Benefits of preserving residual renal function in peritoneal dialysis

B Marrón[1], C Remón[2], M Pérez-Fontán[3], P Quirós[4] and A Ortíz[5]

[1]Renal Division, Baxter Healthcare, Madrid, Spain; [2]Peritoneal Dialysis Unit, Division of Nephrology, Hospital Universitario de Puerto Real, Cádiz, Spain; [3]Peritoneal Dialysis Unit, Division of Nephrology, Hospital Juan Canalejo, A Coruña, Spain; [4]Peritoneal Dialysis Unit, Division of Nephrology, Hospital Universitario de Puerto Real, Cádiz, Spain and [5]Peritoneal Dialysis Unit, Division of Nephrology, Fundación Jiménez Díaz, Madrid, Spain

Residual renal function (RRF) is of paramount importance in patients with end-stage renal disease, with benefits that go beyond contributing to achievement of adequacy targets. Several studies have found that RRF rather than overall adequacy (as estimated from total small solute removal rates) is an essential marker of patient and, to a lesser extent, technique survival during chronic peritoneal dialysis (PD) therapy. In addition, RRF is associated with a reduction in blood pressure and left ventricular hypertrophy, increased sodium removal and improved fluid status, lower serum β_2-microglobulin, phosphate and uric acid levels, higher serum hemoglobin and bicarbonate levels, better nutritional status, a more favorable lipid profile, decreased circulating inflammatory markers, and lower risk for peritonitis in PD. As compared with conventional hemodialysis, PD is associated with a slower decrease in RRF. This highlights the usefulness of strategies oriented to preserve both RRF and the long-term viability of the peritoneal membrane. Several factors contributing to the loss of RRF have been identified and should be avoided. Renoprotective drugs and new glucose-sparing, more biocompatible PD regimes may prove useful tools to preserve RRF and peritoneal membrane function in the near future.

Kidney International (2008) **73,** S42–S51; doi:10.1038/sj.ki.5002600

KEYWORDS: peritoneal dialysis; residual renal function; benefits; preservation; hemodialysis

Correspondence: *B Marrón, Medical Affairs, Renal Division, Baxter Healthcare, P. Emp. San Fernando, Edificio Londres, 28830 Madrid, Spain. E-mail: belen_marron@baxter.com*

THE CONCEPT OF RESIDUAL RENAL FUNCTION AND A HISTORICAL REVIEW

Residual renal function (RRF) is in general defined as the residual glomerular filtration rate (GFR) in patients with end-stage renal disease. A progressive decrease in RRF is commonly observed in incident chronic kidney disease (CKD) stage 5 dialyzed patients as functional renal parenchyma is lost. The rate of decrease depends on several factors such as etiology of end-stage renal disease, treatment modalities, and exposure to nephrotoxic agents. It is important to remark that a residual GFR of $1\,ml\,min^{-1}$ is equivalent to a weekly peritoneal clearance of about 10 l. GFR is, however, not easy to measure in the common clinical setting, especially in patients receiving renal replacement therapy. The best clearance measure is still uncertain and different approaches have been used. Renal creatinine clearance is most frequently used, but it overestimates GFR and has errors of accuracy related to urine collection. Alternatively, the average of renal creatinine and urea clearances balances the overestimation of GFR by creatinine clearance with the underestimation by urea clearance. The presence of residual diuresis is required for RRF to exist. However, there may be discrepancies between the amount of residual diuresis and the residual GFR.

RRF has been a concept in evolution since the first reference to its importance in hemodialysis (HD) patients by Ahmad *et al.*[1] who studied the effect of RRF on the development of dialysis neuropathy and found that RRF played a major determinant role in dialysis requirements. More recently, Suda *et al.*[2] described the important contribution of RRF to overall nutritional status even in chronic HD patients. Despite this, the well-established importance of RRF is still ignored by many nephrologists, particularly in the HD field. Since the initial observation by Rottembourg *et al.*[3] that RRF is better preserved in patients treated with standard peritoneal dialysis (PD) than in those treated with conventional thrice-weekly HD, several other reports have confirmed this original finding.[4–9] In the pre-dialysis setting, maximal efforts are made by most physicians to preserve RRF to retard the need for renal replacement therapy.[10]

GENERAL BENEFITS OF RRF PRESERVATION

RRF has been associated with multiple beneficial effects. Preservation of RRF is associated with better long-term survival (lower relative risk of death) in dialysis patients,[11–17] a reduction in blood pressure (BP)[18] and left ventricular hypertrophy (LVH),[17,19–20] increased sodium removal,[21–22] improved fluid status,[22,23] increased serum β_2-microglobulin clearance and lower serum β_2-microglobulin levels,[24–27] higher serum hemoglobin levels,[17,19] better nutritional status,[17,26,28–29] and decreased circulating inflammatory markers.[30] Preservation of RRF contributes to achievement of adequacy targets,[11–17,31] better control of serum phosphate and uric acid levels,[17,21,32] higher serum bicarbonate levels,[26] a more favorable lipid profile,[33] and lower risk for peritonitis in PD.[28,34–36] We will now discuss in detail the relationship between RRF and PD adequacy, patient survival, cardiovascular disease, nutritional status, incidence of peritonitis, and quality of life.

THE IMPACT OF RRF ON PD ADEQUACY AND SURVIVAL

The relative contribution of endogenous (RRF) and exogenous (delivered dose of PD) clearance to the well-being and clinical outcome of PD patients has been a recurrent matter of interest during the last decade. In 1995, Maiorca *et al.*[37] provided evidence suggesting that total removal of small-size molecules could predict the outcome of PD patients. Their findings were basically confirmed 1 year later by the landmark CANUSA study.[38] Both studies disclosed a specific impact of RRF on survival. Unfortunately, the notion prevailed that the total dose of small solute clearance delivered was the essential point and that the removal rates provided by RRF and dialysis therapy were basically equivalent and interchangeable. This misinterpretation brought changes in the clinical guidelines for PD adequacy, which contributed significantly to hamper the progression of PD therapy during the following years. Ample quality evidence has now accumulated indicating that RRF and the delivered dose of dialysis have a well-differentiated influence on the global results of PD therapy. In 1999, two retrospective studies[11,28] suggested an association of RRF, but not of the dose of PD, with patient and technique survival. One year later, a cohort study of 1446 PD patients[12] showed a survival benefit of 40% for each 10 l per week per 1.73 m^2 increase in GFR, whereas PD removal rates had no apparent impact on outcome. Szeto *et al.*[39] reported similar findings the same year. The following year, an in-depth reanalysis of the CANUSA data showed that RRF and fluid removal, but not the amount of delivered PD, were strongly associated with survival.[14] For each 5 l per week per 1.73 m^2 increment in GFR, a 12% decrease in the risk of death was observed. Interestingly, diuresis (but not ultrafiltration (UF) or total fluid removal) was a stronger predictor of outcome than GFR itself. Also in 2001, another prospective study disclosed a risk reduction of 47% for each 10 l per week per 1.73 m^2 increase in GFR at the start of follow-up; in this case, total fluid and sodium removal did carry an independent effect on survival.[22] In 2003, a comprehensive report from the Netherlands Cooperative Study on the Adequacy of Dialysis, phase 2 (NECOSAD) group[16] confirmed previous findings showing a death risk reduction of 12% and a combined death-technique failure risk reduction of 10% per 10 l per week per 1.73 m^2 of GFR. Once again, the delivered dose of PD showed no apparent effect on clinical outcomes.

