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Fluid status in CAPD patients is related to peritoneal transport and residual renal function: evidence from a longitudinal study

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Abstract

Background. Both peritoneal transport characteristics as well as residual renal function are related to outcome in patients treated with continuous ambulatory peritoneal dialysis (CAPD). It has been suggested that part of this relationship might be explained by an effect of both parameters on the fluid state in CAPD patients or by the relationship between inflammation and peritoneal transport.

Methods. In the present study, the relationship between fluid state [extracellular water (ECW) (sodium bromide); total body water (TBW) (deuterium oxide)] with peritoneal transport characteristics (2.27% glucose dialysate/plasma creatinine [D/P (creat)] ratio), residual renal function (residual glomerular filtration rate [rGFR] by urine collection) and C-reactive protein (CRP) was assessed in 37 CAPD patients in a cross-sectional and longitudinal design, with 25 patients completing the study.

Results. In the cross-sectional part ECW, corrected for height (ECW:height), was inversely related to rGFR ($r=-0.40$, $P=0.016$), whereas during the longitudinal part, D/P[creat] was related to the change in ECW ($r=0.40$, $P=0.05$). Neither D/P[creat] nor rGFR were related to CRP, whereas a significant relationship was observed between ECW:height and CRP ($r=0.58$, $P=0.0001$). Patients were dichotomized according to rGFR (<2 or >2 ml/min). Despite a higher daily peritoneal glucose prescription (216.3 ± 60.0 *vs* 156.5 ± 53.0 g/24 h; $P=0.004$) and peritoneal ultrafiltration volume (1856 ± 644 *vs* 658 ± 781 ml/24 h, respectively; $P=0.0001$), the patients with a rGFR <2 ml/min showed a higher ECW:height compared with the group with rGFR >2 ml/min (12.5 ± 3.8 *vs* 9.2 ± 2.2 l/m, respectively; $P=0.003$). Results for TBW were comparable.

Conclusion. Fluid state was significantly related to peritoneal transport characteristics and rGFR. The larger ECW:height in CAPD patients with a negligible rGFR existed despite a higher peritoneal ultrafiltration volume and higher peritoneal glucose prescription. These findings raise doubts as to whether fluid state in CAPD patients with a diminished rGFR can be adequately controlled on standard glucose solutions without an additional sodium and fluid restriction. The preliminary finding of a relationship between CRP and fluid state might suggest a relationship between overhydration and inflammation.

Keywords: continuous ambulatory peritoneal dialysis; fluid state; glomerular filtration rate; mortality; peritoneal transport; residual renal function; risk factors

Introduction

Interest in the transport characteristics of the peritoneal membrane has increased since the sub-analysis of the CANUSA study, in which a high transport status, characterized by a high dialysate/plasma creatinine (D/P[creat]) ratio [1], was found to be an independent risk factor for mortality. Following this observation, also other studies showed an increased mortality in so-called high transporters, although in some studies, this only appeared to hold true for patients with co-morbid disease [2,3].

Because peritoneal fluid removal is less in patients with a more permeable peritoneal membrane whereas albumin loss is higher [4], it has been suggested that the relationship between transport status and mortality might be partly related to overhydration, which is

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an important risk factor for hypertension and left ventricular hypertrophy [3,5]. Another factor related to outcome in dialysis patients is residual renal function, which has been attributed to an effect of residual function on both total solute clearance and fluid status [6].

Until now, few studies have focused on the relationship between fluid status with peritoneal transport characteristics and residual function in continuous ambulatory peritoneal dialysis (CAPD) patients [7]. Moreover, in the studies performed [8], fluid state was not assessed in great detail.

Another factor widely implicated in the increased mortality in dialysis patients is the presence of an inflammatory state [9]. It has been hypothesized that peritoneal transport state might be influenced by inflammation, although the only study that addressed this topic [4] failed to confirm the hypothesis. In order to gain more insight into the pathogenesis of important determinants for outcome in peritoneal dialysis patients, the aim of the present study was to assess the relationship between fluid state, peritoneal transport characteristics, residual function and inflammation in a cohort of peritoneal dialysis patients, using both cross-sectional and longitudinal designs.

