

Incident diabetic patients on peritoneal dialysis: evaluation of peritoneal membrane status

Sandra Silva¹, Anabela Rodrigues¹, Fernanda Silva¹, Margarida Martins², António Cabrita¹

¹Department of Nephrology

²Department of Clinical Pathology

Hospital Geral de Santo António, Oporto, Portugal

Received for publication: 10/11/2007

Accepted in revised form: 17/12/2007

ABSTRACT

Background: Studies into peritoneal transport and ultrafiltration in incident diabetic patients are scarce and contradictory. While some authors have found higher small solute transport and lower drained volume in diabetics, others have reported no differences.

Our aim was to investigate differences in peritoneal membrane transport function, inflammation and mesothelial cell mass in diabetics and non-diabetics starting peritoneal dialysis.

Methods: Eighty one consecutive incident patients were studied using a 3.86% peritoneal equilibration test within the second and the fifth months of peritoneal dialysis treatment. The following parameters were measured and compared between diabetic (n=22) and non-diabetic (n=59) patients: small solute transport (dialysate to plasma ratio creatinine, mass transfer area coefficient creatinine), glucose absorption (ratio of dialysate glucose at 4 hours' dwell time to dialysis glucose at 0 dwell time), peritoneal ultrafiltration (drained volume), selective water transport (corrected sodium sieving), mesothelial cell mass (effluent cancer antigen 125), systemic (C-reactive protein, albumin and interleukin-6) and intraperitoneal (interleukin-6) surrogates of inflammation and vascular endothelial growth factor.

Results: Mean D/P_{Cr} was 0.77±0.10; 54% of patients were fast/fast-average transporters; mean peritoneal ultrafiltration was 2767±228 ml/day. Diabetics had a

mean HbA_{1c} of 8%. Excluding the Davies comorbidity score, which was higher for diabetics, no other significant difference in demographic features was found. Inflammation markers were similar between groups (C reactive protein: 1.34±1.91 in diabetics *versus* 1.10±1.80 mg/dl; p=0.63; median serum IL6: 12 in diabetics *versus* 10 pg/ml; p=0.93). Small solute and free water transport, drained volume and mesothelial mass were similar in both groups.

Conclusion: In our study, diabetic incident patients did not differ significantly from non-diabetics in the function and structure of the peritoneal membrane.

Key-Words:

CA 125; diabetes mellitus; inflammation; peritoneal transport; vascular endothelial growth factor (VEGF).

INTRODUCTION

Nephrologists are well aware of the devastating consequences of chronic hyperglycaemia. Diabetes mellitus (DM), a major cause of end stage renal disease (ESRD), is characterised by microvascular changes including endothelial dysfunction¹, increased vascular permeability and vascular proliferation². Several animal and human studies have shown that peritoneal membrane changes with time on peritoneal dialysis (PD) treatment³, with progressive loss of ultrafiltration and rise in small solutes transport⁴. These modifications seem to have similar pathophysiological features to

DM⁵, namely, thickening of the sub-mesothelial space, neoangiogenesis and thickening of the vascular wall by type IV collagen⁶. As a consequence, it is tempting to hypothesise that the prior vascular alteration seen in diabetic patients will have an impact on peritoneal membrane structure and function. In addition, while DM is seen as a determinant of peritoneal fast transport status in PD patients⁷, investigation into peritoneal transport characteristics in diabetics has yielded no uniform results. While some authors describe higher solute transport in diabetic⁸⁻¹⁰ than non-diabetic patients, others have found no difference^{11,12}. Also, while ultrafiltration was similar in diabetics in some reports¹³, it was lower in others¹⁴. Free water transport has also been investigated in incident patients on PD by Krediet *et al.*¹⁵, with no differences observed in small solute transport rate and sodium sieving between diabetic and control groups. These conflicting results could be explained, at least in part, by different durations of time on PD, and therefore, different exposure to intraperitoneal glucose. To avoid this possibility, we performed a study at the onset of dialysis, between the second and the fifth month following peritoneal dialysis initiation.

In addition to serum albumin and C reactive protein (CRP), widely known systemic surrogates of inflammation, we also studied the role of intraperitoneal pro-inflammatory cytokines (interleukin 6 – IL-6) and vascular endothelial growth factor (VEGF). It has been speculated that their increase may contribute to high peritoneal small solute transport rate in continuous ambulatory peritoneal dialysis patients¹⁶.

