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Peritoneal Transport Characteristics at the Beginning and in Long Term Peritoneal Dialysis: a Single Center Experience

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ABSTRACT

Introduction: Peritoneal dialysis (PD) is an established treatment for patients with end-srage kidney disease. The method was developed as an alternative to hemodialysis (HD) presenting a patient survival rate equivalent to HD and better preservation of residual renal function. Peritoneal dialysis (PD) patients have different peritoneal membrane permeability (transport) characteristics. High peritoneal membrane permeability is associated with increased mortality risk in the patient population. **Aim:** The aim of this study was to analyze the importance of the peritoneal membrane transport status in patients treated with continuous ambulatory peritoneal dialysis (CAPD). **Methods:** The study included 60 adult continuous ambulatory peritoneal dialysis (CAPD) patients, 29 male and 31 female, mean age 56.63±15.06 years. All patients treated with conventional glucose- based PD fluids. For the short term (within 3 month after start of PD) and long term (more than 12 months) peritoneal dialysis analysis of peritoneal transport characteristics has been used peritoneal functional test (PFT). With the test, categorisation of patients was possible into high (H), high-average (HA), low average (LA), and low (L) transporters. **Results:** Dialysate–to plasma ratio (D/P) of creatinine showed significantly increased over time (0.654±0.141 vs... 0.705±0.13, p<0.001). In multivariate analysis age, gender, time on dialysis, comorbid diseases, diabetes mellitus (DM), serum albumin, were considered as independent factors influencing the PFT. The high transporter group had higher D/P_{creat} (H 0.84±0.03 vs... LA 0.57±0.05, p<0.001), higher proportion of man (H 100% vs... LA 39.5%, p<0.05), higher proportion of patients with comorbid diseases (H 60% vs... LA 20.9%, p<0.05), lower serum albumin concentration (H 29±6.0 vs... LA 37±5.2, p<0.001), lower D4/D0 glucose (H 0.23±0.07 vs... LA 0.42±0.14, p<0.001), and lower drained volume (H 600±173 vs... LA 1016±355, p<0.001). **Conclusion:** The PFT was en easy, inexpensive, reliable test to assess peritoneal transport type and it also provided information about peritoneal clearance of solutes and ultrafiltration. Peritoneal transport type classification was recognized not only as aid for prescription, but also as a prognostic index.

Keywords: peritoneal solute clearance, equilibration test.

1. INTRODUCTION

Peritoneal dialysis (PD) is an established treatment for patients with end-srage kidney disease. The method was developed as an alternative to hemodialysis (HD) presenting a patient survival rate equivalent to HD and better preservation of residual renal function.

In PD, the lining of the peritoneal cavity is used to clear the blood of waste products (1, 2). There are two types of PD: Continuous ambulatory peritoneal dialysis (CAPD) in which the patient performs manual exchange of fluid four or five times per day, and automated peritoneal dialysis (APD) in which the exchange is done by the PD machine at night. CAPD is the usual mode of treatment chosen for patients at the beginning of PD (1, 2). During long term continuous ambulatory peritoneal dialysis (CAPD) treatment, the peritoneal membrane under-

goes functional and structural alterations, which may be the consequence of many factors such as peritonitis and continuous exposure to dialysis solutions with high concentrations of glucose and glucose degradation products, low pH and high osmolality. The peritoneal membrane may develops many structural abnormalities, including loss of the mesothelial cell (MC), an increased number of fibroblasts, submesothelial fibrosis and augmented vessel number (1, 2). The most common functional alteration during long term CAPD is increased peritoneal small solute transport rate (PSTR) resulting in impaired ultra filtrations and decreased dialysis efficiency (3, 4). Fluid management is a fundamental function of dialysis therapy. However, evidence suggests that hydration in PD is frequently not normalized. Symptomatic fluid retention is common in PD patients. Fluid overload is an important cause of hypertension in dialysis patients and studies show frequent occult fluid overload, hypertension, and cardiac dysfunction in PD which may deteriorate with time (5-9). For the adequate prescription of peritoneal dialysis, peritoneal transport characteristics should be known (10). Peritoneal solute transport rate (PSTR) is measured by dialysate-to-plasma (D/P) ratios of low molecular weight solutes. The most widely used test for classifying a patient's peritoneal type has been the peritoneal equilibration test (PET). Peritoneal equilibration test (PET) developed by Twardowski characterizes the transport nature of the patient's peritoneal membrane (10). Peritoneal equilibration test (PET) is an important tool for managing peritoneal dialysis (PD) prescription. Intra-indvidual changes can be detected and adjustments can be made. Also, the results of interventions can be examined and complications can be detected at an early stage. The International Society for Peritoneal Dialysis (ISPD) guidelines suggest that the first PET be performed 4-8 weeks after PD commencement (11). High peritoneal permeability has been regarded as a risk factor predicting both technical failure and high mortality rate ((12-14). In this study, we compared PET in the beginning of the peritoneal dialysis (within 3 month post-PD initiation) and in long term peritoneal dialysis patients (more than 12 months) to evaluate the changes in the peritoneal membrane character with time in patients treated with continuous ambulatory peritoneal dialysis (CAPD) and factors influencing the peritoneal transport rate.

