

Predictors of Residual Renal Function Loss in Peritoneal Dialysis: Is Previous Renal Transplantation a Risk Factor?

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Preservation of residual renal function (RRF) is an important goal in peritoneal dialysis (PD). The present study explored the factors conditioning RRF decline in a PD population.

We studied 148 consecutive patients. Age, sex, diabetes, previous renal replacement therapy time and modality [hemodialysis (HD), renal transplantation (RT), or PD first], peritoneal transport, PD prescription [automated (APD) or continuous ambulatory], and peritonitis were investigated as possible determinants of RRF decline.

In 22 patients (15%), PD was started after RT. Residual renal function was not significantly different between patients who started PD as their first option and those who started after RT, either at baseline or after 1 year on PD. Baseline dialysate-to-plasma creatinine was also similar between those groups.

Transfer from HD was the single significant predictor of baseline anuria [odds ratio (OR): 6.3; $p < 0.001$]. After the start of PD, diabetes was the only predictor of anuria (OR: 2.5; $p = 0.02$). Age, sex, reason for PD, PD after graft failure, peritonitis, use of APD, and fast transport were not predictors of anuria. Despite slow tapering of immunosuppression, peritonitis-free survival was not shortened in patients who started PD after RT.

Diabetes was a determinant of the time course of RRF decline in PD. Peritoneal dialysis after RT failure offered short-term RRF protection that was similar to that seen in PD-first patients.

Key words

Residual renal function, renal graft failure

Introduction

In recent years, greater focus has been given to residual renal function (RRF) in patients on chronic dialysis therapy because RRF plays an important role in the maintenance of fluid balance and biochemical homeostasis in end-stage renal disease patients on dialysis. Several studies have reported that RRF is better preserved in peritoneal dialysis (PD) than in hemodialysis (HD) patients. There is a consensus that RRF has a major effect on quality of life and outcome in PD patients, and therefore preservation of RRF becomes a goal of adequacy beyond the limited role of Kt/V (1). As a result, determining the factors that affect loss of RRF has become an important issue in the care of PD patients.

Several factors have been associated with loss of RRF (2–4): larger body mass index, presence of diabetes, presence of congestive heart failure, use of diuretics, hypotensive events, episodes of peritonitis, inflammation, peritoneal fast transport status, and use of automated PD (APD). However results are not consistent, and studies often exclude patients with a failed renal graft, which is becoming one of the most frequent causes of dialysis initiation (5). Most patients with a failed renal graft are initiated on HD as their next renal replacement modality, and concerns about the success of PD in this population have been expressed, given that few studies have considered outcome in patients with renal graft failure on PD. Sasal *et al.* (6) and Davies (7) reported a more rapid loss of RRF in PD patients with a failed renal allograft than in patients who had never undergone kidney transplantation. However de Jonge *et al.* (8) reported no significant difference in the decline of RRF between PD patients with renal graft failure and never-transplanted patients starting PD.

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Faced with these conflicting findings about predictors of RRF loss among transplantation patients, we explored the factors conditioning RRF decline in our PD population.

Patients and methods

All consecutive incident patients commencing PD at our center between January 2000 and June 2007 were included in the study ($n = 148$). More than 50% of the patients were treated with PD solutions low in glucose degradation products. When needed for ultrafiltration, icodextrin was the standard prescription in the unit; use of hypertonic 3.86% glucose solution has long been abandoned and is only exceptionally prescribed.

Baseline factors such as age, sex, diabetes, total previous time on renal replacement therapy (RRT), previous modality [HD, transplantation (RT), PD as first modality], peritoneal transport category, and PD prescription [continuous ambulatory PD (CAPD) or automated PD (APD)], and peritonitis episodes were investigated as possible determinants of RRF decline. Using timed urine collections, we measured RRF as the arithmetic mean of urinary urea and creatinine clearance at baseline and at approximately 3-month intervals thereafter. The date of development of complete anuria was also recorded.

