

Peritoneal membrane thickness in incident peritoneal dialysis patients is associated with comorbidity, solute transport rate and ultrafiltration failure

Patrícia Matias¹, Patrícia Branco¹, Cristina Jorge¹, Sância Ramos², Rita Birne¹, António Martinho³, Elisabete Costa¹, Margarida Gonçalves¹, Ana Paula Martins²

¹ Peritoneal Dialysis Unit, Nephrology Department.

² Histopathology Department,

³ Surgery Department.

Hospital de Santa Cruz, Carnaxide, Portugal.

Received for publication: 18/08/2008

Accepted in revised form: 28/10/2008

ABSTRACT

Loss of peritoneal function is the major factor leading to treatment failure in peritoneal dialysis. Fibrosis and thickening of the peritoneal membrane is associated with loss of peritoneal function.

The aim of this retrospective study was to evaluate the relationship between peritoneal thickness, measured by peritoneum biopsy at the beginning of peritoneal dialysis, and peritoneum functional parameters. Charlson Comorbidity Index was also measured at the beginning of peritoneal dialysis. Patients were followed using laboratory data and peritoneal equilibration test evaluations. Episodes of peritonitis were also recorded.

We studied 23 incident patients, with a mean age of 60.5±12.2 (33-77) years, 26% female and 30% diabetics. Mean follow-up time was 49.3±37.5 (3-165) months.

Mean peritoneal thickness was 0.40±0.39 (0.02-1.5) mm. Peritoneal thickness was positively correlated with Charlson Comorbidity Index ($r=0.43$, $p=0.04$) and baseline high transport status ($r=0.46$;

$p=0.03$). Peritoneal thickness was negatively correlated with albumin levels ($r=-0.52$; $p=0.01$). Peritoneal membrane thickness was also associated with development of ultrafiltration failure ($p=0.02$). Acquired high transport status, development of peritonitis and duration of peritoneal dialysis treatment were not correlated with peritoneal thickness.

On multivariate analysis, higher peritoneal thickness (>0.8 mm) was associated with Charlson Comorbidity Index ($p=0.01$), baseline high transport status ($p=0.04$) and development of ultrafiltration failure ($p=0.03$). Binary logistic analysis showed that peritoneal thickness was a predictor of ultrafiltration failure ($p=0.03$).

Biopsy of the peritoneum at the beginning of peritoneal dialysis (during peritoneal dialysis catheter placement) is a simple and innocuous procedure which may predict loss of peritoneal function in peritoneal dialysis patients and could help in tailoring peritoneal dialysis prescription.

Key-Words:

Fast peritoneal transport; peritoneal dialysis; peritoneal membrane thickness; ultrafiltration.

■ INTRODUCTION

Loss of peritoneal function, reflected by ultrafiltration (UF) failure or by insufficient efficiency of dialysis, is the main factor leading to treatment failure in peritoneal dialysis (PD)¹⁻³. Although the precise biological mechanisms responsible have not been defined, alterations in peritoneal function are assumed to be related to structural changes in peritoneal membrane.

Fibrosis and thickening of the peritoneal membrane, caused by the use of bioincompatible solutions and repeated episodes of peritonitis, are the major factors associated with loss of peritoneal function^{2,4}. Peritoneal sclerosis is characterised histologically by mesothelial cell loss, thickening of submesothelial connective tissue and vascular alterations^{5,6}.

Transforming growth factor (TGF)- β plays a central role in peritoneal fibrosis⁷. It induces fibroblast activation, collagen deposit, inhibition of matrix metalloproteinase and angiogenesis. TGF- β also mediates the conversion of epithelial cells into myofibroblasts. By doing so, it promotes epithelial-to-mesenchymal transition^{8,9}. In parallel to sclerosis, angiogenesis also occurs¹⁰. Vascular endothelial growth factor (VEGF) is the main factor responsible for the neoangiogenesis, with mesothelial cells being its important source¹¹. It seems that mesothelial cells that have undergone epithelial-to-mesenchymal transition produce more VEGF than epithelioid mesothelial cells, suggesting a link between mesothelial cell transdifferentiation, fibrosis and acquired fast transport status^{7,12}.

Recent studies have demonstrated that both uraemia and presence of diabetes mellitus seem to play a role in the pathogenesis of peritoneal fibrosis found in patients before the beginning of PD^{13,14}.