Several lines of evidence implicate VEGF as a mediator of microvascular hyperpermeability and glucose-induced tissue damage¹⁷⁻¹⁹. In this study we evaluated possible differences in plasma and dialysate IL-6 and VEGF levels in diabetic and non-diabetic patients. Mesothelial cell mass, as measured by effluent cancer antigen 125 (CA 125), was also assessed.

■ SUBJECTS AND METHODS

We analysed data on 81 consecutive incident patients on PD. All were treated with commercially available glucose and lactate based solutions. None of them had ever had peritonitis.

Thirty (37%) patients were male, with mean age 51.7±15.6 years. Twenty two (27%) had diabetes mellitus. Other end stage renal disease aetiologies are described in Table I.

■ Procedures and calculations

The peritoneal equilibration test (PET) was performed with 3.86% glucose solution between the second and the fifth month after start of treatment, in all patients. Creatinine and glucose were measured with standard automatic analyser techniques. Serum albumin was determined by nephelometry. Sodium (effluent and plasma) was measured with indirect ion selective electrodes. We measured the dialysate appearance rate (AR) of IL-6, CA 125 and VEGF (IL-6 AR, CA125 AR and VEGF AR, respectively) at 4 hours. VEGF was measured in serum and effluent, with an enzyme-linked immunosorbent assay (Quantikine -human VEGF-: R&D System, Minneapolis, MN, U.S.A.). Serum and effluent IL-6 measurement was performed with an immunoenzymometric assay (IL-6 Easia: Biosource Europe SA, Nivelles, Belgium). Effluent CA 125 was measured with an electrochemiluminescence method with an automated analyser (Elysys 2010: Boehringer Mannheim, Indianapolis, IN, U.S.A.). Dialysate appearance rate was calculated as the amount in the effluent divided by the dwell time.

Peritoneal transport status was determined using mean values and the standard deviation of dialysate to plasma ratio creatinine (D/P Cr). The mass transfer area coefficient (MTAC) of creatinine was achieved by the simplified Garred model²⁰. As proposed by Krediet *et al.*²¹, we used a model for correction for diffusion of sodium sieving: the MTAC of creatinine was employed to predict the dialysate sodium concentration resulting from diffusion alone. This value was then subtracted from the measured sodium concentration in the dialysate. The latter was used to calculate the D/P sodium. The dip D/P sodium is the difference between the initial D/P sodium and the D/P sodium at 60 minutes.

Residual glomerular filtration rate (GFR) was calculated by averaging the urea and the creatinine clearance by a 24-h urine collection.

Comorbid conditions were recorded at baseline and characterised by the Davies comorbidity score²².

Patients were stratified into two groups according to the mean D/P Cr in the studied population: fast and fast-average transporters (F/FA when the D/P Cr was equal or higher than the mean D/P Cr for the entire population) and slow and slow-average transporters (S/SA when the D/P Cr was lower than the mean D/P Cr value).

Statistical analysis

Statistical analysis was performed using the SPSS software. Categorical variables were expressed as percentage and continuous variables as means ± standard deviation (parametric variables) or median and percentiles (non-parametric variables). Differences between groups were analysed using Student t and Mann-Whitney tests as appropriate. Pearson (parametric variables) and Spearman (non-parametric variables) correlation coefficients were also performed. Significant difference was accepted at $p < 0.05$.

RESULTS

Demographic and clinical characteristics of diabetic and non-diabetic patients are shown in Table II. No significant difference was observed within groups, except for the Davies comorbidity score (Fig. 1). As expected, more diabetic patients had a higher score.

Table I

End stage renal disease aetiology in the study population

	n	%
DM	22	27
Unknown	13	16
Glomerulopathies	10	12
Chronic rejection	2	3
Chronic interstitial nephritis	4	5
ADPKD	2	3
Hereditary/Familiar NOS	5	6
Amyloidosis	1	1
MM	1	1
SLE	3	4
No data available	18	22

ADPKD – autosomal dominant polycystic kidney disease; NOS – no other specification; MM – multiple myeloma; SLE – systemic lupus erythematosus.