The ADEMEX study[40] was the first to provide hard evidence that, above certain limits, total small solute removal does not show an association with survival. Remarkably, RRF was, again, an independent marker of survival (risk reduction 11% for each 10 l per week per 1.73 m^2 increment in creatinine clearance). In summary, the main studies have very consistently shown that RRF rather than the delivered dose of PD is an essential marker of patient survival, whereas the relative effect of both factors on technique survival is less clear.[11,16,28,39]

We have reviewed the experience of the Andalusian Registry (Spain) (Remon C *et al.*, personal communication). All Andalusian incident PD patients from 1999 to 2005 with at least one complete measure of peritoneal kinetics and RRF (mean of urea and creatinine clearance) within the first year of therapy were included (402 patients). The population was divided in two groups of 201 patients each, according to whether the earliest value of RRF following initiation of PD was higher or lower than the median of the sample (4.33 ml min^{-1}). Renal and total small solute clearances and normalized protein catabolism rate were higher in the high

Table 1 | Andalusian registry—kinetic data

	RRF < 4.33	RRF > 4.33	*P*-value
RRF (ml min^{-1})	1.87 ± 1.4	7.48 ± 2.97	< 0.001
Renal Kt/*V*	0.39 ± 0.35	1.46 ± 0.64	< 0.001
Renal ClCr (l per week)	18.66 ± 16.33	72 ± 33.27	< 0.001
Peritoneal Kt/V	1.72 ± 0.43	1.41 ± 0.44	< 0.001
Peritoneal ClCr (l per week)	45.91 ± 13.65	38.65 ± 13.63	< 0.001
Total Kt/V	2.10 ± 0.54	2.82 ± 0.74	< 0.001
Total ClCr (l per week)	65.88 ± 20.03	109.22 ± 32.78	< 0.001
UF (ml)	238 ± 307	256 ± 336	NS
D/P creatinine	0.66 ± 0.13	0.67 ± 0.12	NS
nPCR (g per kg per 24 h)	0.90 ± 0.25	1.04 ± 0.26	< 0.001
Months on PD	22.09 ± 14.53	21.07 ± 15.65	NS

D/P, creatinine dialysate/plasma rate; nPCR, normalized protein catabolic rate; PD, peritoneal dialysis; RRF, residual renal function; UF, ultrafiltration.
Parameters of peritoneal kinetics in patients with RRF higher or lower than the median (median=4.33 ml min^{-1}). Mean 4.67 ± 3.64 ml min^{-1}.

RRF group (Table 1), whereas mean age was similar and there were no differences in the prevalence of dyslipemia, diabetes, or hypertension. However, cardiovascular disease (cardiomyopathy, peripheral vascular disease, or cerebrovascular disease) was more prevalent in patients with lower RRF (49 vs 37%, $P = 0.02$). Patients with lower RRF had a higher dropout rate due to death or technique failure (death or transfer to HD), with a risk ratio of 1.53 (confidence interval 95% 1.16–2.02, $P = 0.008$) and 1.54 (confidence interval 95% 1.21–1.96, $P = 0.005$), respectively (Figure 1). Although this analysis does not allow differentiation between the effect of higher RRF and that of total small solute clearance, it is in line with previous evidence indicating a beneficial role of RRF on patient and technique survival. A multivariate logistic regression analysis showed that a RRF below the median was an independent risk factor for death, independent of other covariables with specific weight in survival such as diabetes, cardiovascular disease, and age (Table 2). The distribution of mortality causes was similar between both groups. Cardiovascular disease was the main cause of mortality (41 and 46% for RPF below and over the median, respectively, *P* non significant).

All the previously quoted studies have limitations for establishing cause-and-effect relationships between RRF and the outcome of PD therapy. For instance, it is possible that patients in a more deteriorated condition present a worse baseline and/or a faster decrease in RRF during follow-up. Actually, this appears to be the case, as shown by some observational studies.[5,41,42] If this were the whole truth, RRF would be a marker, but not a determinant of survival. However, other evidence indicates that the absence or rapid loss of RRF does have a specific impact on the clinical condition of PD patients, particularly influencing the cardiovascular outcome of these patients.

RELATIONSHIP BETWEEN RRF AND CARDIOVASCULAR DISEASE

Cardiovascular disease is the main cause of death in CKD stage 5 patients.[22,43] Factors contributing to the increased prevalence and mortality due to cardiovascular disease in PD patients include chronic volume overload due to inadequate fluid and sodium balance, high peritoneal transport, hypertension, LVH, anemia, and inflammation. The loss of RRF contributes to inflammation, anemia, malnutrition, LVH, volume overload, hypertension and cardiovascular disease, and interacts with these factors to increase morbidity and mortality (Figure 2).[20]

Inadequate fluid and sodium balance is an independent predictor of a high all-cause hospitalization rate, higher prevalence and severity of hypertension, and higher mortality in PD.[22] RRF significantly contributes to adequate fluid and sodium balance. The achievement of this balance and the control of hypertension are more difficult in the absence of RRF,[22] despite increasing peritoneal UF with the prescription of hypertonic PD solutions.[23] The need for more aggressive PD prescriptions to comply with the adequacy and UF targets provides a basis for further metabolic disturbances and chronic damage to the peritoneal membrane if traditional glucose-based PD solutions are used.[44] Membrane function remained stable in icodextrin-treated patients when compared to the glucose-based PD solutions-only group.[44]

BP control improves within the first 6–12 months of PD initiation. This is due to improved fluid and sodium balance. However, the progressive loss of RRF is associated with impaired BP control. RRF, together with age and duration of hypertension before dialysis, are independently associated with impaired BP control.[45] There is a well-established inverse relationship between GFR and prevalence of hypertension,[46] even for very low GFR values.[45]

