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Analysis of Ultrafiltration Failure Diagnosed at the Initiation of Peritoneal Dialysis with the Help of Peritoneal Equilibration Tests with Complete Drainage at Sixty Minutes. A Longitudinal Study

Daniela Machado Lopes,[1] Ana Rodríguez-Carmona,[2] Teresa García Falcón,[2] Andrés López Muñiz,[2] Tamara Ferreiro Hermida,[2] Antía López Iglesias,[2] and Miguel Pérez Fontán[2,3]

Division of Nephrology,[1] Hospital Vilanova de Gaia/Espinho, Portugal; Division of Nephrology,[2] University Hospital A Coruña, Spain; and Department of Medicine,[3] Health Sciences Faculty, University of A Coruña, Spain

Abstract

Background. Ultrafiltration failure (UFF) diagnosed at the initiation of peritoneal dialysis (PD) has been insufficiently characterized. In particular, few longitudinal studies have analyzed the time course of water transport in patients with this complication.

Objective. To investigate the time course of peritoneal water transport during the first year on PD in patients presenting UFF since the initiation of this therapy (study group).

Method. Prospective, observational, single-center design. We analyzed, at baseline and after 1 year of follow-up, peritoneal water transport in 19 patients incident on PD with UFF. We used incident patients without UFF as a control group. Water transport was characterized with the help of 3.86/4.25% dextrose-based peritoneal equilibration tests (PETs) with complete drainage at 60 minutes.

Results. The study group revealed a disorder of water transport affecting both small-pore ultrafiltration (SPUF) (p = 0.054 vs incident without UFF) and free water transport (FW T) (p = 0.001). After 1 year of follow-up, FWT displayed a general increasing trend in the study group (mean variation 48.9 mL, 95% confidence interval [CI] 15.5, 82.2, p = 0.012), while the behavior of SPUF was less predictable (-4.8 mL, 95% CI -61.4, 71.1, p = 0.85). These changes were not observed in incident patients without UFF. Neither initial clinical characteristics, baseline PET-derived parameters, or suffering peritoneal infections during the first year predicted the time course of the capacity of UF in the study group. Recovery from incident UFF was apparently linked to improvement of SPUF.

Conclusions. Patients with UFF at the start of PD suffer a disorder of peritoneal water transport affecting both FWT and SPUF. Free water transport increases systematically in these patients after 1 year of follow-up. The evolution of SPUF is less predictable, and improvement of this parameter marks reversibility of this complication.

Keywords

Peritoneal dialysis, ultrafiltration, ultrafiltration failure, free water transport, small pore ultrafiltration, peritoneal equilibration test

Failure to obtain adequate rates of ultrafiltration (UF) is one of the most feared complications of peritoneal dialysis (PD), resulting in recurrent or persistent volume overload, with well-known detrimental consequences for the cardiovascular outcome of these patients (1). Insufficient UF may be secondary to different causes, including mechanical complications and inadequate prescription of PD, but, in the majority of cases, it is the consequence of an intrinsic disorder of the peritoneal membrane, which prevents sufficient and/or sustained water transport toward the peritoneal cavity. The incidence and prevalence of UF failure (UFF) have not been established with certainty (2), partly due to a lack of a standardized definition of this complication until relatively recent years (3). Clinically significant UFF is, in the majority of cases, a relatively late complication of PD, appearing in response to chronic injury to the peritoneal membrane, precipitated by the bioincompatibility of PD solutions and by peritoneal infections, among other factors. This type of UFF indicates a deep structural disorder of the membrane, is essentially nonreversible, and contributes much to mortality and technique failure in long-term PD patients (4). On the other hand, some patients present features consistent with UFF from the initiation of PD. This complication is usually less consequential than late UFF, because residual kidney function helps to prevent hypervolemia. The mechanisms underlying early UFF are not totally clear, although it has been hypothesized that a large peritoneal vascular surface and fast lymphatic reabsorption rates play significant roles. It would appear that incident UFF has a potential for reversibility in a significant proportion of cases (5).