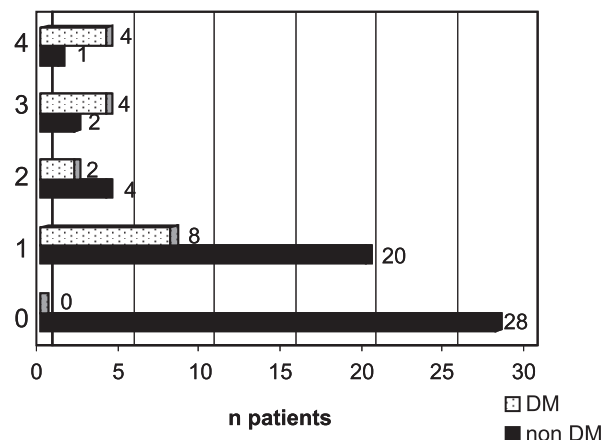


Figure 1

Davies comorbidity score

The majority of non-diabetic patients had classes 0 and 1 of Davies comorbidity score; conversely diabetics had higher score classes.

Thirty eight patients (47%) were on PD due to vascular access problems, with no significant difference between the two groups (59% in diabetic *versus* 42%; $p = 0.21$) (Table II). The mean±SD values for the overall population were D/P Cr 0.77 ± 0.10 ; MTAC for creatinine 11.1 ± 5.8 ml/min per 1.73 m²; D/Do for glucose (ratio of dialysate glucose at 4 hours' dwell time to dialysis glucose at 0 dwell time) 0.28 ± 0.02 ; peritoneal ultrafiltration 2767 ± 228 ml; GFR 3.6 ± 2.6 ml/min; serum albumin 3.8 ± 0.48 g/dl and CRP 1.16 ± 1.8 mg/dl.

The diabetic group had a mean percentage of haemoglobin A1c of 8 ± 1.6 % at the time of performing PET.

Comparing diabetic with non-diabetic patients, no difference was found in mean CRP, serum albumin and plasma interleukin-6 ($p = NS$ for all), although CRP tended to be higher and albumin lower in diabetic patients (Table III). D/P Cr was similar in both groups (0.77 ± 0.11 for diabetics *versus* 0.77 ± 0.09 ; $p = 0.98$) and the percentage of F/FA transporters was equivalent between groups (55% in diabetics *versus* 54% in non-diabetics; $p = 1.0$). Glucose absorption ($1 - D/Do$) was similar among groups (70% in diabetics *versus* 73% in non-diabetics; $p = 0.12$). Small solute transport, peritoneal ultrafiltration (UF) and free water

Table II

Characteristics of patients with and without diabetes

	DM (22)	Non DM (59)	p
Male (n / %)	10 / 45%	20 / 34%	0.43
Age (yrs)	53 ± 16	51 ± 16	0.65
BMI (kg/m ²)	25 ± 3	24 ± 4	0.84
Urine volume (ml/day)	1403 ± 978	1183 ± 863	0.35
Residual GFR (ml/min)	4.4 ± 3.1	3.3 ± 2.5	0.13
Previous time on renal replacement therapy (months; median, p ₅ , p ₉₅)	6, 2, 39	5, 2, 145	0.56
PD choice: vascular access problem (n / %)	13 / 59%	25 / 42%	0.21
Fast/fast-average transporters (n / %)	12 / 55%	32 / 54%	1.0

BMI – Body Mass Index

Table III

Inflammatory markers, fluid and solute transport and mesothelial mass

	DM (22)	Non DM (59)	p
CRP (mg/dl)	1.34 ± 1.91	1.10 ± 1.80	0.63
Serum IL6 (pg/ml; median, p ₅ , p ₉₅)	12, 2, 48	10, 2, 65	0.93
Serum albumin (g/dl)	3.69 ± 0.42	3.85 ± 0.50	0.17
D/P Cr	0.77 ± 0.11	0.77 ± 0.09	0.98
MTAC Cr (ml/min/1.73 m ²)	12.3 ± 6.5	10.6 ± 5.5	0.25
D/Do glucose	0.30 ± 0.05	0.27 ± 0.07	0.12
Peritoneal UF (ml)	2759 ± 228	2771 ± 231	0.83
Corrected D/P Na ₆₀	0.77 ± 0.04	0.77 ± 0.05	0.55
Corrected Dip Na	0.17 ± 0.05	0.16 ± 0.06	0.45
CA 125 AR (U/min)	132 ± 50	168 ± 116	0.16
VEGF AR (U/min; median, p ₅ , p ₉₅)	213, 130, 1800	243, 77, 680	0.67
IL6 AR (U/min; median, p ₅ , p ₉₅)	879, 132, 26962	617, 233, 1910	0.22

transport were similar in diabetics and non-diabetics, as given in Table III. The maximum dip in D/P sodium tended to be deeper in non-diabetics, although not reaching statistical significance (Fig. 2).