Subjects and methods

Study design

In this multi-centre study, including patients from six dialysis centres, fluid state, peritoneal transport, residual renal function, peritoneal ultrafiltration volume and glucose prescription, and C-reactive protein (CRP) were related in a cross-sectional design. Moreover, parameters were compared after dividing patients arbitrarily in two groups according to residual renal function, measured at baseline (residual glomerular filtration rate [rGFR]) <2 or >2 ml/min).

After baseline investigations, patients were followed longitudinally for 4 months, after which the same investigations were performed without changing the treatment regimen. Eligible patients who did not meet the exclusion criteria were asked to participate in the study. Exclusion criteria were acute intercurrent infection, malignancy, cardiac failure (NYHA $>$II), and insulin-dependent diabetes mellitus. The latter group was excluded because the increased transcapillary escape rate of albumin found in type I diabetics could interfere with the reliability of the measurements of fluid state in the present study [10].

Patients

In the cross-sectional part of the study, 37 CAPD patients were included. The baseline characteristics of these patients are given in Table 1. The causes of renal insufficiency were glomerulonephritis, 18 patients; glomerulosclerosis, three patients; hypertension, six patients; polycystic disease, four patients; urological disorders, three patients; type II diabetes mellitus, two patients; scleroderma, one patient.

Of the included patients, 25 completed the longitudinal part of the study. The reasons for drop-out in the longitudinal part of the study were that four patients underwent a renal transplant procedure during follow-up, two patients had peritonitis during follow-up, two switched to haemodialysis because of technique failure, three did not return for the second measurement, and in one patient PD was stopped because of return of renal function (the patient with scleroderma). All patients were treated with standard glucose-containing peritoneal solutions (Dianeal®; Baxter, Castlebar, Ireland) only. The glucose concentration was prescribed at the discretion of the treating physician. None of the patients had clinical signs of overhydration.

Table 1. Patient demographics

Male/Female (*n*)	26/11
Age (years)	55.2 ± 11.8
Weight (kg)	78.4 ± 15.8
BSA (m^2)	1.9 ± 0.2
Time on CAPD (months)	22.6 ± 18.5
Weekly Kt/V urea	2.4 ± 0.7
Weekly creatinine clearance (l/1.73 m^2)	86.4 ± 33.4
Residual GFR (ml/min)	4.3 ± 4.2
D/P[creat] creatinine	0.68 ± 0.10
Serum albumin (g/l)	32.0 ± 4.4
C-reactive protein (mg/l)	7.1 ± 13.0
24-h systolic blood pressure (mmHg)	130.5 ± 15.8
24-h diastolic blood pressure (mmHg)	78.7 ± 10.4
Number of antihypertensive agents	1.7 ± 1.8

Mean ± SD. GFR, glomerular filtration rate; D/P[creat] creatinine, D/P[creat] ratio peritoneal membrane determined after a 4-h dwell with a 2.27% glucose CAPD solution.

Study protocol

Patients were admitted to the research centre at the dialysis department of the Academical Hospital of Maastricht in the early morning after an overnight fast. If patients had a filled abdomen over the night, PD fluid was first drained before the measurements were started. After admission, fluid state was determined by tracer dilution. During the equilibration period, patients were not allowed to eat or drink. At noon, patients were allowed to eat a light meal, of which the total amount of fluid did not exceed 200 ml.

Study parameters

Peritoneal transport characteristics. At inclusion of the cross-sectional part of the study, the transport characteristics of the peritoneal membrane were characterized using a standard peritoneal equilibrium test (PET) after a 4-h dwell with a 2.27% glucose solution. At the day of investigation, 24-h collection of the dialysis fluid and the urine was performed to calculate dialysis adequacy: Kt/V_{urea} and weekly creatinine clearance normalized to 1.73 m^2 body surface area (BSA). All calculations were made using PD Adequest software [11].

Peritoneal ultrafiltration volume and glucose prescription. Peritoneal ultrafiltration volume was calculated from a single 24-h dialysate collection performed on the day of investigation. The 24-h peritoneal glucose dosage prescription was calculated from the volume and glucose concentration of the prescribed peritoneal dialysis fluid.

Fluid state. Fluid state was assessed both by measurement of extracellular water (ECW by sodium bromide dilution) and in the cross-sectional part also by the measurement of total body water (TBW) by deuterium oxide dilution.