The classic peritoneal equilibration test (PET), as designed for Twardowski (6), is not suitable for characterizing peritoneal water transport, which has hampered knowledge about this phenomenon in the past. Several functional tests have been proposed to overcome this limitation, including variants of the classic PET and more complex procedures, such as the peritoneal dialysis capacity (PDC) or the standard peritoneal assessment (SPA) tests (7). The modified PET with complete drainage at 60 minutes, based on 3.86/4.25% dextrose-based dialysate, permits a relatively accurate calculation of water transport during the first 60 minutes of a peritoneal exchange, allowing split estimations of transport across ultrasmall (free water transport [FWT]) and small pores (SPUF) (8,9). To our knowledge, this test has not been applied to assess peritoneal water transport longitudinally, either in PD patients in general or in those suffering from UFF.

We performed a prospective, observational study with the main objective of investigating the time course of peritoneal water transport in a sample of patients incident on PD during a 1-year follow-up period. Our main focus was to assess the evolution of incident patients presenting UFF since the initiation of PD.

Method

General Design

Following a prospective, observational design, we investigated the time course of water transport in a group of patients incident on PD in the University Hospital of A Coruña (Spain), according to the results of 3.86/4.25% dextrose-based PET with complete abdominal emptying at 60 minutes. The recruitment period was from January 2009 to October 2013, and follow-up was closed by December 2014. The main objective of the study was to characterize the evolution of water transport over a period of 1 year, focusing on incident patients with UFF at baseline, comparing them with incident patients without UFF.

The study complied with the requirements of the ethical committee of our center for observational studies, and oral consent for clinical data management was obtained from participants.

Patients

The study population included all patients incident on PD during the recruitment period. We considered the following inclusion criteria:

– Age 15 – 85 years
– Baseline and follow-up clinical records available
– Expected survival of at least 1 year
– PET data available at baseline and after 1 year of follow-up
– No episode of peritonitis, hemoperitoneum, or abdominal surgery for at least 8 weeks before PET studies
– Informed consent given

We screened 72 patients during the recruitment period, but only 52 were finally included for analysis. The remaining patients did not fulfill the 1-year protocol, due to death (n = 4), kidney transplant (n = 7), drop-out to hemodialysis (n = 3), or other reasons (including protocol breaks or loss to follow-up) (n = 6).

Strategy of Analysis

The main objective of the study was to characterize the time course of UF and water transport of incident patients with UFF, which we defined according to the International Society for Peritoneal Dialysis (ISPD) recommendations (< 400 mL at 240 minutes during a 3.86/4.25% dextrose-based PET) (3). We compared this time course with those of a control group of incident patients without UFF. For this purpose, we first compared the clinical and peritoneal functional characteristics (as assessed from PET) of the 2 groups, and then the time course of the latter between the baseline and the follow-up PET. Finally, we focused on incident patients with UFF, comparing patients with transient and persistent UFF at the end of follow-up. General categorization of peritoneal transport was carried out according to the dialysate to plasma ratio (D/P) of creatinine at 240 minutes, as classically described by Twardowski (6).

Pet Procedure

After an overnight dwell with 2.27/2.5% dextrose-based dialysate, PET studies started at 9 a.m. We used 3.86/4.25% dextrose-based solutions of the same brand usually prescribed for the patient. The dialysate volume was that usually used by the patient, with an upper limit of 2 liters. After dialysate infusion, a partial drainage was immediately allowed, and a 10-mL sample was obtained for laboratory estimations. We allowed complete dialysate drainage at 60 and 240 minutes, to estimate UF and obtain new dialysate samples for laboratory estimations. Blood samples were obtained at baseline. Dialysate bags were weighed before infusion, at 60 minutes, and at 240 minutes, to estimate UF. The baseline PET was performed not earlier than 4 weeks and not later than 12 weeks after initiation of PD.

Laboratory Methods and Secondary Calculations

Glucose, creatinine, and sodium (Na) were measured in both plasma and dialysate using standard automated analyzer techniques. Dialysate creatinine was corrected for interference by glucose according to our own laboratory standards. Sodium in dialysate and plasma was measured using an indirect ion selective electrode method. Sodium removal and peritoneal glucose loads were estimated by simple mass balance.