Serum VEGF, dialysate IL-6 AP, VEGF AP and CA 125 AP levels were not significantly different in diabetics and non-diabetics.

In the diabetic subgroup, no correlation was found between HbA_{1c} value and D/P Cr (p=0.53), MTAC Cr (p=0.70), IL-6 AP (p=0.37), VEGF AP (p=0.22) and CA 125 AP (p=0.21).

Taking the overall population into consideration, no correlation was found between D/P Cr and CRP

(p=0.54), serum albumin (p=0.6), serum IL-6 (p=0.99), IL-6 AP (p=0.86), VEGF AP (p=0.33) and Davies comorbidity score (p=0.68). A positive correlation was found between D/P Cr and CA 125 AP (p<0.01).

DISCUSSION

In this report we investigated potential disparities in peritoneal membrane transport function, inflammation and mesothelial mass in diabetic and non-diabetic patients starting peritoneal dialysis treatment. Our study disclosed no differences in patients with or without DM in the first months of beginning PD. These results are in agreement with previous

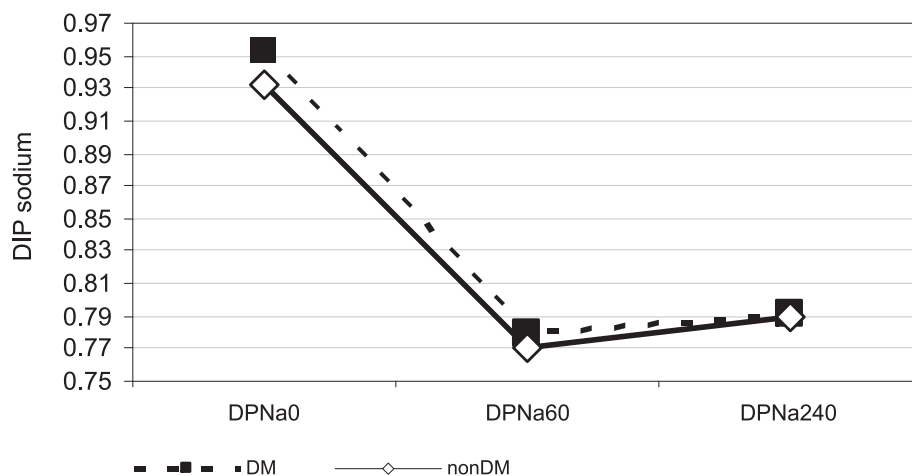


Figure 2

Corrected sieving sodium

Dialysate-to-plasma (D/P) ratios during a 4-hr dwell for diabetics and non-diabetics. No significant difference was seen.

findings by Krediet *et al.*¹⁵. However, in experimental DM models²³, diabetic rats were characterised by vascular proliferation, with increased permeability for small molecules and decreased sodium sieving. In any case, diabetic rats chronically treated with insulin showed similar peritoneal permeability when compared with control rats: after a six week period of insulin treatment, the differences found were abolished. These observations point to a causative role for hyperglycaemia, when not corrected with therapy. Variability on peritoneal function may reflect the control of DM, and glycaemic control seems to exert a key influence on development of vascular peritoneal proliferation. Our group of patients had slightly elevated HbA_{1c} levels, indicating that, although glucose control should have been optimised, it did not exert a strong enough negative impact on peritoneal membrane function.

In a paper from the Peritoneal Biopsy Study Group²⁴, the authors examined the morphologic 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 diabetic patients did not show increased incidence of vasculopathy. This finding was also supported by other reports²⁵, which suggests that

vasculopathy among diabetic patients is organ-related²⁵. Williams *et al.*²⁴ noticed that predialysis uraemic patients demonstrated a significantly thicker submesothelial zone than that observed in healthy individuals. These findings indicate that uraemia itself may induce changes in the peritoneal membranes of patients before they commence PD. Authors concluded that fibrotic and vascular changes may be a unique development specifically driven by the process of PD and/or uraemia, and that uraemia can contribute more than hyperglycaemia²⁶ to peritoneal membrane changes. Consequently, the uraemic environment present at the beginning of the PD treatment would preclude distinction between diabetic and non-diabetic patients. The absence of correlation between HbA_{1c} value and solute transport/mesothelial mass in our results can be, at least partially, explained by these observations.