2. AIM

The aim of this study was to analyze the importance of the peritoneal membrane transport status in patients treated with continuous ambulatory peritoneal dialysis (CAPD).

3. PATIENTS AND METHODS

In prospective a cohort study were included 60 adult continuous ambulatory peritoneal dialysis (CAPD) patients, divided in two groups according to duration of active treatment, first group (within 3 month after start of PD) and second group in long term peritoneal dialysis patients (more than 12 months). For the short term and long term peritoneal dialysis analysis of peritoneal transport characteristics has been used peritoneal functional test (PFT) (Fresenius Medical Care, Bad Homburg, Germany). This computer program is used to give data on renal function, total dialysis weekly clearance urea (Kprt/V) total dialysis weekly creatinine clearance (CcprT), water balance and transport parameters, as well as on nutritional state. The total Kprt/V urea includes two measurements: The peritoneal clearance urea Kpt/V and the renal clearance urea Krt/V. The peritoneal Kpt/V measures the clearance that occurs through the peritoneal membrane. The renal Krt/V measures the clearance performed by the kidney. Also, total dialysis weekly creatinine clearance (CcprT) is the sum of peritoneal (CcpT) and renal (CcrT) creatinine clearance. During the PFT all patients were on CAPD and used using standard four two-liter exchanges glucose-containing dialysis solution per day at standardized intervals. The glucose concentrations varied according to the standard program of the individual patents. For the evaluation of peritoneal small solute transport rate (PSTR) we used the dialysate to plasma concentration ratio of creatinine (D/P_{creat}). The patients were divided according to the PET classification into high ($D/P_{creat} \geq 0.81$), high-average (D/P_{creat} 0.65-0.80), low-average (D/P_{creat} 0.51-0.64) and low ($D/P_{creat} \leq 0.5$) transporters. The mean D/P creatinine ratio at 4 hours was 0.65. Patients with D/P creatinine values lower than 0.5 showed low transport characteristics and high 4–hour dialysate glucose level, which was greater than 52.5 mmol/L. In patients with high solute transport D/P creatinine ratio has been 0.81-1.03 and the 4–hour dialysate glucose level was less than 28.0 mmol/L. The ultrafiltration capacity can be defined as the net fluid removed during a standardized exchange, after 4 hours using 4.25% glucose solution. The diagnosis membrane failure can be made when the net ultra filtered volume is < 400ml after a standardized 4h dwell using a 4.25% glucose solution (ISPD Guidelines) (11). Glucose, urea, and creatinine, C reactive protein (CRP) were measured in each sample, using conventional techniques in a centralized reference laboratory. No restriction criteria were applied for age, gender, comorbid diseases, serum albumin. Exclusion criteria were the presence of active inflammatory disease, disseminated neoplasia, patients on immunosuppressive therapy and those having a peritonitis episode within the previous 30 days. The clinical characteristics were retrieved from patients files.

Statistical analysis were performed using the Statistical Package Med Calc for the Windows (version 12.6.1.0; Med Calc Software, Mariakerke, Belgium). Continuous variables with normal distribution were presented as mean±standard deviation. Statistical analysis for variables with normal distribution was performed using Student's t-test or Wilcoxon signed ranked test were used to compare differences between two groups. The median value was used when normal distribution was absent. The Mann-Whitney U test was used to compare variables without normal distribution between two groups. A difference was considered significant when the p value was less than 0,05.