Patients received an orally administered dose of deuterium oxide (D_2O) of 25 ml (99% D_2O, Sigma Chemicals, St Louis, MO) and 30 ml (150 mM) sodium bromide (NaBr, pharmacological department, Academical Hospital Maastricht, The Netherlands). Dose bottles were washed out and the rinsed water was also ingested by the patients to ensure that all D_2O and NaBr were consumed. Enrichments of D_2O and NaBr in the body fluid were measured in serum. Immediately before D_2O and NaBr intake, a (background) blood sample was taken. After the equilibration time of 4 h, a second blood sample was collected. The concentration of D_2O and bromide in serum was determined by isotope ratio mass spectrometry and gas chromatography, respectively [12,13]. D_2O and bromide dilution spaces were calculated from the enrichment of D_2O and bromide, respectively, after 4 h. TBW was calculated as the D_2O dilution space corrected for the exchange of D_2O with non-aqueous compartments and for the concentration of water in the serum by first dividing the dilution space by 1.04 and thereafter multiplying it by 0.94 [14]. The volume of the ECW compartment was calculated as the NaBr dilution space corrected for intracellular penetration of NaBr in erythrocytes, leukocytes and secretory cells, for unequal NaBr concentrations in the extracellular fluids (Gibbs–Donnan effect), and for the concentration of water in the serum; therefore, NaBr dilution space was multiplied by the following correction factor: $0.90 \times 0.95 \times 0.94 = 0.80$ [15].

As patients were assessed with empty abdomen, no effect of the PD treatment on the bromide and deuterium dilution space is to be expected. The coefficient of variation for ECW measurements obtained with an interval of 4 months was 15%, and 9.4% for TBW measurements. Data for ECW are available in all patients in the cross-sectional and longitudinal parts, whereas data for TBW are available for 32 patients in the cross-sectional part.

Normalization of parameters

Regarding the relation with D/P[creat] and rGFR, fluid status was normalized for BSA and for height, although the optimal normalization procedure for fluid status is not well known in dialysis patients. BSA was also used because an earlier study showed a better relationship between ECW and haemodynamic variables when BSA was used for normalization compared with body weight [16]. Moreover, fluid state was expressed as the ECW:TBW ratio [8].

24-h Ambulatory blood pressure

In all patients, 24-h blood pressure (BP) measurements were performed using a Spacelabs oscillometric BP monitor (Redmond, WA). BP was measured every 15 min from 7 a.m. until 11 p.m. and every 30 min from 11 p.m. until 7 a.m.

Inflammatory parameters

In all PD patients, blood samples were taken for the assessment of albumin and C-reactive protein (CRP) (Syncron LX 20, Beckman Coulter, CA). The detection limit of the CRP assay was 2 mg/ml.

Statistics

Correlations between the different parameters were estimated by the use of Pearson product moment correlations. Differences during the follow-up period were estimated by the use of the paired standard *t*-test. Differences between groups were assessed by the unpaired Student's *t*-test. Stepwise linear multi-regression analysis was used where appropriate.

Calculations were made using SPSS 10 statistical software for Windows. P values <0.05 were considered significant. Data are expressed as means $\pm$ SD.

Results

Peritoneal transport characteristics

In the cross-sectional part, an inverse relationship was observed between the D/P[creat] ratio and the peritoneal ultrafiltration volume ($r = -0.37$, $P = 0.02$), but not between D/P[creat] and daily glucose prescription. Also, no relationship was observed between D/P[creat] and the time on dialysis. D/P[creat] was also unrelated to any parameter of fluid state in the cross-sectional part. Nevertheless, during the 4-month follow-up period, a significant relationship between the D/P[creat] and the change in the ECW ($r = 0.39$, $P = 0.04$) was observed (Figure 1). The change in ECW was significantly related to the change in systolic BP ($r = 0.45$, $P = 0.03$), but not to diastolic blood pressure.