We estimated the following parameters:

- Sodium sieving, as the absolute dip of dialysate sodium concentration at 60 minutes, calculated as follows:

  Na sieving (mmol/L) = dialysate Na at 0' –dialysate Na at 60’

- SPUF at 60’ was calculated as follows:

  SPUF (mL) = (NaR × 1,000) / PNa,

  where NaR (mmol) is Na removal and PNa is plasma sodium concentration (mM/L). Sodium removal was calculated as follows:

  NaR = [dialysate volume at 60' (L) × dialysate Na concentration at 60' (mmol/L)] – [dialysate volume instilled (L) × dialysate Na concentration at 0' (mmol/L)].

- FWT was calculated as follows:

  FWT uncorrected (mL) = total UF volume at 60' (mL) – SPUF(mL).

- We also estimated corrected FWT, according to the algorithm described by Venturoli *et al.* (10):

  FWT corrected = total UF at 60' +15 −0.92× SPUF, where "15" represents tentative cumu lative lymphatic absorption during 60 minutes (18 mL) minus the cumulative UF throug h the large pores over 60 minutes (approx. 3 mL).FWT corrected = total UF at 60' +15 − 0.92× SPUF, where ″15″ represents tentative cumulative lymphatic absorption during 60 minutes (18 mL) minus the cumulative UF through the large pores over 60 minutes (appr ox. 3 mL).

- Small solute transport characteristics were estimated from D/P of creatinine and D/D_0 of glucose at 240’, as described by Twardowski (6).

Data Analysis

Numerical variables are presented as mean values (standard deviation [SD]), unless abnormally distributed (median with range). Categorical variables are presented as *n* (%). Comparisons were performed according to Student's *t*-test (paired and unpaired), χ^2 distribution and nonparametric tests (Mann Whitney, Wilcoxon).

Results

Baseline

Table 1 presents the baseline clinical characteristics of the study population. Patients with UFF were younger and tended to present higher levels of C-reactive protein than those without UFF. All patients were managed with low-glucose degradation product (GDP) solutions. Table 2 shows the main results of the baseline PET, without unexpected differences observed.

TABLE 1
Baseline Clinical Characteristics of Patients, Classified According to UFF

	UFF	No UFF	*P*
Patients (*n*)	19	33	
Age (years)	54.5 (12.9)	63.5 (12.4)	0.02
Gender (male) (%)	13 (68.4)	26 (78.8)	0.41
Diabetes (%)	8 (42.1)	12 (36.4)	0.68
GFR (mL/minute)	8.4 (4.1)	9.1 (3.8)	0.54
Modality of PD (automated PD) (%)	2 (10.5)	7 (21.2)	0.33
Time on PD (months)	1.8 (1.5)	1.7 (1.3)	0.90
Peritonitis (*n*)	0	0.1 (0.2)	—
Glucose load (g/24 h)	83.6 (60.8)	70.1 (29.8)	0.79
Icodextrin (%)	12 (63.2)	13 (39.4)	0.10
RAA (%)	7 (36.8)	17 (51.5)	0.31
C-reactive protein (mg/dL)	0.53 (0.18–6.70)	0.26 (0.02–8.32)	0.07

UFF = ultrafiltration failure; GFR = glomerular filtration rate; PD = peritoneal dialysis; RAA = renin-angiotensin antagonists; SD = standard deviation. Comparisons by Student's *t*-test, Mann-Whitney (C-reactive protein) and χ^2 distribution.
Numerical variables presented as mean (SD), except C-reactive protein (median, range). Categorical variables presented as number (%).

TABLE 2
Baseline Transport Characteristics of Patients, Classified According to UFF

	UFF *n*=19	No UFF *n*=33	*P*
UF, 60′ (mL)	231.1 (108.3)	366.3 (180.9)	0.022
UF, 240′ (mL)	271.6 (85.4)	681.8 (218.6)	0.0005
SPUF (mL)	138.3 (102.6)	192.1 (91.6)	0.054
FWT uncorrected (mL)	92.7 (31.7)	174.3 (89.3)	0.0005
FWT corrected (mL)	114.6 (37.6)	198.9 (87.1)	0.001
D/D_0 240′glucose	0.23 (0.07)	0.35 (0.10)	0.0005
D/P 240′ creatinine	0.77 (0.07)	0.67 (0.10)	0.002
Na sieving 60′ (mmol)	4.9 (1.7)	9.4 (3.4)	0.0005
Final Na balance (mmol)	25.5 (14.2)	67.4 (24.7)	0.0005

UFF = ultrafiltration failure; UF = ultrafiltration; SPUF = small pore UF; FWT = free water transport; D/D0 = ratio of dialysate glucose at 4 hours' dwell time to dialysis glucose at 0 dwell time; D/P = dialysate/plasma; Na = sodium.
Values presented as mean (SD).
Comparisons by Student's *t*-test except SPUF, D/P creatinine 240′, and D/D_0 glucose 240′ (Mann Whitney).