The prevalence of LVH is 75–90% among patients who start dialysis,[19,20,43] and its presence is one of the most important predictors of survival in these patients.[47,48] The severity of LVH is inversely associated with RRF as an independent factor, with several mechanisms contributing to this association.[19] These include reduced synthesis of erythropoietin resulting in anemia,[19,49] lower clearance of uremic toxins,[50] increased pulse pressure related to a lower

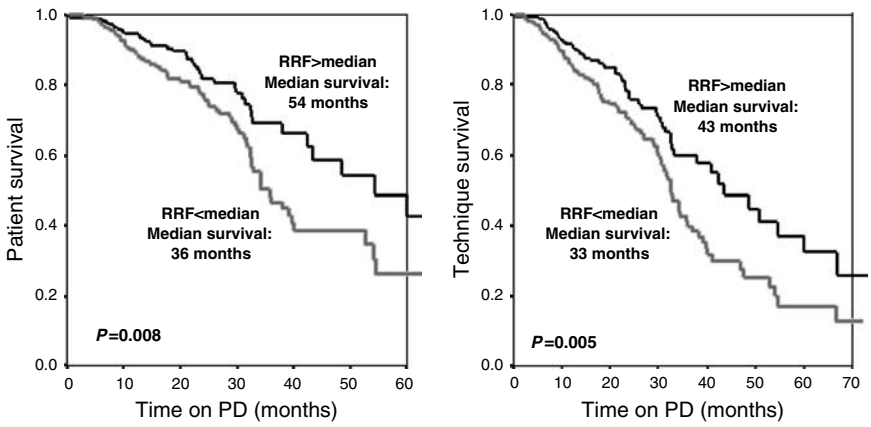

Figure 1 | Patient survival and technique success curves, according to RRF from the Andalusian Registry. Technique success refers to the probability of being both alive and on PD therapy.

Table 2 | Andalusian registry—regression analysis for risk of death

	P-value	RR	CI 95%
RRF (below median)	0.015	2.03	1.15–3.57
Diabetes	0.027	1.97	1.08–3.61
Cardiovascular disease	0.003	2.45	1.35–4.45
Age (per year)	0.001	1.07	1.05–1.1

CI, confidence interval; RR, risk ratio; RRF, residual renal function.
RRF below the median is a risk factor for death, independent of other covariables.

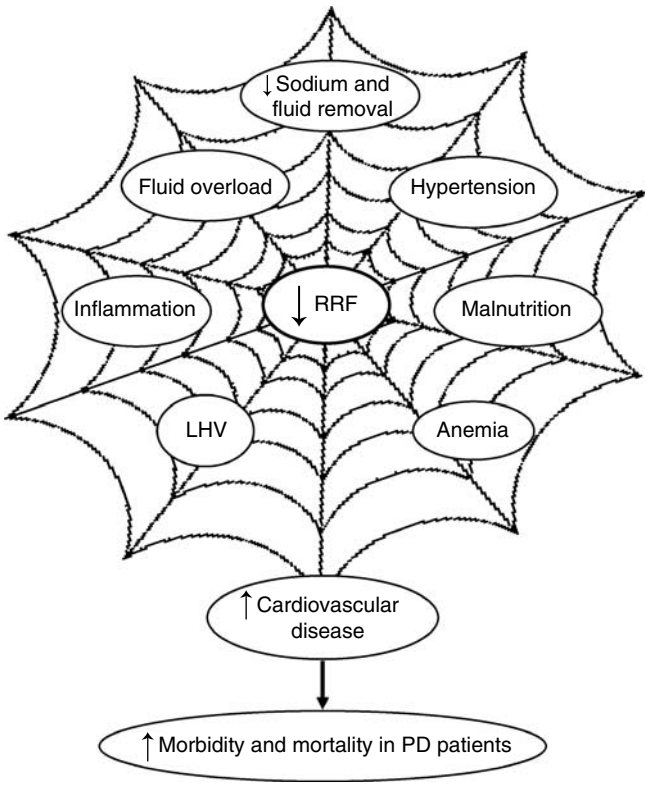

Figure 2 | Loss of RRF contributes to inflammation, anemia, malnutrition, LVH, volume overload, hypertension and cardiovascular disease in PD patients, and interacts with them to increase morbidity and mortality. The decrease or absence of RRF itself is an independent adverse risk factor.

fluid and sodium clearance,[19] activation of the renin–angiotensin system,[51] sympathetic hyperactivity mediated by renal failure,[52] and hypoalbuminemia.[2]

Inflammation, assessed by C-reactive protein levels, is inversely related to RRF.[17,30] A prospective observational study showed that the combination of inflammation, loss of RRF, and LVH increases the risk of death in PD patients, and this risk is independent of atherosclerotic vascular disease.[20] The authors hypothesize that inflammation may be the link between RRF and LVH in patients with advanced CKD.[20] In another study, mortality was higher in patients with low RRF, high C-reactive protein levels, and high peritoneal transport rates. By contrast, the absence of these factors was associated with a 100% survival at 5 years.[41]

RRF AND NUTRITION

Nutrition is intimately related to inflammation and vascular injury[30] and preservation of RRF is associated with better nutritional status.[17,26,28–29] Effects on both food intake and metabolic rate may contribute to this observation. Indeed, RRF was more important than dialysis dose for preservation of appetite,[53] likely related to its ability to clear molecules that inhibit satiety acting in the brain that are not adequately cleared by current dialysis methods.[54] On the contrary, non-biocompatible PD fluids and HD membranes may be an important source of cytokine production.[55] RRF may interact with inflammation and promote malnutrition and accelerated atherosclerosis. In a 15-month follow-up of 17 PD patients with systemic inflammation, those without RRF showed poorer appetite, worse nutritional status, and elevation of endothelial dysfunction markers.[56] Loss of RRF may also contribute to increased malnutrition in PD patients via its close relationship to increase energy expenditure.[57]

RRF AND PERITONITIS

At least four studies have investigated the potential association between RRF and the incidence of peritonitis during PD therapy. During an analysis on the global prognostic significance of RRF, the incidence of peritonitis in patients presenting a GFR $< 1\,ml\,min^{-1}$ at the start of follow-up was found to be three-fold greater than that of patients with GFR $> 1\,ml\,min^{-1}$.[28] The impact of these findings was limited by the retrospective nature of the study, the inclusion of prevalent patients, and the absence of a multivariate analysis strategy. In 2005, Pérez-Fontán *et al.*[34] scrutinized the risk profile for peritonitis and peritonitis-related mortality in a cohort of 565 patients starting PD over a period of 18 years. Multivariate analysis identified RRF at the start of therapy as an independent predictor of the risk of peritonitis (risk reduction 4% per ml per min per $1.73\,m^2$ of GFR) and peritonitis-related mortality (risk reduction 25% per ml per min per $1.73\,m^2$). Two other studies have presented additional evidence supporting the association with peritonitis (overall)[35] and fungal peritonitis.[36]