Residual renal function

In the cross-sectional part of the study, rGFR was significantly related to the time on dialysis treatment ($r = -0.44$, $P = 0.003$) (Figure 2). There was a significant

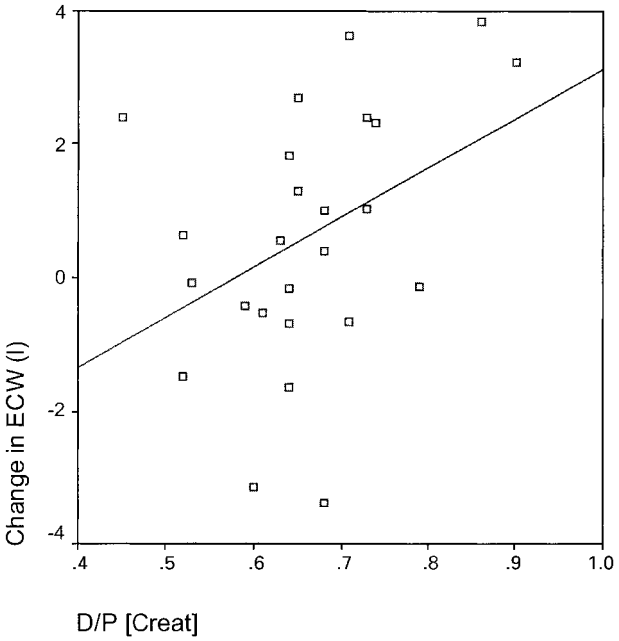

Fig. 1. D/P[creat] *vs* the change in ECW during 4 months follow-up. ECW, extracellular volume determined by bromide dilution; D/P[creat], D/P[creat] creatinine ratio peritoneal membrane determined after a 4-h dwell with a 2.27% CAPD glucose solution.

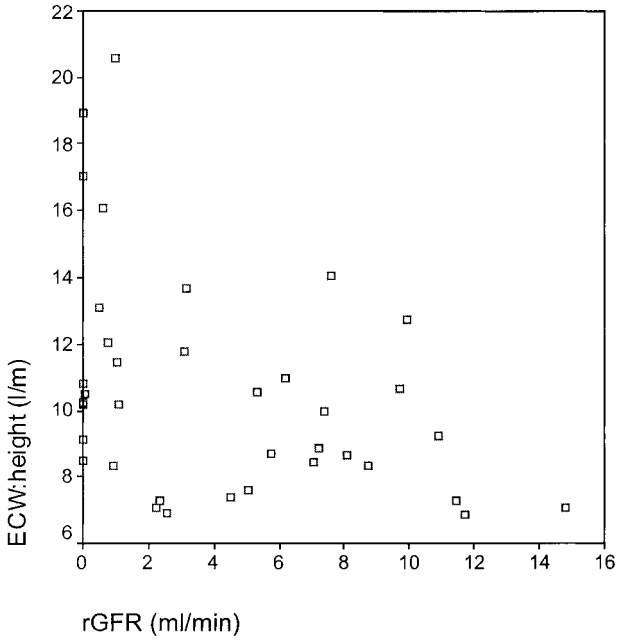

Fig. 2. rGFR in relation to fluid state. rGFR, residual glomerular filtration rate; ECW:height, extracellular volume determined by bromide dilution, corrected for height. $r=-0.40$; $P=0.016$.

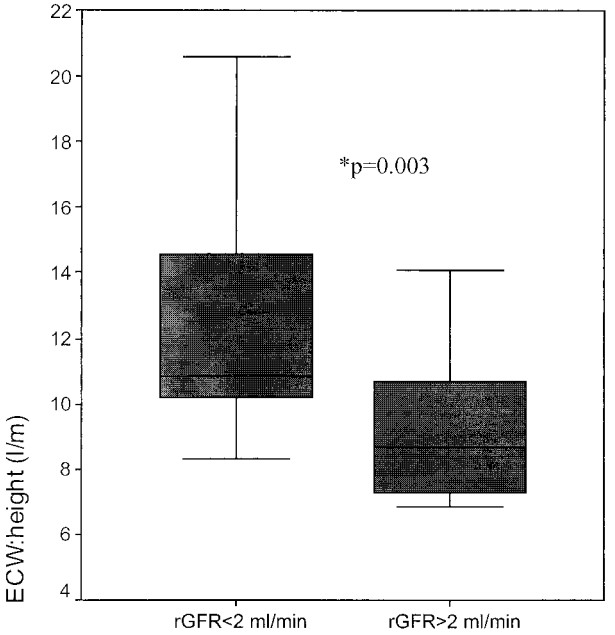

Fig. 3. ECW in patients with rGFR <2 and >2 ml/min. rGFR, residual glomerular filtration rate; ECW:height, extracellular volume determined by bromide dilution, corrected for height. Box indicates the 25th–75th percentile range (line across box = median). Capped bars indicate minimum and maximal values (with exception of outliers).