Variations between First and Second Pet

When patients were reassessed after 1 year, 8 out of 19 patients (42.1%) with baseline UFF presented an UF at 240 minutes ≥ 400 mL, while UFF persisted in 11 (57.9%). Only 5 patients without UFF at baseline (15.2%) presented UFF after 1 year. Table 3 displays the time course of transport characteristics between baseline and follow-up PET studies. Incident patients with UFF experienced a significant increase in their UF capacity, based on an improvement in FWT, while SPUF did not change overall. On the contrary, patients without UFF at initiation of PD did not experience significant changes during the follow-up period.

In patients with UFF, a comparison of baseline characteristics between those who improved their UF capacity 1 year later and those who did not showed that the latter tended to use icodextrin more frequently from baseline (81.8% vs 37.5%, $p = 0.048$ χ^2) (age, diabetes, glomerular filtration rate [GFR], renin-angiotensin antagonists [RAA], C-reactive protein, and peritoneal glucose load were not significant). Moreover, baseline peritoneal transport characteristics did not differ significantly between the 2 subgroups (Table 4). Four out of 11 patients (36.4%) in whom UFF persisted suffered peritonitis between the baseline and the second PET, as compared with 3 of the 8 patients (37.5%) who improved their UF capacity ($p = 0.68$). Table 5 compares the time course of peritoneal transport characteristics in these 2 subgroups. The main difference affected SPUF, which increased in patients improving their UF capacity, with an opposite (not significant) trend for those with persistent UFF. Interestingly, FWT tended to improve in both groups, although to a significant extent only in those who recovered from UFF.

TABLE 3
Changes Between First and Second PET, According to Baseline UFF

	UFF *n*=19	No UFF *n*=33
UF 60′ (mL)	43.5	-43.5
	-25.6, 112.5	-120.3, 33.3
	0.20	0.26
UF 240′ (mL)	123.2	-62.1
	20.2, 228.3	-110.4, 23.5
	0.022	0.20
SPUF (mL)	-4.8	-43.4
	-61.4/71.1	-110.3, 23.6
	0.85	0.20
FWT uncorrected (mL)	48.7	-0.2
	14.9, 72.4	-34.8, 34.6
	0.012	0.99
FWT corrected (mL)	48.9	-2.3
	15.5, 82.2	-37.3, 32.7
	0.015	0.90
D/D_0 240′ glucose	0.06	0.00
	0.01, 0.11	-0,04, 0.05
	0.019	0.88
D/P creatinine 240′	-0.04	0.01
	-0.10, 0.03	-0.02, 0.05
	0.20	0.43
Na sieving 60′ (mmol)	2.9	0.1
	1.0, 4.6	-1.4, 1.5
	0.003	0.93
Final Na balance (mmol)	10.8	-7.1
	-2.1, 23.8	-19.0, 4.8
	0.095	0.23

PET = peritoneal equilibration test; UFF = ultrafiltration failure; UF = ultrafiltration; SPUF = small pore UF; FWT = free water transport; D/D0 = ratio of dialysate glucose at 4 hours' dwell time to dialysis glucose at 0 dwell time; D/P = dialysate/plasma; Na = sodium; CI = confidence interval.
Values calculated as second – first PET (mean, 95% CI, *p* value).
Comparisons by Student's *t*-test (paired).
Bold values represent $p < 0.05$.

