription could not be adapted [7]. Tailoring treatment according to patients characteristics is thus of prime importance.

Serum sodium

In our analyses, serum sodium was the third factor consistently associated with a positive dissociation between DSR and UF. This finding is relatively intuitive as higher serum sodium increases the diffusive gradient, driving sodium removal without having a significant effect on water removal through aquaporins. Our result is consistent with previous observations in a similar clinical context [12].

Other factors associated with DSR/UF

In our main model, two other factors were associated with dissociation between peritoneal sodium and water removal although we were not able to confirm this interaction in our secondary analyses. First, the presence of diabetes increased the relative efficiency of DSR compared with UF. A potential hypothesis is that the higher serum glucose of diabetic patients could decrease the osmotic gradient driving free water through aquaporin thus lowering initial UF rate to a relatively greater extent than DSR rate. We could not find results in the related literature to confirm or reject this hypothesis. Secondly, the use of 2.27% glucose solution was found to decrease the relative efficiency of DSR compared with UF. As Wang *et al.* previously showed, hypertonic solutions tend to increase UF rates as well as DSR rates compared with isotonic solutions [13]. Our finding suggests that the initial faster free-water removal achieved with higher glucose-containing dialysates leads to a net lower DSR/UF, as any increase in DSR is lower than the increase in UF.

Factors not associated with DSR/UF

Factors that were not associated with DSR efficiency in our models are also of interest. Of particular importance is the use of icodextrin solution. As a colloid osmotic agent, icodextrin induces UF mainly via small pores and not via aquaporins [29]. Theoretically, this would induce a slower and more sustained UF and maximize DSR in the absence of sodium sieving [9]. Clinically, this has been shown in some studies where DSR and UF were increased with icodextrin compared with 2.27% glucose solution [30, 31]. Volume status has also been shown to improve with icodextrin compared with hypertonic glucose solution [32]. Confounders, however, are of prime importance, as Rodríguez-Carmona *et al.* reported lower DSR and UF rate in ADP patients compared with CAPD, despite far more extensive use of icodextrin [23]. More importantly, the same authors observed that icodextrin use was able to improve DSR in CAPD and APD patients but only in univariable analysis, whereas icodextrin use had no

