

Peritoneal Protein Losses in Diabetic Patients Starting Peritoneal Dialysis: Is There a Relationship with Diabetic Vascular Lesions?

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During peritoneal dialysis (PD), a significant amount of protein is lost through the peritoneal membrane, and these losses could influence the patient's nutrition status. It has been reported that peritoneal protein loss (PPL) is greater in diabetic (D) patients than in nondiabetic (ND) patients, but the topic is still controversial, and the factors involved are not totally defined. We studied 23 patients on continuous ambulatory PD (12 with diabetes) who had experienced no episodes of infection during the preceding months. We measured peritoneal transport, PPL, proteinuria, and parameters of inflammation and nutrition. Our study was carried out during the first months of PD (2 – 4 months), which coincided with the first evaluation of peritoneal transport.

The PPL was higher in D patients than in ND patients (8.4 ± 2.2 g vs. 5.7 ± 1.7 g daily, $p < 0.001$), as was proteinuria (3.7 ± 2.7 g vs. 0.9 ± 0.7 g daily, $p = 0.003$). In 83% of D patients and 54% of ND patients, peritoneal transport ($p = 0.002$) was high or high-average. Dialysate-to-plasma creatinine in D patients was 0.77 ± 0.12 as compared with 0.66 ± 0.09 in ND patients ($p = 0.031$). Parameters of nutrition and inflammation were normal in both groups of patients and showed no significant differences, except for serum total protein, which was significantly lower in D patients. Ultrafiltration, Kt/V , and weekly creatinine clearance were similar in both groups. The D patients with a higher PPL had the highest proteinuria values.

We conclude that the higher PPL seen in D patients starting PD seems to be related to high membrane transport in these patients. The condition of high transport in D patients could be a result of

diabetic microvascular lesions that cause a similar pattern of permeability in the peritoneal and glomerular membranes.

Key words

Diabetes mellitus, peritoneal protein loss, diabetic nephropathy, proteinuria, peritoneal membrane transport

Introduction

Patients with diabetes mellitus (DM) who develop diabetic nephropathy frequently experience significant urinary protein loss, and this sustained proteinuria may cause malnutrition. Many patients with diabetic nephropathy evolve to end-stage renal disease (ESRD), and many of those patients are treated with peritoneal dialysis (PD). In PD, a marked loss of protein through the peritoneal membrane occurs, and the type of membrane transport may be a cause of this protein loss through the peritoneum. Greater transmembrane protein loss has been reported in patients with high membrane transport, affecting serum albumin levels (1,2). In some studies, diabetic (D) patients treated with PD were observed to have a greater peritoneal protein loss (PPL) than nondiabetic (ND) patients did (3). Greater or lesser PPL in D patients continues to be a subject of debate, because other studies have observed PPL to be equal in D and ND patients (4). The proteinuria frequently seen in patients with diabetic nephropathy, in addition to the probably higher PPL in these patients, could contribute to major malnutrition.

Our working hypothesis is based on the premise that microvascular lesions caused by DM could affect the permeability of the peritoneal membrane just as they affect the glomerular membrane. We compared protein loss (urinary and peritoneal) in D patients and

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ND patients starting treatment with PD to determine any relationships with nutrition, inflammation, transport, and adequacy of dialysis.

Patients and methods

We studied 23 incident patients on continuous ambulatory PD (CAPD), 12 with diabetes (11 men, 1 woman; mean age: 60.6 ± 11.6 years) and 11 without diabetes (7 men, 4 women; mean age: 63.2 ± 7.7 years), on PD for 2 – 4 months, without any episodes of infection since starting PD. All patients were treated using the same dialysis scheme of 3 day exchanges and 1 night exchange. Eleven patients (6 D patients, 5 ND patients) were being treated with angiotensin converting-enzyme inhibitors (ACEIs) or with angiotensin II receptor blockers (ARBs).

Parameters of peritoneal transport and adequacy of dialysis were measured: peritoneal equilibration test (PET), ultrafiltration (UF), weekly Kt/V, and weekly creatinine clearance (CCr). Daily PPL was measured, and in 22 patients with preserved diuresis, daily proteinuria was also measured. All kinetics and protein loss studies were carried out between month 2 and month 4 of PD at the first assessment of peritoneal transport.