The subgroup of patients started on PD after renal graft failure was compared with PD-first patients. The RT patients all received tapering immunosuppression: immediate withdrawal of antiproliferative drugs (azathioprine, mycophenolate mofetil, sirolimus) after PD induction, with a slow reduction of calcineurinic drugs and prednisolone over several months.

Statistical analysis

All data are expressed as mean \pm standard deviation or median with interquartile range (IQR). Comparisons between groups of continuous variables used the Student independent *t*-test or the Mann–Whitney test, as appropriate. Proportions of categorical variables were compared using the chi-square test.

The outcomes examined were anuria at PD baseline (logistic regression) and time to loss of RRF (anuria) after the start of PD (survival analysis by the Kaplan–Meier method and Cox regression for multivariate analysis). Kaplan–Meier survival curves were compared using the log-rank test. The Cox proportional hazards model was used to examine the effects of

demographic, clinical, and dialysis variables on the outcome variable. The relative risks for loss of RRF (anuria) were determined by univariate and multivariate Cox regression analysis and are presented as hazard ratios (HRs) with a 95% confidence interval (CI).

A *p* value below 0.05 was considered to be statistically significant. Statistical analyses were performed using the statistical software package SPSS (version 15.0: SPSS, Chicago, IL, U.S.A.).

Results

Of the 148 consecutive incident patients included in the study, 69% were women (102 of 148). The mean age of the patients was 47.2 ± 16.0 years, 26 (17.6%) had diabetes, and 84 (56.8%) were on APD. Table I shows the baseline characteristics of the study patients.

Patients had been on renal replacement therapy for a mean of 3.9 ± 6.5 years (range: 0 – 34 years): 72 (48.6%) had transferred from HD (PD-after-HD group), 22 (14.9%) started PD after renal graft failure (PD-after-RT group), and the remaining 54 (36.5%) initiated dialysis with PD as the first modality (PD-first group). Of the 148 patients, 49 (33.1%) were anuric [glomerular filtration rate (GFR) < 1 mL/min] at baseline: 31 (63.3%) in the PD-after-HD group, 8 (16.3%) in the PD-after-RT group, and 10 (20.4%) in the PD-first group.

As expected, patients transferring from HD (mainly because of vascular access failure) had a higher prevalence of anuria (42.3% vs. 24.2%, $p = 0.023$), and this association was confirmed by multivariate

TABLE I Characteristics of the study patients

Characteristic	[n (%)]
Patients	148
Sex (men)	46 (31.1)
With diabetes	26 (17.6)
On APD	84 (56.8)
Reason for PD	
Choice	68 (45.9)
Access failure	80 (54.1)
Renal replacement therapy	
PD first	72 (48.6)
PD after HD	54 (36.5)
PD after RT	22 (14.9)
Baseline anuria	49 (33.1)
With peritonitis	74 (50)

APD = automated peritoneal dialysis; PD = peritoneal dialysis; HD = hemodialysis; RT = renal transplantation.

analysis. Transfer from HD was the only significant predictor of baseline anuria (OR: 6.3; $p < 0.001$) after adjustment for age, sex, decision for PD (optional or after access failure), previous renal replacement therapy, and diabetes (Table II).

Peritonitis-free survival was similar in PD-after-RT patients and PD-first patients (estimate: 391 days vs. 378 days; $p = 0.92$).

At baseline, median RRF was not significantly different between PD-first patients and PD-after-RT patients: 5.8 (IQR: 4.3 – 8.3 mL/min) versus 8.1 (IQR: 4.2 – 16.1 mL/min; Mann-Whitney U : $p = 0.26$). After 1 year on PD, no significant differences in median RRF emerged: 3.9 (IQR: 2.0 – 6.7 mL/min) versus 4.5 (IQR: 0.4 – 5.6 mL/min; Mann-Whitney U : $p = 0.74$). Baseline peritoneal transport as measured by dialysate-to-plasma (D/P) creatinine from a 4-hour peritoneal equilibration test using 3.86% glucose was also similar between the groups (0.76 ± 0.13 vs. 0.73 ± 0.11 ; Mann-Whitney U : $p = 0.42$).