TABLE 4
Baseline Transport Characteristics of Incident Patients with UFF, According to Results of Second PET

	No UFF in second PET	Persistent UFF	*P*
Patients (*n*)	8	11	
UF 60′ (mL)	205.0 (97,5)	250.0 (116.2)	0.38
UF 240′ (mL)	288.8 (43.2)	259.1 (106.8)	0.47
SPUF (mL)	112.7 (88.5)	157.0 (112.0)	0.37
FWT uncorrected (mL)	92.3 (26.8)	93.0 (44.8)	0.97
FWT corrected (mL)	113.0 (28.0)	115.9 (44.6)	0.87
D/D_0 240′ glucose	0.24 (0.08)	0.23 (0.07)	0.62
D/P 240′ creatinine	0.74 (0.07)	0.80 (0.06)	0.07
Na sieving (mmol)	5.3 (1.4)	4.8 (2.0)	0.61
Final Na balance (mmol)	29.8 (6.9)	22.4 (17.5)	0.28

UFF = ultrafiltration failure; PET = peritoneal equilibration test; UF = ultrafiltration; SPUF = small pore UF; FWT = free water transport; D/D0 = ratio of dialysate glucose at 4 hours' dwell time to dialysis glucose at 0 dwell time; D/P = dialysate/plasma; Na = sodium. Comparisons by Mann-Whitney's test.

TABLE 5
Changes Between First and Second PET in Incident Patients with UFF, According to UF Status in Second PET

	No UFF in second PET *n*=8	Persistent UFF *n*=11
UF 60′ (mL)	197.0	-22.7
	26.1, 367.9	-117.0/71.5
	0.03	0.60
UF 240′ (mL)	305.0	-9.0
	188.7, 421.3	-118.6/100.1
	0.0005	0.86
SPUF (mL)	137.3	-50.6
	-50.6, 325.3	-144.8/43.5
	0.11 (**0.036 Wilcoxon**)	0.26
FWT uncorrected (mL)	59.7	27.9
	-3.9, 123.3	-7.2/68.1
	0.062	0.11
FWT corrected (mL)	66.5	26.1
	6.3, 126.8	-3.8/64.8
	0.035	0.09
D/D_0 240′ glucose	0.06	0.05
	0.01, 0.12	-0.03/0.14
	0.028	0.16
D/P creatinine 240′	-0.06	-0.02
	-0.19, 0.06	-0.11/0.06
	0.24	0.56
Na sieving 60′ (mmol)	4.1	1.8
	0.9, 7.3	-0.6/4.3
	0.020	0.13
Final Na balance (mmol)	28.4	1.9
	10.1, 46.8	-17.4/13.6
	0.008	0.79

PET = peritoneal equilibration test; UFF = ultrafiltration failure; UF = ultrafiltration; SPUF = small pore UF; FWT = free water transport; D/D0 = ratio of dialysate glucose at 4 hours' dwell time to dialysis glucose at 0 dwell time; D/P = dialysate/plasma; Na = sodium; CI = confidence interval.
Values calculated as second – first PET (mean, 95% CI, *p* value). Comparisons by Student's *t*-test (paired). Results of Wilcoxon's test displayed when different from Student's *t*-test.
Bold values represent $p < 0.05$.

Discussion

According to our results, patients presenting with UFF at initiation of PD suffered a disorder of peritoneal water transport affecting both SPUF and FWT (Table 2). On reevaluation 1 year later, a trend to a general improvement of FWT was observed, while the evolution of SPUF was less predictable (Table 3). Improvement of SPUF appeared to mark patients who recovered from UFF during follow-up (Table 5).

Several longitudinal studies have analyzed the time course of peritoneal water transport in the PD population at large. Struijk *et al.* (11) reported a bimodal evolution of UF and small solute transport during the first 2 years on PD, with an increase in the UF capacity during the first 6 months, followed by a decrease thereafter. As a consequence, UF rates after 2 years of follow-up were similar to baseline values. Davies (12) analyzed the results of classic PET in 574 patients incident on PD, observing an essential stability of the UF capacity during the first 12 months, followed by a progressive decay in the ensuing years. Small solute transport rates showed a simultaneous regression to mean values, increasing in slower transporters and decreasing in fast transporters. Similar findings were reported by Fernandez-Reyes *et al.* (13), with nonsignificant trends to an increase in UF during the first year, and a later progressive decay. A more recent in-depth study (14), based on SPA tests, partially confirmed the results of previous investigations, by reporting an overall stability of the capacity of UF during the first years, followed by a later decline, particularly after the fourth year on PD.