The reasons why RRF at the start of PD therapy could be predictive of the later risk of peritonitis are not clear, but there are several possible explanations for this association. First, initiating PD without significant RRF is often a consequence of delayed referral, secondary selection of PD (e.g., after HD technique failure), or stormy renal disease. These three settings are potential harbingers of a complicated course during PD therapy. Thus, the absence of RRF at the start of PD could simply be a marker of the poor overall condition of the patient. As an alternative, lack of RRF may compromise the general condition and immunocompetence of PD patients.

From the opposite point of view, peritonitis may theoretically accelerate the decrease in RRF in PD patients either directly, as in severe infections, or indirectly, following the use of nephrotoxic antibiotics. The practical significance of these considerations remains controversial.[58,59]

RRF AND QUALITY OF LIFE

Given the important contribution of RRF to survival, cardiovascular disease, and nutritional status of PD patients, it is easy to assume that RRF may improve quality of life as perceived by PD patients. The NECOSAD reported an important contribution of RRF to most dimensions of quality of life, especially physical functioning, vitality, kidney disease-specific symptoms, daily life and sleep disorders, but quality of life was not associated with peritoneal clearance or with etiology of end-stage renal disease.[16]

FACTORS INFLUENCING THE RATE OF DECREASE OF RRF

Determinants of RRF decrease in dialysis patients are obviously multifactorial. Dialysis-related factors have been clearly identified as among the most important ones. PD is widely thought to better preserve long-term RRF than HD.

PD versus chronic intermittent HD

When RRF decline is compared between incident HD and PD patients, there is a strong body of evidence suggesting that PD better preserves RRF, at least when compared to conventional HD. HD is associated with a 24–80% higher rate of RRF loss[4–8] (Table 3). The prospective study NECOSAD-2 followed 522 incident patients for 12 months.[8] It showed that RRF is better preserved in PD than in HD, even after adjustments for basal GFR, age, etiology of CKD, comorbidity, body mass index, systolic and diastolic BP, use of antihypertensive medication, and timing and cause of dropout (including change of dialysis modality). Contrary to prior studies, most HD patients in this study used biocompatible membranes. This may explain the smaller differences observed in the loss of RRF between both dialysis techniques. A few studies have compared the impact of newer, more biocompatible HD regimes. In these, the rate of decrease was less in PD[7] despite the use of hemodiafiltration regimes that minimize hemodynamic instability.[60] Another study showed no differences when high-flux synthetic membranes and ultrapure bicarbonate-buffered dialysis fluids with UF control preventing intradialytic hypotensive events was compared with traditional continuous ambulatory PD (CAPD) regime and solutions.[61] In this regard, the use of more biocompatible membranes has been associated with a lower decrease in RRF in HD[61–63] except in one report, in which the case mix included a majority of hypertensive patients.[64] Moreover, just the use in a randomized manner of ultrapure water in HD has been associated with a better RRF outcome.[65] New approaches such as the bimodal dialysis concept might protect RRF.[66]

However, most of this information was obtained from observational or retrospective single center or single country studies with relatively small numbers of patients and data obtained from patient records and non-routine interventions, with the exception of measuring RRF. Unmeasured comorbid conditions and/or disease severity, dialysis dose, nutritional status, and the use of nephrotoxic agents may explain the faster rate of decrease in GFR in HD patients. In addition, available data might reflect the experience of patients receiving dialysis during 1980–1990. Changes in practice patterns and technological advances in both PD and HD since that time may play a role in patient outcome. Therefore, the results of these studies may not accurately represent contemporary differences in decline in RRF between PD and HD.

Several mechanisms may account for the better RRF preservation in PD. The most important one is the less abrupt fluctuations in volume and osmotic load leading to a more stable hemodynamic status.[4] This is probably associated with more stable glomerular capillary pressure and more constant glomerular filtration. Episodes of renal ischemia occurring because of rapid changes in osmolality and contraction of circulating volume during HD might be avoided in PD.[8] Mild overhydration of some patients in PD has been pointed out to contribute to better RRF preservation,[67] but we are not aware of clinical studies focusing on this matter. It has also been suggested that native kidneys may be damaged by repeated exposure to inflammatory mediators, such as interleukin-1 generated by the extracorporeal circulation of HD. Consequently, bioincompatible HD membranes should be associated with a more rapid deterioration in RRF,[4] whereas PD is a more biocompatible therapy.

Another striking finding is the fact that PD might delay the progression of advanced renal failure, preserving or improving RRF.[68–73] Actually, recovery of renal function

Table 3 | Summary of main studies comparing the decrease in RRF in PD vs HD

References	Type of study	Number of patients HD/PD	Baseline GFR HD/PD (ml min^{-1})	GFR after 12 months HD/PD (ml min^{-1})	Average % monthly rate of RRF decrease HD/PD	Difference in rate of RRF decrease HD/PD (%)
Rottembourg *et al.*[3]	Prospective	25/25	4.3/4.4	2.1/3.8	6.0/1.2[a]	80
Lysaght *et al.*[4]	Retrospective	57/58	5.0/4.5	—	5.8/2.9	50
Moist *et al.*[5]	Prospective	811/1.032	7.33/7.5	—	—	65
Misra *et al.*[6]	Retrospective	39/102	4.2/5.1	—	7.0/2.2	69
Lang *et al.*[7]	Prospective	30/15	7.5/7.4	3.8/6.0	5.8/1.8[a]	69
Jansen *et al.*[8]	Prospective	279/243	Adjusted 5.1/5.8	1.4/2.2	10.7/8.1[a]	24

GFR, glomerular filtration rate; HD, hemodialysis; PD, peritoneal dialysis; RRF, residual renal function.
Modified from Horinek *et al. Adv Perit Dial 2004*; **20**: 137–140.
[a]Decrease in rate calculated from data presented in study, based on GFR values at 0, 6, and 12 months after start of dialysis.