Biopsy studies in PD patients have also shown that increased submesothelial thickness correlates with increased solute transport, as measured by dialysate-plasma creatinine ratio (D/P creatinine)¹⁵ and loss of mesothelial cells¹³.

The aim of this study was to evaluate the relationship between baseline peritoneal membrane thickness, measured in the peritoneal biopsy performed during PD catheter placement, functional parameters

of peritoneum, comorbidity and PD treatment survival.

■ PATIENTS AND METHODS

■ Study design

This was a retrospective study which analysed peritoneal biopsies performed in a single-centre by a single surgeon during placement of the first PD catheter over the last 15 years (1992-2007).

■ Population

The study included 23 incident chronic PD patients. At baseline, mean age was 60.5 \pm 12.2 years (range 33 to 77 years), six patients were female (26%) and seven (30%) were diabetics. Mean follow-up time was 49.3 \pm 37.5 months (range 3 to 165 months) and seventeen (74%) patients were on automatic PD.

■ Methods

Peritoneal biopsies were performed during placement of the first PD catheter at the beginning of PD. Peritoneal samples were assessed by light microscopy (with hematoxylin-eosin stain), using a standardised method. The evaluation of parietal peritoneal membrane thickness included the mesothelial cells and the underlying submesothelial compact zone. For each biopsy, the measurement of peritoneal membrane thickness was performed by considering the average of two determinations, taken at the areas of larger and smaller thickness (Figs. 1 and 2). For each biopsy, the measurements were performed by two independent observers.

Peritoneal membrane thickness was correlated with clinical, laboratory and peritoneum functional data at the beginning of PD. Clinical data included calculation of Charlson Comorbidity Index (CCI)^{16,17} at baseline for all patients. The development of peritonitis during the follow-up time was also evaluated.

Laboratory data included semestral evaluations of haemoglobin, albumin, C-reactive protein (CRP), serum calcium, serum phosphorus and intact PTH.

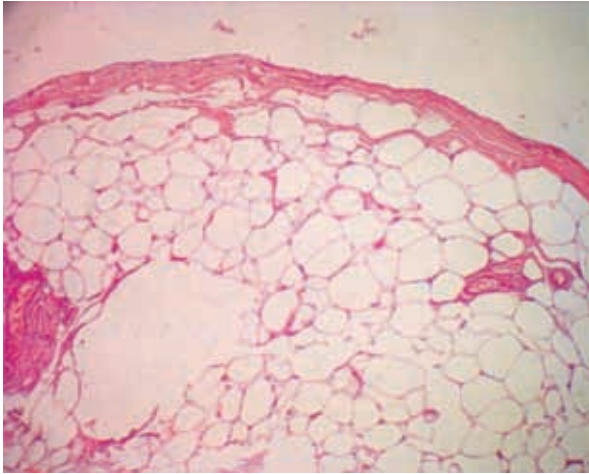


Figure 1
Microscopic aspect of a thin area of the peritoneal membrane (HE X100)

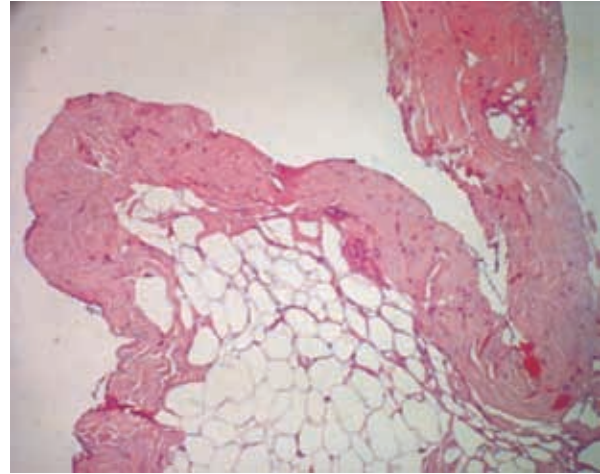


Figure 2
Microscopic aspect of a thick area of the peritoneal membrane (HE X100)

Peritoneum functional parameters studied were D/P creatinine, weekly Kt/V_{urea} and amount of removed fluid obtained at the beginning of PD and in the annual peritoneal equilibration test (PET). The PET was performed with 3.86% glucose solution between the second and the sixth month after the start of treatment and then annually in all patients. Peritoneal transport status was determined using mean values and the standard deviation of D/P creatinine. Patients were stratified into two groups according to the mean D/P creatinine in the studied population: high transporters (with D/P creatinine equal to or higher than the mean D/P creatinine for the entire population) and non-high transporters (D/P creatinine lower than the mean D/P creatinine).