For comparison purposes, we considered as “high transporters” those patients that were categorized high or high-average, and as “low transporters” those that were categorized low or low-average. The parameters of nutrition that we measured were total plasma protein, serum albumin, prealbumin, transferrin, and normalized protein equivalent of nitrogen appearance. In addition, we measured parameters of inflammation such as C-reactive protein (CRP), fibrinogen, β_2 -microglobulin, and haptoglobin.

Statistical analysis

Data are expressed as mean \pm standard deviation. Comparisons of continuous variables between the two groups used the unpaired Student *t*-test. Between-group comparisons of nominal variables used the chi-square test. The Spearman rank correlation was used to assess correlations between pairs of variables. Analysis of variance was used as appropriate, to determine significant differences between groups. To measure the degree of association between variables, analysis of variance was used. A generalized linear model identified possible interactions between parameters, and a *post hoc* test was used if a significant

interaction was observed. A *p* value below 0.05 was considered statistically significant. Data were analyzed using the software package SPSS for Windows, version 16.0 (SPSS, Chicago, IL, U.S.A.).

Results

In Table I, the values for PPL, proteinuria, and total daily protein loss (PPL + proteinuria) are seen to be significantly higher in D patients. The dialysate-to-plasma ratio (D/P) of creatinine at 4 hours of a PET is greater in D patients, and the percentage of patients classified as high transporters is also greater in the D group than in the ND group (Table I). In the D group, only 2 patients were low-average transporters, and they had the lowest proteinuria levels. Of the other 10 D patients, 6 were classified as high and 4 as high-average transporters, with a mean proteinuria value of 3.1 ± 1.8 g daily in 9 of these who had preserved diuresis. Ultrafiltration was similar in both groups.

Table II shows the parameters of nutrition, where it can be seen that only serum total protein is significantly lower in D patients. There are no differences in the other values between the D and ND patients, and all these values are normal. Similarly, there are no differences in inflammatory markers or in dialysis efficacy markers between the two groups of patients. Weekly Kt/V and weekly CCr values are adequate in all patients, and practically the same in D and ND patients (Table III). We found no correlation for parameters of nutrition or inflammation with protein loss.

TABLE I Protein losses, ultrafiltration, and results of peritoneal equilibration tests in peritoneal dialysis patients with and without diabetes

Parameter	Diabetes status		p Value
	With	Without	
Protein losses (g/day)			
Peritoneal	8.4 \pm 2.2	5.7 \pm 1.7	<0.001
Proteinuria	3.7 \pm 2.7	0.9 \pm 0.7	0.003
Total ^a	11.7 \pm 2.6	6.6 \pm 1.8	<0.001
D/P creatinine	0.77 \pm 0.12	0.66 \pm 0.09	0.031
Ultrafiltration (mL/4 hours)	320.8 \pm 177.69	277.27 \pm 147.25	NS
High transporters ^b	83%	54%	0.002

^a Peritoneal + proteinuria.

^b High + high-average.

D/P = dialysate-to-plasma ratio; NS = nonsignificant.

TABLE II Parameters of nutrition in peritoneal dialysis patients with and without diabetes

Parameter	Diabetes status		p Value
	With	Without	
Transferrin (mg/dL)	188.17±25.52	202.55±36.92	NS
Daily nPNA (g/kg)	1.15±0.43	1.10±0.33	NS
Total serum			
proteins (g/dL)	6.30±0.61	6.56±0.58	<0.001
Prealbumin (mg/dL)	31.53±5.9	38.03±12.70	NS
Albumin (g/dL)	3.52±0.42	3.75±0.36	NS

NS = nonsignificant; nPNA = normalized protein equivalent of nitrogen appearance.