inverse relationship between rGFR with ECW:height ($r=-0.40$, $P=0.016$) and ECW:BSA ($r=-0.48$, $P=0.003$). rGFR was also significantly related to TBW, corrected for height ($r=-0.36$, $P=0.045$) and BSA ($r=-0.41$, $P=0.014$). The ECW:TBW ratio tended to be significantly related to rGFR ($r=-0.31$, $P=0.08$). In multi-regression analysis, rGFR ($t=-2.2$, $P=0.035$), but not time on dialysis treatment ($t=-0.44$, $P=0.6$), was a significant predictor of ECW:height. When patients were divided according to rGFR (<2 or >2 ml/min), all parameters of fluid state were significantly higher in the group with rGFR <2 ml/min (Figure 3), despite a significantly higher peritoneal ultrafiltration volume and peritoneal glucose prescription (Table 2).

As sex may influence the ratio between body water compartments, males and females were analysed separately. In both males and females, ECW:height and ECW:BSA were significantly higher in the group with rGFR <2 ml/min compared with the group with rGFR >2 ml/min ($P<0.05$). Moreover, sex was included as dummy variable in multi-regression analysis with RCW:height as dependent parameter and rGFR as independent parameter. Also after correction for sex, rGFR remained an independent predictor for rGFR ($t=-2.1$, $P<0.05$).

Inflammation

CRP was not significantly related to either D/P[creat] or rGFR. Nevertheless, there was a significant relationship between CRP and ECW:height ($r=0.54$, $P<0.001$) and ECW:BSA ($r=0.43$, $P=0.007$), which also held true for the relation with logCRP ($r=0.44$, $P=0.006$ and $r=0.31$, $P=0.06$) (Figure 4). The relationship remained significant when the outlier value had been removed from the analysis. CRP was also significantly related to fluid state, expressed as TBW:height ($r=0.48$, $P=0.006$) and the ECW:TBW ratio ($r=0.56$, $P<0.001$). Multi-regression analysis showed that ECW:height ($t=3.4$, $P=0.002$), but not rGRF ($t=-0.185$, $P=0.9$), was an independent predictor of ECW.

Especially in severely overhydrated patients (arbitrarily expressed as ECW:height above 0.14), mean CRP was very high despite a high standard deviation (35.6 ± 30.2 mg/l).

Serum albumin was inversely related to D/P[creat] ($r=-0.38$, $P=0.02$), but not to any parameter of fluid state.

Discussion

The main findings of the study were first, the significant relationship of fluid state with peritoneal transport characteristics and rGFR; secondly, the significantly higher ECW and TBW in patients with a rGFR below 2 ml/min despite a significantly higher daily peritoneal glucose prescription and peritoneal ultrafiltration volume compared with patients with a higher rGFR; and finally, the significant relationship between fluid status and CPR levels.