UF failure was also assessed annually in all studied patients. The net UF was estimated based on the net negative balance (weighing the bag after drainage) after a 2 L 3.86% glucose exchange with 4 hours of dwell time. This value represents mostly the convective transport capacity of the peritoneum. A negative balance lower than 400 mL was taken as an indicator of UF failure.

Residual glomerular filtration rate at baseline was calculated by averaging the urea and the creatinine clearance by a 24-hour urine collection.

■ Statistical analysis

Laboratory values were obtained by calculating the average semester determination and the PET parameters were obtained by calculating the average annual determination.

We used Spearman correlation and Mann-Whitney U test for univariate analysis and binary regression for multivariate analysis (confidence interval of 95%).

Statistical analysis was performed with SPSS system 14.0 (SPSS Inc., Chicago, IL). For all comparisons, a $p < 0.05$ was considered statistically significant.

■ RESULTS

Comorbid conditions recorded at baseline according to CCI are shown in Table I. Laboratory and peritoneum functional data as well as residual glomerular filtration rate at the beginning of PD are shown in Table II.

Eleven (47%) patients became high transporters (D/P creatinine > 0.67) during the follow-up time. Acquired high transport status did not correlate with

Table I

Distribution of Charlson Comorbidity Index in the studied population

Charlson Comorbidity Index*	Condition	n (%)
1	Coronary disease	6 (27.2%)
	Congestive heart failure	4 (17.1%)
	Peripheral vascular disease	4 (17.1%)
	Cerebrovascular disease	3 (13.0%)
	Dementia	0 (0%)
	Chronic pulmonary disease	1 (4.3%)
	Connective tissue disorder	0 (0%)
	Peptic ulcer disease	3 (13.0%)
	Mild liver disease (without portal hypertension)	2 (8.7%)
	Diabetes mellitus	7 (30.4%)
2	Hemiplegia	0 (0%)
	Moderate or severe renal disease	23 (100%)
	Diabetes with end-organ damage	7 (30.4%)
3	Any solid tumor, leukemia or lymphoma	1 (4.3%)
	Moderate or severe liver disease	1 (4.3%)
6	Metastatic solid tumor	0 (0%)
	AIDS	0 (0%)

* Plus 1 – for each decade above 40 years

peritoneal membrane thickness. Nine (39%) patients left the technique because of UF failure, in a mean time of 49.4±28.9 months. Sixteen (68%) patients had at least one peritonitis episode during the follow-up time.

Mean peritoneal membrane thickness in the general group was 0.40±0.39 (0.02-1.5) mm. Peritoneal thickness was positively correlated with CCI ($r=0.43$, $p=0.04$) and with baseline high transport status ($r=0.46$, $p=0.03$). Peritoneal thickness was negatively correlated with albumin ($r=-0.52$, $p=0.01$) (Fig. 3). Using Mann-Whitney U test, peritoneal membrane thickness was associated with the development of UF failure ($p=0.02$). The presence of diabetes mellitus, the development of peritonitis and the duration of PD did not correlate with peritoneal membrane thickness.

On multivariate analysis, higher peritoneal thickness (>0.8 mm) was associated with higher CCI (OR: 2.13, CI 95%: 1.32-4.80, $p=0.01$), lower albumin levels (OR: 0.22, CI 95%: 0.03-0.12, $p=0.02$), baseline high transport status (OR: 1.24, CI 95%: 1.01-2.87, $p=0.04$) and development of UF failure (OR: 1.67, CI 95%: 1.02-4.35, $p=0.03$). Binary logistic analysis showed peritoneal thickness to be a predictor of UF failure (OR: 1.81, CI 95%: 1.03-3.74, $p=0.03$).

DISCUSSION

Over recent years, histological evaluation of peritoneal membrane during PD technique has become important in determining the extent of peritoneal damage as a result of PD treatment and in deciding whether PD treatment can be continued. However, few studies have analysed the morphologic changes in peritoneal membrane in pre-dialysis patients^{13,14}.