TABLE III Parameters of inflammation and dialysis efficacy in peritoneal dialysis patients with and without diabetes

Parameter	Diabetes status		p Value
	With	Without	
Haptoglobin (mg/dL)	190±49.6	162.5±42.7	NS
C-Reactive protein (mg/L)	0.63±0.55	0.62±0.69	NS
Fibrinogen (mg/dL)	608±131	559±120	NS
β ₂ -Microglobulin (mg/dL)	32.31±43.19	19.35±6.36	NS
Weekly Kt/V	2.5±0.6	2.4±0.8	NS
Weekly CCr (L)	106.9±38	106.8±31	NS

NS = nonsignificant; CCr = creatinine clearance.

Discussion

In this study of protein loss in patients treated with PD, greater permeability of the peritoneal membrane to protein leakage is observed in incident D patients. Previous studies have shown that D patients with a longer duration on PD have greater peritoneal membrane permeability to proteins (3). In general, D patients are thought to have a degree of malnutrition that is greater than that experienced by ND patients. The loss of proteins through the peritoneal membrane of patients on PD is a well-known cause of lower levels in parameters of nutrition (5), and the high permeability seen in D patients is one of the reasons for this loss (3).

In the present study, we found a higher PPL in D patients than in ND patients—and a coincidently greater urinary loss of protein. Proteinuria is a consequence of the vascular damage caused by DM to the capillaries of the glomerular membrane; this vascular damage caused by DM affects all the blood vessels in the body, and the vessels of the peritoneal membrane are no exception. Diabetic microangiopathy is probably

the cause of the greater peritoneal permeability seen in our D subjects, who as patients starting PD, without a long period of exposure to peritoneal fluid that could damage the membrane and alter its transport properties, are, in a high percentage of cases, high or high-average transporters. In comparison, many more ND patients are low transporters. It is precisely this group of D patients with high transport—the group that has greater proteinuria—that maybe are the most affected by diabetic microangiopathy.

In studies using peritoneal biopsies, mesothelial damage was related to the duration of PD and glucose overload, and greater peritoneal membrane thickness from mesothelial sclerosis was found to be more frequent in high transporters (6). In those patients, an increased submesothelial fibrous layer (7) was described. However, in uremic patients with diabetes, even before beginning treatment with PD, peritoneal biopsy showed a greater degree of mesothelial cell loss, greater inflammatory infiltration of the peritoneum, greater mesothelial basement membrane thickening, and a higher proportion of vascular wall thickening than was observed in ESRD patients without diabetes (8). These histology findings in the peritonea of diabetic patients before the start of PD could explain the status of high transport with greater protein loss in our D patients when they were just starting PD. Ultrafiltration and dialysis efficacy were the same in both groups, and it therefore seems that those factors had no influence on protein loss in our patients.

In D patients, only total plasma protein is lower than the levels seen in ND patients. The levels of the other markers of nutrition in this study are no different in D patients than in ND patients, and all of the nutrition—and inflammation—markers are at normal levels. These normal values for parameters of nutrition and inflammation in D patients, despite greater urinary and peritoneal loss of protein, may be a result of the fact that these patients are just starting PD, with a short treatment time by this method, and are therefore not yet showing an effect in their parameters of nutrition or an elevation in their markers of inflammation such as CRP, as is seen in D patients on PD for a longer period (9).

Spaia *et al.* found no differences in PPL between D and ND patients during their first month on CAPD, but they did find differences between D and ND patients starting PD and those with more than 1 year on PD (4). In their description of the PET, Twardowski

et al. indicated that the D/P ratios for urea and creatinine were slightly higher in D than in ND patients, but that the D/P for protein was not different (10). In D patients on CAPD followed over 4 years, we described PPL stabilization, without the incidence of peritonitis affecting PPL (11).

Certain measures, such as treatment with ACEIs or ARBs, may reduce PPL in patients on PD and prevent malnutrition, because in addition to the well-known effects of these agents on proteinuria, they have also been shown to act on peritoneal membrane permeability (12,13).

Conclusions

At the start of treatment with PD, D patients experience a greater PPL than do ND patients, and this greater loss seems to be related to the condition of high transport. The greater proteinuria seen in the D patients suggests that greater permeability of the peritoneal membrane to proteins could be a result of diabetic microvascular lesions in a pattern similar to that seen in glomerular membrane damage.

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