sufficient to come off dialysis has been described in several reports of patients with interstitial nephritis[68] and malignant hypertension.[69] In an experimental model, PD retarded the progression of glomerular sclerosis in rats.[70] Berlanga *et al.*[71] in a small series showed that PD might slow the natural progression of renal disease. The RRF decrease in the PD period was –0.06 ± 0.16 vs –0.94 ± 0.74 ml per min per month in the same patients during a mean predialysis follow-up of 47 months. Two other studies have confirmed these findings.[72,74] If, indeed, PD slows the progression of CKD, this would be a major advantage of early start incremental PD. The issue has not been solved because there are no controlled studies addressing the influence of incremental PD on RRF and no homogeneous definition of incremental PD. Several authors have reported on the stability of RRF in a number of patients started on incremental PD.[75,76]

CAPD vs APD

It is still controversial whether the decline in RRF might be different in CAPD or APD regimes. In the early days of APD, Hiroshige *et al.*[77] described that patients on night-time intermittent PD or continuous cycling PD experienced a more rapid decrease in RRF than CAPD patients. Three more investigators have reported similar results.[74,78–79] Although there was no significant difference in peritoneal UF rate, it was hypothesized that the intermittent nature of APD may contribute to the results. As a consequence, they recommended avoiding the frequent use of hypertonic dialysate, the presence of a dry abdomen during the day, and a strict regular assessment of RRF from the start of APD.[74,77–78,80]

By contrast, no statistical differences were observed in the only two prospective randomized studies comparing the decrease in RRF with both techniques,[81–82] nor in a three-phase crossover study.[83] Furthermore, a thorough search of the published literature reveals more studies concluding that the decrease in RRF in APD patients is not significantly different from CAPD[5,8,59,81–86] (Table 4).

Other factors influencing RRF

Other factors besides dialysis modality correlate with the loss of RRF. An observational study that randomly selected incident patients from the US Renal Data System applied a multivariate logistic regression model to search for factors associated to loss of RRF, defined as diuresis <200 ml per 24 h (Figure 3).[5] Factors associated with loss of RRF included female gender, non-white race, diabetes, chronic heart failure, time of follow-up, and HD. Factors associated with preservation of RRF included higher calcemia, use of angiotensin-converting enzyme inhibitors or calcium channel blockers, and PD. Other authors have confirmed the predictive value for more rapid loss of RRF of diabetes or heart failure.[85] However, male gender and increased body mass index were also found to predict loss of RRF.[85] The potential protective role of higher calcium levels has been challenged because hypercalcemia is nephrotoxic.[87] Diastolic hypertension,[8] severe proteinuria,[85] and a high peritonitis rate[58,85] have also been associated with a faster loss of RRF.

STRATEGIES FOR MAINTAINING RRF

In view of the paramount importance of RRF preservation, clinical strategies oriented to preserving RRF have been evaluated in PD patients. We are not aware of such studies in the HD field.

As routine use of loop diuretics, eventually in combination with a thiazide, may contribute to the maintenance of residual diuresis in the pre-dialysis setting, this approach has been evaluated in PD patients. In the 7-year collaborative Colmar (France) and Gent (Belgium) study, French patients maintained a better diuresis that was attributed to the routine prescription of high doses of furosemide.[88] However, French

Table 4 | Summary of studies comparing the decrease in RRF between CAPD and APD patients

References	Type of study/duration	No. of patients CAPD/APD	Loss of RRF in APD
Hiroshige *et al.*[77]	Prospective, nonrandomized/6 m	5/13	Faster
Hufnagel *et al.*[78]	Prospective, observational/12 m	18/36	Faster
Hidaka and Nakao[74]	Observational/up to 42 m or anuria	27/7	Faster
Rodríguez-Carmona *et al.*[79]	Prospective, observational/>24 m	53/51	Faster
Parikova A (2005)[a]	Prospective/18 m	65/36	Faster
Fernández Rodríguez AM (1998)	Prospective sequential (CAPD—CPD–TPD)	45	Equal
Bro *et al.*[82]	Prospective, randomized/6 m	17/17	Equal
Singhal *et al.*[85]	Prospective, 27 ± 14 m	242	Equal
De Fijter *et al.*[81]	Prospective, randomized/24 m	11/13	Equal
Moist *et al.*[5]	Registry	1032	Equal
Gallar *et al.*[86]	Prospective/12 m	11/9	Equal
Holley *et al.*[84]	Retrospective database	184	Equal
Jansen *et al.*[8]	Necosad registry, prospective/12 m	243	Equal
Johnson *et al.*[59]	Prospective/78 m	146/12	Equal
Petras DI (2005)[a]	Retrospective	24/14	Equal
Gallar P (2005)[a]	Acute study	10/14	Equal
Ramos Bodi V (2006)[b]	Retrospective study/36 m	70	Equal

APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; RRF, residual renal function.
[a]Communication to EuroPD Congress (Praha, 2005).
[b]Communication to Latinoamerican and Spanish Congress (Madrid, 2006).

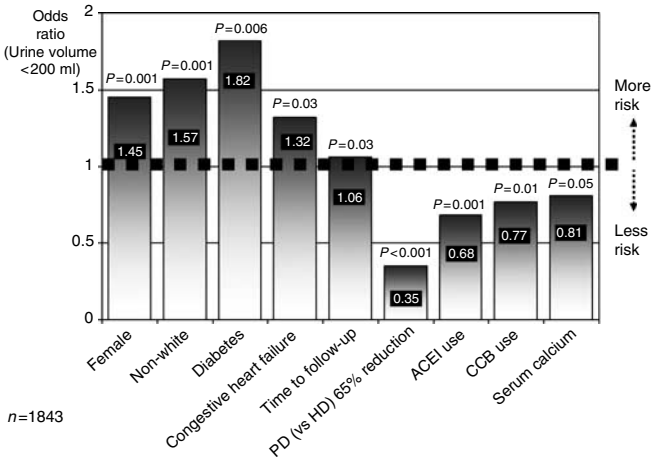

Figure 3 | Factors associated with risk of loss of RRF. Adapted from Moist *et al.*[5]

patients also showed a more rapid loss of peritoneal UF, thought to be related to the use of acetate-buffered PD solutions.[88] Nevertheless, considerable controversy remains, as there are different clinical practices worldwide. To investigate further the benefits of long-term diuretic therapy, an open-label randomized single-center study in incident patients in PD was carried out. It demonstrated that furosemide contributed to the maintenance of residual diuresis, improved natriuresis and volume control, but failed in the objective of protecting RRF, measured as solute clearance.[89] It would thus be reasonable to prescribe a loop diuretic to patients starting PD therapy. For patients starting on HD, these agents are frequently discontinued.