In a study from the Peritoneal Biopsy Study Group¹³, the authors examined the morphologic

Table II

Demographic and peritoneum functional variables at the beginning of peritoneal dialysis

Haemoglobin (g/dL)	11.5±1.9 (9.3 - 13.1)
Albumin (g/dL)	3.4±0.5 (2.6 - 4.4)
CRP (mg/dL)	1.7±1.4 (0.05 - 5.7)
Calcium (mg/dL)	8.4±0.6 (7.4 - 9.3)
Phosphorus (mg/dL)	5.1±0.9 (3.2 - 6.8)
iPTH (pg/mL)	371.1±189.6 (77 - 638)
D/P creatinine	0.69±0.10 (0.46 - 0.84)
Weekly Kt/V	2.38±0.61 (1.2 - 4.1)
Removed fluid (mL)	1168±624 (115 - 2850)
RRF (mL/min)	3.3±3.3 (0 - 9.3)
CCI	6.4±3.2 (2 - 17)

CCR (C-reactive protein); RRF (residual renal function); CCI (Charlson Comorbidity Index)

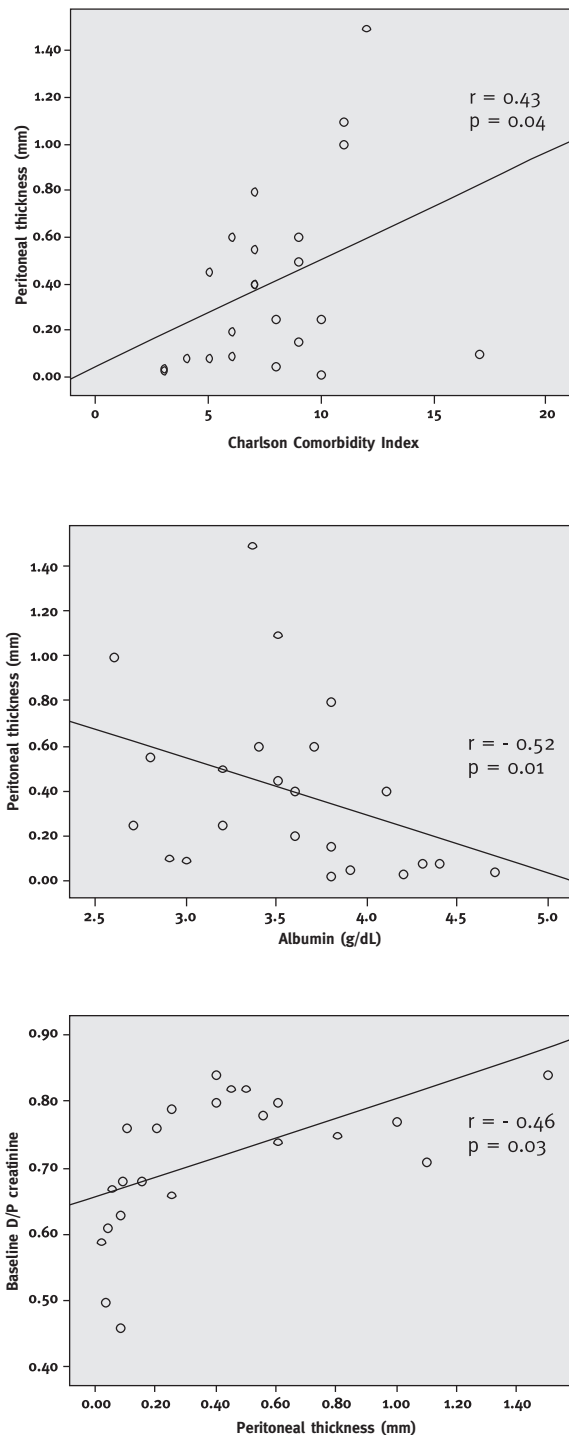


Figure 3
Correlations between peritoneal thickness and Charlson Comorbidity Index, albumin and baseline D/P creatinine

features of peritoneal membrane of 130 patients on peritoneal dialysis and compared them with features of normal individuals, uraemic predialysis patients and patients undergoing haemodialysis. Biopsies from uraemic predialysis patients demonstrated a significantly thicker submesothelial zone than that observed in healthy individuals. The thickness was similar to that of biopsies obtained from patients who had undergone haemodialysis for varying periods before initiation of PD. These findings indicate that uraemia itself may induce changes in the peritoneal membrane of the patients even before the beginning of PD. The thickness of peritoneal membrane obtained from patients undergoing PD demonstrated a progressive significant increase in thickness with time on PD. Authors concluded that fibrotic and vascular changes may be a unique development specifically driven by the process of PD and/or uraemia.