Another major factor that could contribute to different transport characteristics in incident PD patients is inflammation²⁷. As widely reported, intraperitoneal IL-6 may be regarded as a marker of ongoing local inflammation²⁸⁻²⁹ and VEGF as a surrogate of vascular proliferation. In our study, no differences were found in systemic or intraperitoneal markers of inflammation or in VEGF appearance rate among the two groups. Also, we found no correlation

between fast solute transport and inflammation. These results suggest that DM in uraemic patients is not inevitably associated with higher inflammation or with higher peritoneal neoangiogenesis, in comparison with other uraemic non-diabetic patients. There are many other known stimuli for the inflammatory response in chronic kidney disease patients, such as fluid overload, decreased cytokine clearance, presence of uraemia-modified proteins, presence of chronic infections and metabolic disturbances³⁰.

While some evidence supports that residual renal function deteriorates faster in diabetics than in patients with non-diabetic end stage renal disease^{14,31}, at the beginning of renal replacement therapy our group of diabetics showed equivalent GFR and daily urine volume to non-diabetic patients.

We are well aware of the limitations of our study. First, our sample size, in particular the number of diabetics, was relatively small, which can be associated with low statistical power. Second, our study design (cross-sectional) might not be the ideal methodology to allow for the analysis of glucose control; the latter would imply a longitudinal design. Even so, considering one measurement in a period of 4 months for each patient, we found no correlation between glycaemic control and peritoneal function.

In summary, our data suggest that at the time point of initiation of PD, diabetic were not disadvantaged with respect to peritoneal transport characteristics, as measured by the markers we used, though confirmation awaits a structural study (e.g., peritoneal biopsy).

Conflict of interest statement. None declared.