Blockade of the renin–angiotensin system with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers might be effective in slowing the decrease in RRF in PD patients.[5] The angiotensin-converting enzyme inhibitor ramipril reduced the rate of RRF decrease in a 12-month open-randomized clinical study when compared with no treatment and despite a higher risk of anuria in the third month of treatment.[90] Another study addressed the modulation of RRF decrease by valsartan, an angiotensin II receptor blocker, compared to any other antihypertensive drug except angiotensin-converting enzyme inhibitors. After 2 years of follow-up, and despite identical good BP control, valsartan significantly slowed the progressive decrease in both RRF and total clearance in CAPD patients.[91]

The role of new PD solutions in slowing the decrease in RRF seems promising. In a double-blind randomized controlled trial, icodextrin improved fluid status and residual diuresis in PD patients compared to patients treated with 2.27% glucose for the long dwell. This effect was apparent within 1 month and was sustained for 6 months without harmful effects on RRF.[92] Other investigators have confirmed this positive effect of icodextrin (Adachi *et al.*,[93] and oral communications by Bajo *et al.* and Schalkwijk *et al.* at the 7th European Peritoneal Dialysis Meeting (EuroPD 7), Prague, Czech Republic, 2005). The better hemodynamic profile of icodextrin for the long dwell may be one of the explanations for such a finding. Icodextrin is able to maintain osmotic forces over extended periods of time. As a high-molecular-weight colloid osmotic agent, icodextrin does not readily diffuse across the peritoneal membrane but rather is slowly removed from the peritoneal cavity via lymphatic absorption. This results in sustained UF and solute clearance over longer dwell periods compared with glucose-based solutions.[94] For a given increase in UF, residual urine volume is relatively well preserved, but severe volume depletion puts RRF at a risk.[95] It has been a tentative hypothesis that icodextrin alters hydration status by (a) increasing peritoneal fluid removal and (b) altering fluid distribution between the interstitial and intravascular compartments (Davies *et al.* at oral communications, American Society of Nephrology Annual Meeting, San Diego, CA, USA, 2004 and EuroPD 7, Prague, Czech Republic, 2005). This might explain the relative preservation of RRF and lack of effect on BP observed in clinical trials.[92] Another interesting discovery might be the use of icodextrin in the treatment of acute renal failure with nephrotic syndrome in diabetic patients resulting in a recovery of renal function, increase in residual diuresis, better BP control, and regain of serum albumin levels (Kuriyama *et al.* oral communication, American Society of Nephrology Annual Meeting, Philadelphia, PA, USA, 2005).

The use of glucose-sparing regimes might be of interest in terms of RRF protection. The protective effect may be related to the lower glucose and glucose degradation product exposure.[96] NEPP regime, a daily combination of intraperitoneal amino acids, icodextrin, and low-glucose degradation product lactate/bicarbonate-buffered glucose solution was evaluated in a crossover design of 54 weeks in incident CAPD patients. The loss of RRF was more marked in the standard glucose-NEPP group compared with the NEPP-standard glucose one. If the higher initial RRF in the former group contributed to a steeper decrease in RRF remains uncertain.[97] On the other hand, the use of a single exchange of a glucose degradation product-free amino-acid-based solution as part of a regimen of conventional glucose-based solutions resulted in no significant changes in RRF in patients with severe hypoalbuminemia treated with CAPD for 30 months.[98] The use of other neutral and physiologic pH, low-glucose degradation product PD solutions resulted in higher urine volume although accompanied by a lower peritoneal UF.[99,100]

In summary, the idea that dialysis may totally replace native renal function has never gained acceptance in the nephrology community. Even a malfunctioning kidney is able to carry out functions that go well beyond the capacities of dialysis therapy such as the regulation of the internal environment. RRF rather than overall adequacy (as estimated from total small solute removal rates) is an essential marker of patient and, to a lesser extent, technique survival during chronic PD therapy. This association may be partially explained by selection biases, but there is ample clinical

evidence suggesting that the loss of RRF can unleash potentially deleterious consequences on the clinical course of these patients, including relentless volume overload. This highlights the usefulness of strategies oriented to preserve both RRF and the long-term viability of the peritoneal membrane, as well as to optimize the fluid status of PD patients. Renoprotective drugs and new glucose–sparing, more biocompatible PD regimes may prove useful tools to approach these problems in the near future.

DISCLOSURE

BM is a Baxter employee; AO has a grant from Baxter; MP-F has received consulting fees and lecture fees from Baxter. All the other authors declared no competing interests.