Diabetes was significantly associated with an increase in the risk of RRF decline, with a mean estimate of 19.7 months to anuria in diabetic patients as compared with 37.6 months in nondiabetic patients ($p = 0.028$, Figure 1). Time to anuria was shorter in PD-after-RT patients (estimate: 23.4 months in the PD-after-RT group, 29.6 months in the PD-after-HD group, and 36 months in the PD-first group), but the PD-after-RT group was small ($n = 14$), and the differences did not reach statistical significance.

By multivariate analysis (and excluding all patients with anuria at baseline), the predictors for anuria developing after the start of PD were diabetes

(OR: 2.27; $p = 0.033$) and previous time on RRT (OR: 1.005; $p = 0.028$). Age, sex, peritonitis, reason for initiating PD (access failure or choice), previous RRT modality (PD first, PD after RT), baseline D/P creatinine, and PD prescription (APD) were not significant predictors for the development of anuria (Table III).

Discussion

Preservation of RRF is an important goal in the management of PD patients. However, in the literature, results concerning the factors that influence the rate of decline of RRF are conflicting.

Diabetes mellitus as one of the predictors of RRF loss has been addressed by several studies, but not all (9). In a recent study that enrolled 270 incident PD patients (18% with diabetes), Liao *et al.* (2) reported that the annual rate of RRF decline in patients with diabetes was almost twice that of patients without diabetes (2.38 ± 1.38 mL/min/1.73 m² vs. 1.14 ± 1.27 mL/min/1.73 m²). In the present study, we also found that diabetes was a major determinant of RRF decline, given that in the multivariate analysis, it was the only predictor of anuria.

The contribution of peritonitis episodes to RRF decline is more inconsistent. Some studies (2,10) reported that peritonitis rate was an independent risk factor for the decline of RRF in PD patients, but the link remains unclear. Along with others (11), we were not able to document any association between anuria and peritonitis rate.

TABLE II Predictors of anuria at baseline of peritoneal dialysis (logistic regression^a)

Predictor	OR	95% CI	p Value
Reason (access failure vs. optional)	1.8	0.7 to 4.1	0.18
Diabetes (yes vs. no)	0.5	0.2 to 1.5	0.21
Age (years)	1.0	0.9 to 1.0	0.81
PD after HD vs. PD first	6.3	2.6 to 9.3	<0.001
PD after RT vs. PD first	2.3	0.7 to 7.6	0.17

OR = odds ratio; CI = confidence interval; PD = peritoneal dialysis; HD = hemodialysis; RT = renal transplantation.

^a After including age, diabetes, reason for peritoneal dialysis [PD (after access failure or optional)], and dialysis modality before PD, transfer from hemodialysis was the only factor independently associated with the presence of anuria at the beginning of PD.

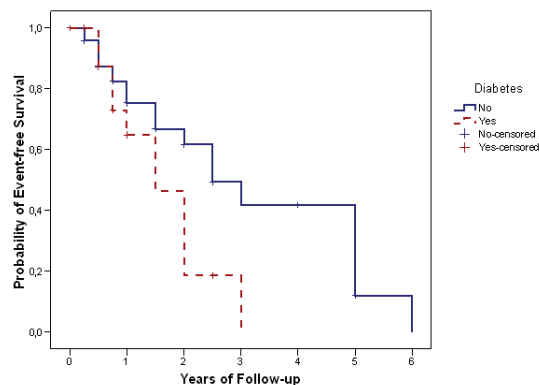


FIGURE 1 Effect of diabetes on residual renal function (Kaplan-Meier method). Time to the loss of residual renal function (anuria) was significantly shorter in patients with diabetes ($p = 0.028$).