References

- Bigazzi R, Bianchi S. Insulin resistance, metabolic syndrome and endothelial dysfunction. *J Nephrol* 2007;20:10-14
- Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature* 2001;414:813-820
- del Peso G, Fernández-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;20:1201-1206
- 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
- Combet S, Miyata T, Moulin P, Pouthier D, Goffin E, Devuyst O. Vascular proliferation and enhanced expression of endothelial nitric oxide synthase in human peritoneum exposed to long term peritoneal dialysis. *J Am Soc Nephrol* 2000;11:717-728
- Krediet RT, Zweers MM, van der Wal AC, Struijk DG. Neoangiogenesis in the peritoneal membrane. *Perit Dial Int* 2000;20(2):S19-S25
- Correa-Rotter R, Cueto-Manzano A. The problem of the high transporter: is survival decreased? *Perit Dial Int* 2001;21(3):S75-S79
- Tzamaloukas AH, Murata GH, Malhotra D *et al.* Small solute clearances in diabetic subjects on continuous ambulatory peritoneal dialysis: comparison to nondiabetic patients. *Adv Perit Dial* 1999;15:179-182
- Lin JJ, Wadhwa NK, Suh H, Cabralda T, Patlak CS. Increased peritoneal solute transport in diabetic peritoneal dialysis patients. *Adv Perit Dial* 1995;11:63-66
- Nakamoto H, Imai H, Kawanishi H *et al.* Effect of diabetes on peritoneal function assessed by personal dialysis capacity test in patients undergoing CAPD. *Am J Kidney Dis* 2002;40:1045-1054
- Lee HB, Park MS, Chung SH *et al.* Peritoneal solute clearances in diabetics. *Perit Dial Int* 1990;10:85-88
- Graff J, Fugleberg S, Nielsen SL, Feldt-Rasmussen B. Transperitoneal transport in diabetic and non-diabetic patients on peritoneal dialysis. *Clin Physiol* 1999;19:510-518
- Rubin J, Walsh D, Bower JD. Diabetes, dialysate losses and serum lipids during continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1987;10:104-108
- Lamb EJ, Worrall J, Buhler R, Harwood S, Cattell WR, Dawney AB. Effect of diabetes and peritonitis on the peritoneal equilibration test. *Kidney Int* 1995;47:1760-1767
- Smit W, van Esch S, Struijk DG, Krediet RT. Free water transport in patients starting with peritoneal dialysis: a comparison between diabetic and non diabetic patients. *Adv Perit Dial* 2004;20:13-17
- Pecoits-Filho R, Carvalho MJ, Stenvinkel P, Lindholm B, Heimbürger O. Systemic and intraperitoneal interleukin-6 system during the first year of peritoneal dialysis. *Perit Dial Int* 2006;26:53-63
- Neufeld G, Cohen T, Gengrinovitch S, Poltorak Z. Vascular endothelial growth factor and its receptors. *FASEB J* 1999;13:19-22
- Tilton RG, Kawamura T, Chang KC *et al.* Vascular dysfunction induced by elevated glucose levels in rats is mediated by vascular endothelial growth factor. *J Clin Invest* 1997;99:2192-2202
- de Vriese AS, Tilton RG, Elger M, Stephan CC, Kriz W, Lameire NH. Antibodies against vascular endothelial growth factor improve early renal dysfunction in experimental diabetes. *J Am Soc Nephrol* 2001;12:993-1000
- Garred LJ, Canaud B, Farrell PC. A simple kinetic model for assessing peritoneal mass transfer in chronic ambulatory peritoneal dialysis. *ASAIO J* 1983;6:131-137
- Westra WM, Smit W, Zweers MM, Struijk DG, Krediet RT. Diffusion correction of sodium sieving applicable in a peritoneal equilibration test. *Adv Perit Dial* 2003;19:6-9
- Davies SJ, Russell L, Bryan J, Phillips L, Russell GI. Comorbidity, urea kinetics and appetite in continuous ambulatory peritoneal dialysis: their interrelationship and prediction of survival. *Am J Kidney Dis* 1995;26:353-361
- Stoenoiu MS, De Vriese AS, Brouet A *et al.* Experimental diabetes induces functional and structural changes in the peritoneum. *Kidney Int* 2002;62:668-678
- Williams JD, Craig KJ, Topley N *et al.* Morphologic Changes in the Peritoneal Membrane of Patients with Renal disease. *J Am Soc Nephrol* 2002;13:470-479
- De Las Casas LE, Finley L. Diabetic microangiopathy in the small bowel. *Histopathology* 1999;35:267-270
- Miyata T, Fu MX, Kurokawa K, van Ypersele de Strihou C, Thorpe SR, Baynes JW. Autoxidation products of both carbohydrates and lipids are increased in uremia plasma; is there oxidative stress in uremia? *Kidney Int* 1998;54:1290-1295

- ²⁷ Chung SH, Heimbürger O, Stenvinkel P, Wang T, Lindholm B. Influence of peritoneal transport rate, inflammation, and fluid removal on nutritional status and clinical outcome in prevalent peritoneal dialysis patients. *Perit Dial Int* 2003;23:174-183
- ²⁸ Cooker LA, Luneburg P, Holmes CJ. Dialysate levels of IL-6 and VEGF in patients using bicarbonate/lactate-based peritoneal dialysis solutions. *Perit Dial Int* 2001;21(3):S102-S107
- ²⁹ Pecoits-Filho R, Araújo MR, Lindholm B *et al*. Plasma and dialysate IL-6 and VEGF concentrations are associated with high peritoneal solute transport rate. *Nephrol Dial Transplant* 2002;17:1480-1486
- ³⁰ Cueto-Manzano AM, González-Espinoza L, Martín del Campo F, Fortes PC, Pecoits-Filho R. Inflammation in peritoneal dialysis: a Latin-American perspective. *Perit Dial Int* 2007;27:347-352

- ³¹ Bargman JM, Thorpe KE, Churchill DN; CANUSA Peritoneal Dialysis Study Group. Relative Contribution of Residual Renal Function and Peritoneal Clearance to Adequacy of Dialysis: A Reanalysis of the CANUSA Study. *J Am Soc Nephrol* 2001;12:2158-2162

Correspondence to:

Dr Sandra Silva
Rua Barranha 1055 E 3 Esq Tras/ 4460-256 Sra Hora, Matosinhos,
Portugal.
Email: oliveirasilva.sandra@gmail.com