REFERENCES

1. Ahmad S, Babb AL, Milutinovic J *et al.* Effect of residual renal function on minimum dialysis requirements. *Proc Eur Dial Transplant Assoc* 1979; **16**: 107–114.
2. Suda T, Hiroshige K, Ohta T *et al.* The contribution of residual renal function to overall nutritional status in chronic haemodialysis patients. *Nephrol Dial Transplant* 2000; **15**: 396–401.
3. Rottembourg J, Issad B, Gallego JL *et al.* Evolution of residual renal function in patients undergoing maintenance haemodialysis or continuous ambulatory peritoneal dialysis. *Proc EDTA* 1983; **19**: 397–403.
4. Lysaght MJ, Vonesh EF, Gotch F *et al.* The influence of dialysis treatment modality on the decline of remaining renal function. *ASAIO Trans* 1991; **37**: 598–604.
5. Moist LM, Port FK, Orzol SM *et al.* Predictors of loss of residual renal function among new dialysis patients. *J Am Soc Nephrol* 2000; **11**: 556–564.
6. Misra M, Vonesh E, Van Stone JC *et al.* Effect of cause and time of dropout on the residual GFR: a comparative analysis of the decline of GFR on dialysis. *Kidney Int* 2001; **59**: 754–763.
7. Lang SM, Bergner A, Topfer M *et al.* Preservation of residual renal function in dialysis patients: effects of dialysis-technique-related factors. *Perit Dial Int* 2001; **21**: 52–57.
8. Jansen MA, Hart AA, Korevaar JC *et al.* Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney Int* 2002; **62**: 1046–1053.
9. Cancarini GC, Brunori G, Camerini C *et al.* Renal function recovery and maintenance of residual diuresis in CAPD and hemodialysis. *Perit Dial Bull* 1986; **6**: 77–79.
10. Chandna SM, Farrington K. Residual renal function: considerations on its importance and preservation in dialysis patients. *Semin Dial* 2004; **17**: 196–201.
11. Diaz-Buxo JA, Lowrie EG, Lew NL *et al.* Associates of mortality among peritoneal dialysis patients with special reference to peritoneal transport rates and solute clearance. *Am J Kidney Dis* 1999; **33**: 523–534.
12. Rocco M, Soucie JM, Pastan S, McClellan WM. Peritoneal dialysis adequacy and risk of death. *Kidney Int* 2000; **58**: 446–457.
13. Shemin D, Bostom AG, Laliberty P *et al.* Residual renal function and mortality risk in hemodialysis patients. *Am J Kidney Dis* 2001; **38**: 85–90.
14. Bargman JM, Thorpe KE, Churchill DN. 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.
15. Rocco MV, Frankenfield DL, Prowant B *et al.* Risk factors for early mortality in US peritoneal dialysis patients: impact of residual renal function. *Perit Dial Int* 2002; **22**: 371–379.
16. Termorshuizen F, Korevaar JC, Dekker FW *et al.* The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Am J Kidney Dis* 2003; **41**: 1293–1302.
17. Wang AY, Woo J, Wang M *et al.* Important differentiation of factors that predict outcome in peritoneal dialysis patients with different degrees of residual renal function. *Nephrol Dial Transplant* 2005; **20**: 396–403.
18. Menon MK, Naimark DM, Bargman JM *et al.* Long-term blood pressure control in a cohort of peritoneal dialysis patients and its association with residual renal function. *Nephrol Dial Transplant* 2001; **16**: 2207–2213.
19. Wang AY, Wang M, Woo J *et al.* A novel association between residual renal function and left ventricular hypertrophy in peritoneal dialysis patients. *Kidney Int* 2002; **62**: 639–647.
20. Wang AY, Wang M, Woo J *et al.* Inflammation, residual kidney function, and cardiac hypertrophy are interrelated and combine adversely to enhance mortality and cardiovascular death risk of peritoneal dialysis patients. *J Am Soc Nephrol* 2004; **15**: 2186–2194.
21. Morduchowicz G, Winkler J, Zabludowski JR *et al.* Effects of residual renal function in haemodialysis patients. *Int Urol Nephrol* 1994; **26**: 125–131.
22. Ates K, Nergizoglu G, Keven K *et al.* Effect of fluid and sodium removal on mortality in peritoneal dialysis patients. *Kidney Int* 2001; **60**: 767–776.
23. Konings CJAM, Kooman JP, Schonck M *et al.* Fluid status in CAPD patients is related to peritoneal transport and residual renal function: evidence from a longitudinal study. *Nephrol Dial Transplant* 2003; **18**: 797–803.
24. Mistry CD, O'Donoghue DJ, Nelson S *et al.* Kinetic and clinical studies of beta 2-microglobulin in continuous ambulatory peritoneal dialysis: influence of renal and enhanced peritoneal clearances using glucose polymer. *Nephrol Dial Transplant* 1990; **5**: 513–519.
25. Montenegro J, Martinez I, Saracho R, Gonzalez R. Beta 2 microglobulin in CAPD. *Adv Perit Dial* 1992; **8**: 369–372.
26. Suda T, Hiroshige K, Ohta T *et al.* The contribution of residual renal function to overall nutritional status in chronic haemodialysis patients. *Nephrol Dial Transplant* 2000; **15**: 396–401.
27. Bammens B, Evenepoel P, Verbeke K *et al.* Time profiles of peritoneal and renal clearances of different uremic solutes in incident peritoneal dialysis patients. *Am J Kidney Dis* 2005; **46**: 512–519.
28. Szeto CC, Lai KN, Wong TY *et al.* Independent effects of residual renal function and dialysis adequacy on nutritional status and patient outcome in continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1999; **34**: 1056–1064.
29. Wang AY, Sea MM, Ip R *et al.* Independent effects of residual renal function and dialysis adequacy on actual dietary protein, calorie, and other nutrient intake in patients on continuous ambulatory peritoneal dialysis. *J Am Soc Nephrol* 2001; **12**: 2450–2457.
30. Pecoits-Filho R, Heimburger O, Barany P *et al.* Associations between circulating inflammatory markers and residual renal function in CRF patients. *Am J Kidney Dis* 2003; **41**: 1212–1218.
31. Gao H, Lew SQ, Ronco C *et al.* The impact of residual renal function and total body water volume on achieving adequate dialysis in CAPD. *J Nephrol* 1999; **12**: 184–189.
32. Page DE, Knoll GA, Cheung V. The relationship between residual renal function, protein catabolic rate, and phosphate and magnesium levels in peritoneal dialysis patients. *Adv Perit Dial* 2002; **18**: 189–191.
33. Kagan A, Elimalech E, Lemer Z *et al.* Residual renal function affects lipid profile in patients undergoing continuous ambulatory peritoneal dialysis. *Perit Dial Int* 1997; **17**: 243–249.
34. Pérez-Fontán M, Rodríguez-Carmona A, García Naveiro R *et al.* Peritonitis-related mortality in patients undergoing chronic peritoneal dialysis. *Perit Dial Int* 2005; **25**: 274–284.
35. Han SH, Lee SC, Ahn SV *et al.* Reduced residual renal function is a risk factor for peritonitis in continuous ambulatory peritoneal dialysis patients. *Nephrol Dial Transplant* 2007; **22**: 2653–2658.
36. Liu YL, Huang CC, Kao MT. Residual renal function predicts outcome of fungal peritonitis in peritoneal dialysis patients. *Perit Dial Int* 2006; **26**: 407–409.
37. Maiorca R, Brunori G, Zubani R *et al.* Predictive value of dialysis adequacy and nutritional indices for mortality and morbidity in CAPD and HD patients: A longitudinal study. *Nephrol Dial Transplant* 1995; **10**: 2295–2305.
38. Churchill DN, Taylor DW, Keshaviah PR. Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. *J Am Soc Nephrol* 1996; **7**: 198–207.
39. Szeto CC, Wong TYH, Leung CB *et al.* Importance of dialysis adequacy in mortality and morbidity of Chinese CAPD patients. *Kidney Int* 2000; **58**: 400–407.
40. Paniagua R, Amato D, Vonesh E *et al.* Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. *J Am Soc Nephrol* 2002; **13**: 1307–1320.
41. Chung SH, Heimburger O, Stenvinkel P *et al.* Association between residual renal function, inflammation and patient survival in new peritoneal dialysis patients. *Nephrol Dial Transplant* 2003; **18**: 590–597.
42. Szeto CC, Wong TYH, Chow KM *et al.* Are peritoneal dialysis patients with and without residual renal function equivalent for survival study?