4. RESULTS

Table 1 showed the patient demographics and clinical parameters as taken et entry into the clinical study. A total of 60 patients were included in the study. The mean age was 56.63 years (SD of±15.06) and there were twenty-nine

males (48%) and 31 females (52%). Median period of continuous peritoneal dialysis was 23.05±22.32 months, range 2–96 months. Diabetic nephropathy was the cause of end stage renal disease in 51.7% patients. Other causes of their chronic uremia included nephrosclerosis 9 (15%), chronic glomerulonephritis 2 (3.3%), obstructive nephropathy 1 (1.7%), polycystic kidney disease 3 (5%) and other 14 (23.3%) cases. The high rate of comorbid diseases in these patients is an independent risk factor for mortality, especially cardiovascular and respiratory diseases are. The major causes of comorbidities were cardiovascular diseases defined as previous history of congestive heart failure, myocardial infarction, angina, peripheral vascular disease, or cerebrovascular disease. They were presented, but it was not significant intergroup differences. No statistically significant differences were noted in any of the measured parameters except according to duration of active treatment (2.43± 0.18 months vs.. 40.67±19.04, p<0.0001) and number of peritonitis (0.13±0.43 vs.. 0.9±1.09, p<0.0004) between two groups in terms of other demographic and clinical parameters.

The biochemical parameters of this study are shown in Table 2. Between the two groups, significant change was observed between cholesterol (4.709±1.388 vs.. 5.312±1.407, p=0.0442), LDLC (2.469±1,063, vs.. 3.300±1.560, p=0.0266) and CRP (2.7 vs.. 5.45, p=0.0412). Serum albumin concentration was significantly lower into a short-term group, compared to a long-term PD group **(** 33.367±3.184 vs.. 37.033±4.327, p=0.0002).

The measurements of peritoneal solute transport rate (PSTR) of small solute, dialysis adequacy and nutritional status are shown in Table 3. Significant differences in membrane characteristics evolved using plasma dialysate (D/P) creatinine were found in patients on peritoneal dialysis less than 3 months compared to patients treated with long-term CAPD. Dialysate–to plasma ratio (D/P) of creatinine in the first group was 0.654±0.141 and in the second group 0.705±0.13, showed significantly increased over time (p<0.001). In the second group, the dialysis adequacy parameter was significantly reduced (total weekly Kt/V urea and total weekly creatinine clearance).

	CAPD < 3 months (n=30)	CAPD > 12 months (n=30)	p
Sex (male vs.female) (n)	17/13	12/18	0.3014
Age (years)	53.63±14.44	59.63±15.32	0.1239
PD duration (months)	2.43±0.18	40.67±19.04	<0.0001
Body mass index (kg/m^2)	24.50±3.46	25.91±4.01	0.1516
Primary renal disease	CAPD <3 months	CAPD > 12 months	p
Diabetic nephropathy	17	14	0.6054
Nephrosclerosis	4	5	1.0000
Glomerulonephritis	0	2	0.4915
Obstructive nepropathy	0	1	1.0000
Polycystic kidney disease	1	2	1.0000
Other	8	6	0.1804
Comorbid disease	CAPD < 3 months (n=30)	CAPD > 12 months (n=30)	p
Myocardial infarction	1/29	2/28	1.0000
Angina pectoris	0/30	1/29	1.0000
CMP	1/29	3/27	0.6120
HTA	21/9	26/4	0.2100
Cerebrovascular disease	0/30	1/29	1.0000
PVD	0/30	1/29	1.0000
Peritonitis	0.13±0.43	0.9±1.09	0.0004

Table 1. The demographic and clinical parameters Legend: PD=peritoneal dialysis; CMP=cardiomyopathy; HTA= hypertensio arterialis; PVD=peripheral vascular disease; Values are express as mean as ± standard deviation except for gander, diabetes mellitus, comorbid disease which are absolute frequencies and percentages;

	CAPD < 3 months (X±SD)	CAPD > 12 months (X±SD)	p
Cholesterol (mmol /L)	4.709±1.388	5.312±1.407	0.0442
Triglicerides (mmol /L)	2.166±1.227	2.224±1.332	0,7710
LDLC(mmol /L)	2.469±1.063	3.300±1.560	0.0266
HDLC(mmol /L)	4.555±1.671	4.839±1.662	0.8815
Serum albumin (mmol /L)	33.367±3.184	37.033±4.327	0.0002
	CAPD < 3 months (Md, IR)	CAPD > 12 months (Md, IR)	
CRP (mg/l)	2.7 (1.5-4.7)	5.45 (1.75-7.1)	0.0412

Table 2. The biochemical parameters. Legend: LDLC=Low Density Lipoprotein Cholesterol; HDLC= HighDensity Lipoprotein Cholesterol; CRP= C reactive protein; Md= median; IR= interquartile range; (X±SD)= mean±standard deviation

In both groups, normalize catabolic rate (nPCR) did not show any significant differences compared with each other.