In a recent study from the Peritoneal Biopsy Study Group of the Japanese Society for Peritoneal Dialysis¹⁴, the authors postulate that two factors other than PD treatment could affect the development of peritoneal sclerosis in PD patients: uraemia and diabetes. Like some previous studies^{13,18}, they demonstrated the presence of peritoneal fibrosis and vasculopathy in the peritoneum before PD induction. This evidence clearly suggested an impact of uraemia on the pathogenesis of peritoneal sclerosis.

Data from biopsy-based¹⁵ and ultrasonographic-based^{19,20} studies in patients on PD pointed out that high transporters had a significantly thicker peritoneum, with an increased submesothelial fibrous layer, than slow transporters. Our study demonstrates that also before the beginning of PD, a thicker peritoneal membrane is associated with baseline high transport status and can predict the development of UF failure. In spite of that, peritoneal membrane thickness did not predict time on PD.

Some studies have shown that peritoneal hyperpermeability at the beginning of PD might impact on patient mortality due to a serious associated comorbidity, such as atherosclerosis, chronic inflammatory status or insufficient management of fluid and humoral abnormalities^{21,22}. Our results show that a higher peritoneal thickness is associated with increased comorbidity index and lower albumin serum levels, probably because these patients have a systemic and peritoneal inflammatory state.

Unlike the study from Williams *et al*¹³, Honda *et al*¹⁴ evidenced that in comparison of uraemic pre-PD peritoneum between patients with or without diabetes, uraemic patients with diabetes had more severe vasculopathy than uraemic patients without diabetes, suggesting an additional adverse effect of diabetes on the development of hyalinising vasculopathy in uraemic peritoneum. Advanced glycation end-products (AGE) and glucose degradation products (GDP) are possible candidates for adverse effectors to the peritoneal membrane²³, because both of them are very common in uraemia. Another suspect is diabetes in various organs, including the peritoneum. In our study, diabetics did not show increased peritoneal membrane thickness, only the incidence and severity of vasculopathy was higher in those patients.

The major limitations of this study are the relatively small sample size and the fact that it is a retrospective study, both of which may be associated with a lower statistical power.

In summary, our study demonstrates that peritoneal membrane thickness at the beginning of PD is associated with baseline high transport status and is a predictor of development of UF failure. Biopsy of the peritoneum at the beginning of PD during Tenckhoff catheter placement is a simple and innocuous procedure. Histologic evaluation of the peritoneal membrane could show morphologic changes capable of predicting peritoneal function decline, and therefore contribute to suitably tailoring PD prescription.

Conflict of interest statement. None declared.