Few studies have attempted to characterize UFF present since the initiation of PD. During a longitudinal analysis, del Peso *et al.* (15) detected an increase of the capacity of UF and a decrease of small solute transport rates at the end of the first year in these patients. Only 2 out of 12 patients with incident UFF still suffered this condition after this period. This study, based on a specific kinetic software, did not investigate UF fractions. More recently, a cross-sectional, SPA-based analysis (16) compared patients with UFF, according to permanence on PD at the time of diagnosis, although incident patients with the condition were not assessed separately. Patients treated for less than 2 years with PD and suffering from UFF presented relatively fast small solute transport rates, rapid lymphatic absorption rates, decreased FWT, preserved SPUF, and similar hydraulic permeability and osmotic conductance to glucose, when compared with their controls without UFF. On the contrary, patients with late UFF presented a more diffuse disorder of UF fractions (affecting both FWT and SPUF) and decreased hydraulic permeability and osmotic conductance to glucose. For the authors, the changes observed in earlier UFF were consistent with a large number of perfused peritoneal vessels and a fast lymphatic absorption. Moreover, preserved osmotic conductance to glucose suggested that changes were, at least for the most part, functional and, consequently, potentially reversible. These changes have been suggested to follow the release of vasoactive substances by mesothelial cells, in response to contact with dialysate (17). These observations are consistent with current classification of UFF (18). According to the latter, early UFF could be secondary to either endothelial dysfunction (often related to an inflammatory state) or to a large peritoneal vascular surface area. The former subgroup could explain the poor prognosis associated with early UFF observed in some studies (19). On the other hand, changes observed in late UFF indicate a structural and irreversible injury to the peritoneal membrane, more consistently associated with decreased patient and technique survival rates (19).
In our study, incident patients with UFF experienced a systematic increase of FWT and sodium sieving at 60 minutes after 1 year of follow-up, while SPUF rates remained unchanged for the whole subgroup (Table 3). Remarkably, these changes were not observed in incident patients with a normal capacity of UF at inception of PD. On the other hand, comparison between incident patients with UFF, according to recovery from this condition after 1 year (Table 5) suggested that FWT improved in both subgroups (although not to the same extent), while the more variable evolution of SPUF determined recovery, in practical terms. At first sight, the improvement of FWT could be attributed to a regression of the functional component of fast solute transport present at the initiation of PD. However, the increase in FWT was not systematically paralleled by an improvement in SPUF. The explanation for this discrepancy is not clear, but the consistent

increase in FWT might be explained by an increase in aquaporin-driven UF, which could be a result of peritoneal exposure to dextrose-based solutions (20). On the other hand, changes observed for SPUF and small solute (particularly glucose) transport rates suggest an early increase in peritoneal vascular surface area, which was reversible in only a fraction of these patients. Our study was unable to identify factors which may portend reversibility of these disorders. In particular, baseline plasma levels of C-reactive protein or the rates of peritoneal infection during the first year were not discriminative for this purpose. Previous studies have disclosed associations among several genetic polymorphisms, on one hand, and both baseline small solute transport characteristics and their evolution in time, on the other (21). The relevance of genetic factors for the time course of incident UFF awaits further clarification.

This study has significant weaknesses, including a limited statistical power. The longitudinal design offers clear advantages and a relatively novel approach, but has some drawbacks, including a risk for selective biases, due to a significant proportion of patients lost during follow-up. Moreover, the modified PET-based analysis did not permit direct estimations of lymphatic absorption rates, which demand specific methodologic approaches, beyond routine clinical practice (22). Despite these limitations, the study offers a longitudinal view of water transport in patients with UFF since the inception of PD, contributing to a clearer knowledge of this disorder.
In summary, patients with UFF since the start of PD suffer a disorder of peritoneal water transport affecting both FWT and SPUF. Our data confirm that early UFF has a potential for reversibility, in many patients. Free water transport increases systematically in these patients after 1 year of follow-up, while the evolution of SPUF is less predictable. Improvement in SPUF marks patients in whom UFF is reversible. We did not detect consistent baseline markers that would serve to identify patients in whom UFF may be reversible. Peritoneal infections during the first year did not appear to influence the time course of water transport among incident patients with UFF. Further studies will be necessary to characterize early UFF in PD patients.

Disclosures

The authors have no financial conflicts of interest to declare.

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