Transport status was categorized as low, low average, high average and high as per the standard definition. As can be seen from Table 4. the PET demonstrated that there were 2 high transporter patients (6.6%), 5 high average transporters (16.7%), 23 low average transporters (76.7%) in the first group (within 3 month post-PD initiation). In the second group, there were more patients with high transporters 5 (10%) and high average transporters 7 (23.3%), and less low average transporters 20 (66.7%). In both groups there were no patients in low category. Low average transporters were most numerous in both study groups.

The clinical characteristics of the four transport groups are described in Table 5. There was a significant difference

	I group (CAPD <12 months)	II group (CAPD >12 months)	p
D/P_{creat}	0.654±0.141	0.705±0.13	p<0.001
Kprt/V	2.04±0.598	1.74±0.363	0.041
CcpT (L/1,73m^2)	41.36±15.88	40.66±8.319	0.807
CcprT (L/1,73m^2)	75.36±23.16	62.91±28.59	0.008
nPCR (gr/24h)	0.70±0.264	0.67±0.150	0.9823

Table 3. Evolution of peritoneal solute transport rate and dialysis adequacy. Legend: Creat= creatinine; D/P_{creat}=dialysate-to-plasma ratio creatinine; Kprt/V = total weekly clearance urea (peritoneal+residual renal); CcpT= total weekly peritoneal clearance creatinine; CcprT= total weekly clearance creatinine (peritoneal+residual renal); nPCR-normalise catabolic rate; All values mean ±SEM

	I group (CAPD <3 months)	II group (CAPD >12 months)	p
(L)	0	0	NS
(LA)	23 (76.7%)	20 (66.7%)	NS
(HA)	5 (16.7%)	7 (23.3%)	NS
(H)	2 (6.6%)	3 (10%)	NS

Table 4. Compression PET of early to long lasting CAPD. Legend: L= Low; LA= Low average;HA= High average; H= High; Values are express as absolute frequencies and percentages;

between the groups regarding prevalence of male gender (p<0.05), and comorbid diseases (p<0.05). Serum albumin levels were significantly lower in the H/HA group (p<0.001 vs... LA). There were significant differences in gender, comorbid diseases, serum albumin, ratio of dialysate glucose concentration at 4 hours and at 0 dwel time (D4/D0 glucose), and the volume drained in 4 hours. The H transporters had high proportion of man, more comorbid diseases, lower serum albumin, higher D4/D0 glucose, lower drained volume.

5. DISCUSSION

The most serious problem in long term treatment with peritoneal dialysis is worsening of functional and morphological states of peritoneal membrane with increased permeability or decreasing ultrafiltration as well as efficacy of dialysis. In our study significant changes in dialysis-related parameters were found. The peritoneal solute transport, which was evaluated using the dialysate-to-plasma ratio (D/P) of creatinine, was increased over time. Studies have shown that solute transfer increases and ultrafiltration declines along with time on peritoneal dialysis (15, 16). Our results support the hypothesis that there may exist two distinct types of high transporters, the early inherent high transporter and late acquired high transporter (associated with comorbidities, inflammation and protein leakage) (14, 17, 18). The present study showed that CAPD patients, who were high transporters, had more comorbid diseases, a higher proportion of males, lower serum albumin and lower drained volumes. We found that high peritoneal transport rate was related to comorbid diseases. It is generally accepted that peritoneal transport rate depends on both effective peritoneal surface area and permeability and that peritoneal permeability is affected by peritoneal blood circulation (19, 20). Many of the mediators produced in the inflammatory process can affect microvascular permeability and vascular tone (21). Thus, our finding of a significant relation between peritoneal transport rate and comorbid diseases suggests that comorbid diseases may affect microcirculation, and may also affect peritoneal transport characteristics in CAPD patients (22). The CANUSA study showed that a grater proportion of patients had diabetes mellitus with higher peritoneal membrane transport rate, according to PET at 1 month after initiation of dialysis (23). Reyes et al. reported that initial D/P_{creat} was significantly higher in patients with cardiovascular disease (CVD) (24). In the present study, high transporters had more comorbidities compared to the other groups. The significantly higher proportion of men in the high transporter group is also consistent with previous studies (25, 26). In a study of 60 CAPD patients, Devuyst et al. reported that D/P_{creat} was strongly correlated with male gender (27). The CANUSA study showed a significantly increased proportion of man with increased transport rate (23). The cause of this effect is not clear. However, our finding of significantly more comorbid diseases in male patients leads us to speculate that the effect of comorbid diseases on the peritoneal transport rate may explain the relation between men and high transport rate. The CANUSA study showed that increased transport rate was associated with low serum albumin but not with other initial nutritional parameters such as subjective global assessment, percent lean body mass, or normalized protein catabolic rate (23). In addition to comorbid diseases, our study reveals that initial serum albumin concentration is significantly lower in initial H peritoneal transport rate, a finding consistent with previous reports. Coester et al. found that initial D/P_{creat} was negatively correlated with initial serum albumin and positively correlated with low hyaluronan (20). Acute