References

1. Davies SJ, Phillips L, Griffiths AM, Russell LH, Naish PF, Russell GI. What really happens to people on long-term peritoneal dialysis? *Kidney Int* 1998;54:2207-17
2. Davies SJ, Bryan J, Phillips L, Russell GI. Longitudinal changes in peritoneal kinetics: the effects of peritoneal dialysis and peritonitis. *Nephrol Dial Transplant* 1996;11:498-506
3. Churchill DN, Thorpe KE, Nolph KD, Keshaviah PR, Oreopoulos DG, Page D. Increased peritoneal membrane transport is associated with decreased patient and technique survival for continuous peritoneal dialysis patients. The Canada-U.S.A. (CANUSA) Peritoneal Dialysis Study Group. *J Am Soc Nephrol* 1998;9:1285-92
4. Selgas R, Fernandez-Reyes MJ, Bosque E *et al*. Functional longevity of the human peritoneum: how long is continuous peritoneal dialysis possible? Results from a prospective medium long-term study. *Am J Kidney Dis* 1994;23:64-73
5. Mateijsen MA, van der Wal AC, Hendriks PM *et al*. Vascular and interstitial changes in the peritoneum of CAPD patients with peritoneal sclerosis. *Perit Dial Int* 1999;19:517-25
6. Dobbie JW. Morphology of the peritoneum in CAPD. *Blood Purif* 1989;7:74-85
7. Margetts PJ, Gyorffy S, Kolb M *et al*. Antiangiogenic and antifibrotic gene therapy in a chronic infusion model of peritoneal dialysis in rats. *J Am Soc Nephrol* 2002;13:721-28
8. Yanez-Mo M, Lara-Pezzi E, Selgas R *et al*. Peritoneal dialysis and epithelial-to-mesenchymal transition of mesothelial cells. *N Engl J Med* 2003;348:403-13
9. Selgas R, Jimenez-Heffernan J, Lopez-Cabrera M. On the epithelial-mesenchymal transition of mesothelial cells. *Kidney Int* 2004;66:866-7
10. Margetts PJ, Bonniaud P. Basic mechanisms and clinical implications of peritoneal fibrosis. *Perit Dial Int* 2003;23:530-41
11. Aroeira LS, Aguilera A, Selgas R *et al*. Mesenchymal conversion of mesothelial cells as a mechanism responsible for high solute transport rate in peritoneal dialysis: role of vascular endothelial growth factor. *Am J Kidney Dis* 2005;46:938-48
12. Del Peso G, Fernandez-Reyes MJ, Hevia C *et al*. Factors influencing peritoneal transport parameters during the first year on peritoneal dialysis: peritonitis is the main factor. *Nephrol Dial Transplant* 2005;20:1201-6
13. Williams JD, Craig KJ, Topley N *et al*. Peritoneal Biopsy Study Group: Morphologic changes in the peritoneal membrane of patients with renal disease. *J Am Soc Nephrol* 2002;13:470-79
14. Honda K, Hamada C, Nakayama M *et al*. Peritoneal Biopsy Study Group of the Japanese Society for Peritoneal Dialysis: Impact of uremia, diabetes, and peritoneal dialysis itself on the pathogenesis of peritoneal sclerosis: a quantitative study of peritoneal membrane morphology. *Clin J Am Soc Nephrol* 2008;3:720-8
15. Plum J, Hermann S, Fusholler A *et al*. Peritoneal sclerosis in peritoneal dialysis patients related to dialysis settings and peritoneal transport properties. *Kidney Int* 2001; 78 (Suppl 2):S42-S47
16. Beddhu S, Bruns FJ, Saul M, Seddon P, Zeidel ML. A simple comorbidity scale predicts clinical outcomes and costs in dialysis patients. *Am J Med* 2000;108:609-13
17. Fried L, Bernardini J, Piraino B. Charlson comorbidity index as a predictor of outcomes in incident peritoneal dialysis patients. *Am J Kidney Dis* 2001;37:337-42
18. Sherif AM, Nakayama M, Maruyama Y *et al*. Quantitative assessment of the peritoneal vessel density and vasculopathy in CAPD patients. *Nephrol Dial Transplant* 2006; 21:1675-81
19. Duman S, Ozbek SS, Gunay ES *et al*. What does peritoneal thickness in peritoneal dialysis tell us? *Adv Perit Dial* 2007;23:28-33
20. Lee TC, Yang JY, Wang HP, Tsai TJ, Yang Y. Peritoneal thickening is not inevitable in long-term peritoneal dialysis and is associated with peritoneal transport characteristics: a two-center sonographic study. *Nephrol Dial Transplant* 2008;23:1005-10
21. Stenvinkel P, Chung SH, Heimbürger O, Lindholm B. Malnutrition, inflammation and atherosclerosis in peritoneal dialysis patients. *Perit Dial Int* 2001;21(Suppl 3):S157-S162
22. Heimbürger O, Jogestrand T, Wang T, Lindholm B, Stenvinkel P. High peritoneal transport rate in patients starting PD is related to early signs of atherosclerosis. *Perit Dial Int* 1999;19(Suppl 1):S7-S12
23. Nakamura S, Niwa T. Advanced glycation end-products and peritoneal sclerosis. *Semin Nephrol* 2004; 24:502-5

Correspondence to:

Dr Patrícia Matias
Department of Nephrology, Hospital de Santa Cruz
Avenida Prof. Dr. Reinaldo dos Santos
2790-134 Carnaxide, Portugal.
E-mail: patriciajoomatias@hotmail.com