Table 2. Comparison between patients with rGFR <2 ml/min and >2 ml/min

	GFR <2 ml/min	GFR >2 ml/min	*P*
n	15	22	
Sex (male/female)	12/3	14/8	
ECW:height (l/m)	12.5 ± 3.8	9.3 ± 2.2	0.003
ECW:body surface area (l/m^2)	11.0 ± 3.2	8.2 ± 1.4	0.001
TBW: height (l/m)	23.4 ± 3.3	20.4 ± 3.9	0.026
TBW: body surface area (l/m^2)	20.7 ± 2.3	18.8 ± 2.5	0.035
ECW:TBW	41.4 ± 7.7	35.3 ± 8.4	0.020
Peritoneal ultrafiltration volume (ml/day)	1856 ± 644	658 ± 781	0.0001
Peritoneal glucose prescription (g/day)	216.3 ± 60.0	156.5 ± 53.0	0.004
Residual diuresis (ml/day)	270 ± 566	1438 ± 1213	0.001
Serum albumin (g/l)	31.5 ± 3.08	32 ± 5.2	NS
C-reactive protein (mg/l)	11.4 ± 19.7	4.1 ± 3.5	NS
24-h systolic blood pressure (mmHg)	130.8 ± 19.4	130.3 ± 13.1	NS
24-h diastolic blood pressure (mmHg)	77.6 ± 11.4	79.5 ± 9.9	NS
Number of antihypertensive agents	1.3 ± 1.0	1.9 ± 1.1	NS
Weekly Kt/V urea	2.0 ± 0.3	2.7 ± 0.8	NS
D/P[creat] creatinine	0.69 ± 0.11	0.67 ± 0.11	NS
Time on PD (months)	31.9 ± 17.4	16.7 ± 16.5	0.016
rGFR (ml/min)	0.40 ± 0.45	6.9 ± 3.4	0.0001

rGFR, residual glomerular filtration rate; ECW, extracellular volume determined by bromide dilution; TBW, total body water, assessed by deuterium oxide.

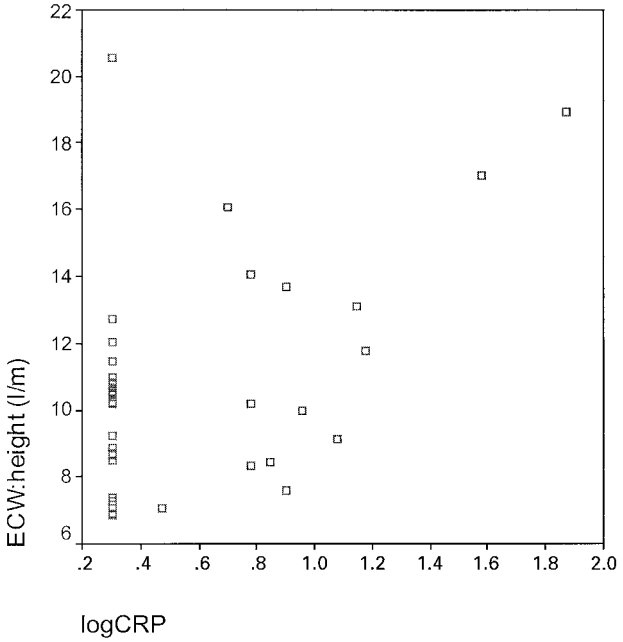

Fig. 4. LogCRP in relation to fluid state. ECW:height, extracellular volume determined by bromide dilution, corrected for height; logCRP, log transformation of C-reactive protein. $r = 0.44$; $P = 0.006$.

The relationship between peritoneal transport characteristics (D/P[creat]) and fluid state), which only became apparent during the longitudinal part of the study, was not very pronounced. Nevertheless, it appears likely that the relationship between the D/P[creat] ratio, measured at the start of the study, and the change in ECW during the follow-up period is explained by a reduced fluid removal caused by a higher permeability of the peritoneal membrane, which is also suggested by the inverse relationship between D/P[creat] and daily peritoneal ultrafiltration volume. Despite the rather weak correlation, these findings suggest that a more permeable peritoneal membrane is a risk factor for progressive overhydration, as could be expected theoretically.

The relationship between rGFR and fluid state appeared to be more pronounced. Also, when patients were divided in two subgroups according to GFR, a highly significant difference in fluid state was observed between the two groups, probably due to the progressive loss of kidney function for the removal of salt and water. It was remarkable that the higher ECW in the patients with a rGFR <2 ml/min occurred despite a significantly higher peritoneal ultrafiltration volume (nearly 2 l/day), and a higher 24-h glucose prescription. Although it should be acknowledged that a cut-off point of 2 ml/min is arbitrary, the present study suggests that it may be difficult to maintain normal hydration in CAPD patients with negligible renal function by the use of standard glucose solutions without a stronger emphasis on sodium and fluid restriction [17].

In contrast to the strong relationship between rGFR and fluid state observed in the cross-sectional part of the study, rGFR was not related to the change in ECW during the 4-month period. Although this may seem counterintuitive, it can be hypothesized that the lack of such a relationship is explained by the fact that in patients with negligible rGFR, ECW is stabilized at a higher level by the use of more concentrated glucose solutions, without reaching normal hydration. This might also explain why rGFR is not normalized in patients with absent rGFR despite a near comparable daily fluid removal, as observed in patients with rGFR >2 ml/min.