Transport Groups	H(n=5)	HA(n=12)	LA(n=43)	L (n=0)	p value
Age (years)	65±12.5	58±13.8	57±13.4		NS
Male (n) %	5 (100.0%)	7 (58.3%)	17 (39.5%)		< 0.05
CD (n) %	3 (60.0%)	6 (50.0%)	9 (20.9%)		<0.05
Serum albumin (gr/L)	29±6.0	32±3.0	37±5.2		<0,001
D/P_{Creat}	0.84±0.03	0.74±0.06	0.57±0.05		<0.001
D4/D0 glucose	0.23±0.07	0.26±0.04	0.42±0.14		<0.001
Drained volume (ml /24h)	600±173	800±268	1016±355		<0.001

Table 5. Clinical Characteristics of Four Transport Groups of CAPD patients. Legend: H=high transporter; HA=high-average transporter; LA=low-average transporter; L=low transporter; CD=comorbid disease; D4/P4Creat =dialysate-to-plasma creatinine concentration ratio at 4 hours of dwell; D4/D0 glucose = ratio of dialysate glucose concentration at 4 hours and at 0 dwel time; Values are express as mean as ± standard deviation except for gander, diabetes mellitus, CVD and respiratory which are absolute frequencies and percentages;

and chronic infections and inflammation are present in a large proportion of predialysis patients, and serum albumin is generally accepted as an indicator of inflammation (28). Cueto-Manzano and Correa-Rotter showed that diabetes mellitus was significantly more frequent in high transporters, and was the most important risk factor for mortality on CAPD (25). In the present study, however, we found no significant difference in the proportion of diabetics among different transport groups. Some diabetic patients had more than one comorbid disease. The high rate of comorbid disease in diabetes explains why diabetes is not an independent risk factor for mortality, while CVD and respiratory disease are (29). Nutritional problems were common among PD patients (19). They may be caused by poor appetite, inadequate food intake, insufficient dialysis, and protein loss though the peritoneal membrane. The role of inflammation in connection with malnutrition and atherosclerosis has been recognized only in recent years (30). Low albumin is a strong predictive factor for mortality in CAPD (31). Thus, it seems unlikely that inadequate dialysis would have caused deterioration of the nutritional status.

6. CONCLUSION

The proper classification of patient peritoneal transport type is an important issue in the practice of peritoneal dialysis. Our findings are indicated that peritoneal solute transport rate (PSTR) of small solute, which was evaluated measuring dialysate/plasma ratio of creatinine (D/P_{creat}) increased over time on peritoneal dialysis. In the same time, there were significantly decreased in the parameters of dialysis adequacy (total weekly Kprt/V urea and total weekly cratinine clearance CcprT) in long term peritoneal dialysis patients. The patients classified as high transporters have more comorbid diseases, lower initial serum albumin, lower D4/D0 glucose, lower drained volume and a higher mortality risk than patients classified in other transport categories. The increased PSTR (based on small solute transport) may indicate different mechanisms of solute transport, depending on the moment when it is evaluated. In summary, our findings indicate that peritoneal solute transport increase over time on PD, and are closely interrelated.

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