TABLE III Predictors of anuria (loss of residual renal function) after the start of peritoneal dialysis (Cox proportional hazards analysis^a)

Predictor	HR	95% CI	p Value
Peritonitis episodes (1 vs. 0)	0.6	0.3 to 1.4	0.25
Peritonitis episodes (≥ 2 vs. 0)	0.9	0.4 to 1.9	0.76
Reason for PD (access failure vs. optional)	1.5	0.8 to 3.0	0.22
Diabetes (yes vs. no)	2.5	1.1 to 5.5	0.02
Age (years)	1.0	0.9 to 1.0	0.46
Sex (men vs. women)	1.1	0.5 to 2.3	0.75
PD after HD vs. PD first	0.9	0.4 to 2.3	0.87
PD after RT vs. PD first	2.1	0.8 to 5.4	0.12

HR = hazard ratio; CI = confidence interval; PD = peritoneal dialysis; HD = hemodialysis; RT = renal transplantation.

^a Considering the variables sex, age, reason for peritoneal dialysis [PD (access failure/option)], type of previous renal replacement therapy, and number of peritonitis episodes in the model, diabetes was the only independent predictor of residual renal loss after PD start.

In a number of studies, fast peritoneal transport status has been associated with increased technique failure and mortality, but a recent investigation highlighted the heterogeneity of fast transport status both in cause and in outcome (12). Johnson *et al.* (11) reported that a high D/P ratio was a risk factor for rapid loss of RRF. The reason for that association is uncertain, but the authors speculate that inflammation may have caused both an increase in the peritoneal transport rate and a decline of RRF. We were not able to document this association between high peritoneal transport status and RRF loss in our group, but inflammation status presumably depends more on associated comorbidity and PD treatment strategy. Information on peritoneal transport profiles in renal graft failure patients under PD treatment is scarce, but notably, we did not find faster transport rates in our PD-after-RT group than in our PD-first patients.

Evidence has also emerged that APD, as compared with CAPD, might have a deleterious effect on RRF. It is hypothesized that the acute changes in volume and osmotic load induced at each nightly PD session could potentially accelerate deterioration of RRF. However, we—like others (2,11,13)—were not able to document any difference in decline of RRF between patients on cyclo-assisted PD and patients on CAPD. Our study lends further support to the argument that APD therapy *per se* does not significantly affect the decline of RRF.

In the integrated care model of renal replacement therapy, patients with renal allograft failure returning to a second chronic PD program represent a special subgroup of end-stage renal disease patients. The

reasons that very few patients initiate PD after failed allograft may be related to uncertainty about the success of PD in this patient population (5): outcome studies are few, and there are concerns about an increased risk of therapy-related infection. We previously reported similar cumulative patient and technique survival and no difference in peritonitis-free survival between our PD patients coming from transplant and our incident PD patients (14). Favorable results have also been reported by other groups (15,16). But contradictory findings have been reported for the rate of decline of RRF in this population: one study suggested that patients on PD after a failed renal transplant have a faster rate of RRF decline than do other patients on PD (7); and yet another observed similar findings in PD patients with renal graft failure as compared with matched PD patients who had never received a graft (17).

Like de Jonge *et al.* (8), we found no difference in the decline of RRF between patients starting PD after renal transplant failure and a group starting PD as their first renal replacement therapy. A determining factor might be immunosuppression management after PD induction (18). Our policy of slowly tapering immunosuppressors—immediate withdrawal of antiproliferative drugs (azathioprine, mycophenolate mofetil, sirolimus) because of the major infectious risk, but slow reduction of calcineurinic drugs and prednisolone over several months—presumably protect renal graft function. However, this issue remains open.

Conclusions

In spite of the limitations typically found in our study and others (for example, limited number of PD

patients with renal graft failure, absence of prospective investigation of the link between immunosuppression tapering protocol and outcomes), our findings suggest that, compared with PD-first patients, PD-after-RT patients experience similar short-term RRF protection without a shorter peritonitis-free survival.

Diabetes seems to be an unmodifiable baseline epidemiologic risk factor for development of anuria after PD start, but further multicenter prospective studies are needed to examine whether good glycemic control and other modifiable determinants of RRF loss can be identified, and to evaluate whether interventions targeting those determinants could slow the deterioration of RRF in patients on chronic PD. The promising role of icodextrin and alternative solutions low in glucose degradation products in reducing RRF decline must also be validated (19).

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