Regarding inflammation, no relationship between peritoneal transport characteristics and CRP was observed. These results should be interpreted with some caution, because in the present study, CRP was not assessed with an ultra-sensitive assay. Nevertheless, the absent relationship between CRP and peritoneal transport characteristics is in agreement with earlier observations by Wang *et al*. [4].

An interesting finding of the present study is the significant relationship between (log)CRP levels and fluid state. Especially in the severely overhydrated patients, mean CRP was very high despite a large standard deviation. Although the limitations of our CRP assay have already been outlined, and the present data should, also in view of the skewed distribution of the CRP data, be regarded as preliminary, a pathophysiological basis for the present findings might be found in earlier observations in non-uraemic patients, in which an increase in inflammation was observed in patients with congestive heart failure. In these patients, it was hypothesized that gut oedema, resulting from overhydration, might lead to an increased passage of endotoxins from the intestines into the blood [18]. Another explanation for the relationship between CRP and fluid state might be a reduction in 'dry weight' because of loss of lean body mass in the inflammatory state, which leads to progressive overhydration that was not appropriately detected and treated.

In contrast, serum albumin was not related to any parameter of fluid state, which is in contrast to observations of others [8,19], but in agreement with the findings of Kaysen *et al*. in haemodialysis patients [20]. The pathogenesis of hypoalbuminaemia is multifactorial in dialysis patients, and includes factors such as albumin loss through the peritoneum, inflammation and malnutrition [20,21]. This might explain the fact that some studies found a relationship between fluid state and serum albumin, whereas others, including the present one, did not.

Drawbacks of the present study are the short follow-up period, the relatively small number of patients included and the large number of drop-outs in the longitudinal part. The first drawback is, however, inherent in the complexity and the expense of the methodology. Moreover, in a study including relatively small numbers of patients, longer follow-up periods will undoubtedly lead to an increase in drop-outs, as was indeed already apparent. Another point of criticism might be the fact that transport characteristics were only assessed by the D/P[creat] ratio, assessed at the start of the study. Nevertheless, this approach was chosen because the D/P[creat] ratio still appears to be the most widely used test to assess peritoneal transport characteristics and was used in most other studies assessing the influence of transport state on outcome parameters in PD patients [2,7].

Moreover, when looking at the results in more detail, in some patients ECW decreased during the follow-up period despite the fact that the peritoneal dialysis prescription was not changed. The reason for this finding is not entirely clear. Nevertheless, we believe that it is not due to methodological problems, since the acceptable coefficient of variation for ECW measurements at baseline and after 4 months follow-up is a strong arguments for the reliability of the bromide assay. One might question if changes in sodium or fluid intake may have played a role. It should be mentioned that neither sodium intake nor urinary and peritoneal sodium removal were measured in the present study.

Therefore the results presented in this paper should be regarded as preliminary, and should be followed by a more detailed study that also takes these potentially very important parameters into account. Moreover, due to the fact that patients with heart failure and type I diabetes were excluded, the data may not be extrapolated to the entire dialysis population because severe co-morbidity might confound the relationships found in the present study.

It should also be pointed out that patients were included with different dialysis durations. However, at present, and to the best of our knowledge, there are very limited and circumstantial data regarding the determinants of fluid state in PD patients. Therefore we chose not to apply strict matching criteria for the duration of CAPD treatment in the present study, also in order to assess the effect of this parameter on fluid state. In multi-regression analysis, it was shown that rGFR *per se* and not the duration of dialysis treatment was an independent predictor of fluid state.

In conclusion, the present study shows fluid state to be significantly related to peritoneal transport characteristics and rGFR. Compared with patients with a rGFR >2 ml/min, ECW was significantly higher in CAPD patients with negligible rGFR despite a higher peritoneal ultrafiltration volume and glucose prescription. These findings raise doubts about whether fluid state in patients with negligible residual renal function can be adequately maintained on standard glucose solutions without additional sodium and fluid restriction. The relationship between CRP and fluid state found in the present study might suggest one between overhydration and inflammation.

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