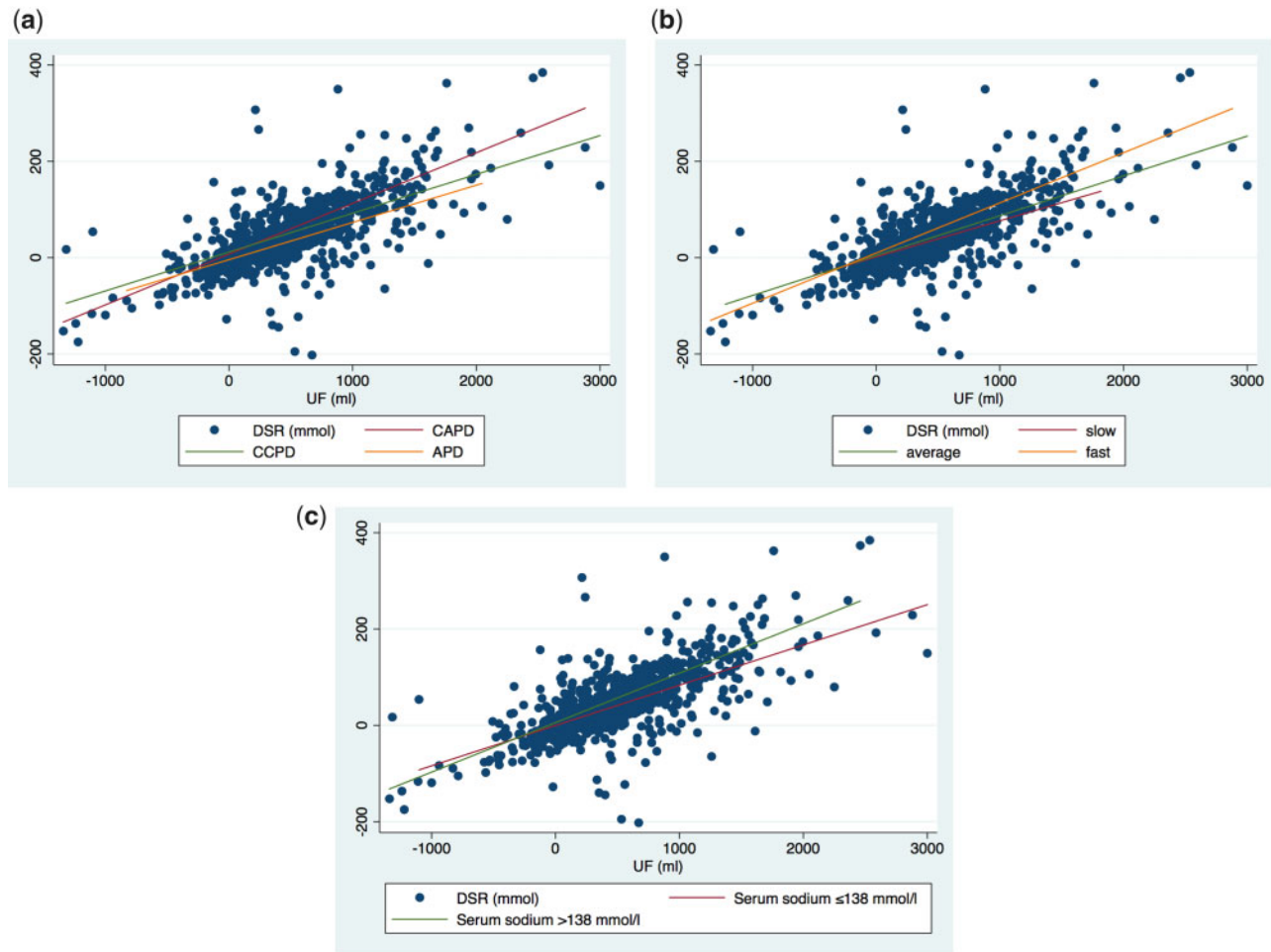


FIGURE 2: Scatterplot of association between DSR and UF according to significant variables in multivariable linear regression (second model, see text) ($n = 718$). (a) According to PD mode. (b) According to transport type. (c) According to serum sodium.

apparent effect on sodium removal after controlling for UF [11]. In line with this finding, the use of icodextrin could not explain the high heterogeneity of DSR observed in the Borrelli *et al.* [14] meta-analysis. Our results support these latter findings as the use of icodextrin did not allow a relative increase in DSR efficiency compared with UF. Moreover, absolute sodium removal was not affected by icodextrin prescription after accounting for UF rate and other confounding factors. This tends to show that icodextrin solutions have the capacity to increase sodium removal only to the extent that it increases UF. Moreover, the hypothesis whereby icodextrin could improve diffusive removal of sodium independently of UF by reducing sodium sieving could not be verified in our study [33].

Inflammatory states induce hypoalbuminaemia and increased vascular permeability leading to an increase in ECW [34]. CRP, albumin and ECW/TBW may have thus been expected to influence DSR and UF but we found no effect of these variables on sodium removal efficiency. It should be noted, however, that we studied an outpatient population attending for routine assessments, which excluded patients with recent hospitalizations and episodes of PD peritonitis.

Limitations

The main limitation of our study is the observational and cross-sectional nature of the association between clinical predictors

and DSR efficiency, which limits causal inference. Moreover, despite adjusting for clinically relevant variables, including known confounders, as with any study, we cannot exclude potential residual confounding. Specifically, dwell time was not taken into account as we focused on a patient-level analysis. Dwell volumes and cycles number, however, serve as proxies in our analyses. Moreover, as the original 2.27% peritoneal equilibration test procedure was used as part of routine clinical follow-up, advanced peritoneal function parameters such as D/P sodium could not be taken into account thus potentially limiting pathophysiological insights. Compared with other studies, the strengths of our work include the important number of patients included and the number of potential confounders taken into account. We also corrected DSR and UF values for the flush before fill technique in CAPD patients thus limiting measuring bias. Finally, our results are supported by two distinct conceptual and statistical approaches.

CONCLUSION

In this study, we present a novel insight into sodium and volume control in PD by describing the intrinsic relationship between DSR and UF in a large population of patients. We describe a robust association between DSR and PD mode, transport type as well as serum sodium, while accounting for UF effect. CAPD,

fast transport and high serum sodium were independently predictive of higher peritoneal sodium compared with fluid removal efficiency. On the other hand, the prescription of icodextrin had no effect on the absolute amount of sodium removed or the relative efficiency of DSR compared with UF after accounting for potential confounders. This supports the hypothesis that colloid solutions do not have an independent effect on DSR *per se* but merely enhance both sodium and water removal. In light of these findings, although widely used in the assessment of PD patients, UF should not be considered as a surrogate for DSR in clinical practice.

SUPPLEMENTARY DATA

Supplementary data are available at [ckj online](#).

CONFLICT OF INTEREST STATEMENT

All authors declare no conflict of interest. This manuscript has not been published and is not being considered for publication elsewhere, in whole or in part, in any language.

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