Insight from a retrospective review of the cause of death. *Nephrol Dial Transplant* 2003; **18**: 977–982.
43. Foley RN, Parfrey PS, Sarnak MJ. The clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998; **32**(Suppl 3): S112–S119.
44. Davies SJ, Brown EA, Frandsen NE *et al.* Longitudinal membrane function in functionally anuric patients treated with APD: Data from EAPOS on the effects of glucose and icodextrin prescription. *Kidney Int* 2005; **67**: 1609–1615.
45. Menon MK, Naimark DM, Bargman JM *et al.* Long term blood pressure control in a cohort of peritoneal dialysis patients and its associations with residual renal function. *Nephrol Dial Transplant* 2001; **16**: 2207–2213.
46. Buckalew Jr VM, Berg RL, Wang SR *et al.* Prevalence of hypertension on 1975 subjects with chronic renal disease: the modification of diet in renal disease study: the modification of diet in renal disease study baseline cohort. Modification of Diet in Renal Disease Study Group. *Am J Kidney Dis* 1996; **28**: 811–821.
47. Foley RN, Parfrey PS, Harnett JD *et al.* Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. *Kidney Int* 1995; **47**: 186–192.
48. Silberberg JS, Barre PE, Prichard SS *et al.* Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int* 1989; **36**: 286–290.
49. Silberberg JS, Rahal DP, Patton R *et al.* Role of anemia in the pathogenesis of left ventricular hypertrophy in endstage renal disease. *Am J Cardiol* 1989; **64**: 222–224.
50. Levin A, Thompson CR, Ethier J *et al.* Left ventricular mass index increase in early renal disease: Impact of decline in hemoglobin. *Am J Kidney Dis* 1999; **34**: 125–134.
51. Vlahakos DV, Hahalis G, Vassilakos P *et al.* Relationship between left ventricular hypertrophy and plasma renin activity in chronic hemodialysis patients. *J Am Soc Nephrol* 1997; **8**: 1764–1770.
52. Converse RL, Jacobsen TN, Toto R *et al.* Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 1992; **327**: 1912–1918.
53. Aguilera A, Codoceo R, Selgas R *et al.* Anorexigen (TNF-α, cholecystokinin) and orexigen (Neuropeptide Y) plasma levels in peritoneal dialysis (PD) patients: their relationship with nutritional parameters. *Nephrol Dial Transplant* 1998; **13**: 1476–1483.
54. Plata-Salamán C. Cytokines and feeding suppression: an integrative view from neurologic to molecular levels. *Nutrition* 1995; **11**: S674–S677.
55. Amore A, Coppo R. Immunological basis of inflammation in dialysis. *Nephrol Dial Transplant* 2002; **17**: S16–S24.
56. Aguilera A, Velásquez E, Bajo MA *et al.* Systemic inflammation induces endothelial dysfunction in peritoneal dialysis patients. *Vasc Dis Prevent* 2007 (in press).
57. Wang AY, Sea MM, Tang N *et al.* Resting energy expenditure and subsequent mortality risk in peritoneal dialysis patients. *J Am Soc Nephrol* 2004; **15**: 3134–3143.
58. Shin SK, Noh H, Kang SW *et al.* Risk factors influencing the decline of residual renal function in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 1999; **19**: 138–142.
59. Johnson DW, Mudge DW, Sturtevant JM *et al.* Predictors of decline of residual renal function in new peritoneal dialysis patients. *Perit Dial Int* 2003; **23**: 276–283.
60. Fischbach M, Terzic J, Menouer S *et al.* Effects of automated peritoneal dialysis on residual daily urinary volume in children. *Adv Perit Dial* 2001; **17**: 269–273.
61. McKane W, Chandna SM, Tattersall JE *et al.* Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. *Kidney Int* 2002; **61**: 256–265.
62. Van Stone JC. The effect of dialyzer membrane and etiology of kidney disease on the preservation of residual renal function in chronic hemodialysis patients. *ASAIO J* 1995; **41**: M713–M716.
63. Hartmann J, Fricke H, Schiffl H. Biocompatible membranes preserve residual renal function in patients undergoing regular hemodialysis. *Am J Kidney Dis* 1997; **30**: 366–373.
64. Caramelo C, Alcazar R, Gallar P *et al.* Choice of dialysis membrane does not influence the outcome of residual renal function in haemodialysis patients. *Nephrol Dial Transplant* 1994; **9**: 675–677.
65. Schiffl H, Lang SM, Fischer R. Ultrapure dialysis fluid slows loss of residual renal function in new dialysis patients. *Nephrol Dial Transplant* 2002; **17**: 1814–1818.
66. McIntyre CW. Bimodal dialysis: an integrated approach to renal replacement therapy. *Perit Dial Int* 2004; **24**: 547–553.
67. Lameire NH. The impact of residual renal function on the adequacy of peritoneal dialysis. *Nephron* 1997; **77**: 13–28.
68. Rottembourg J, Issad B, Allouache M *et al.* Recovery of renal function in patients treated by CAPD. *Adv Perit Dial* 1989; **5**: 63–66.
69. Katz IJ, Sofianou L, Butler O *et al.* Recovery of renal function in Black South African patients with malignant hypertension: superiority of continuous ambulatory peritoneal dialysis over hemodialysis. *Perit Dial Int* 2001; **21**: 581–586.
70. Wang T, Ye RG, Zhen ZH *et al.* Influence of peritoneal dialysis on the progression of chronic renal failure. *Adv Perit Dial* 1995; **11**: 139–141.
71. Berlanga JR, Marron B, Reyero A *et al.* Peritoneal dialysis retardation of progression of advanced renal failure. *Perit Dial Int* 2002; **22**: 239–242.
72. Van Biesen W, Dequidt C, Vanholder R *et al.* The impact of healthy start peritoneal dialysis on the evolution of residual renal function and nutrition parameters. *Adv Perit Dial* 2002; **18**: 44–48.
73. Coronel F, Pérez-Flores I, Calvo N *et al.* Impact of cardiovascular events on residual renal function during the first year of peritoneal dialysis. *Perit Dial Int* 2007; **27**: 454–456.
74. Hidaka H, Nakao T. Preservation of residual renal function and factors affecting its decline in patients on peritoneal dialysis. *Nephrology* 2003; **8**: 184–191.
75. Foggensteiner L, Baylis J, Moss H *et al.* Timely initiation of dialysis – single-exchange experience in 39 patients starting peritoneal dialysis. *Perit Dial Int* 2002; **22**: 471–476.
76. Burkart JM, Satko SG. Incremental initiation of dialysis: one center's experience over a two-year period. *Perit Dial Int* 2000; **20**: 418–422.
77. Hiroshige K, Yuu K, Soejima M *et al.* Rapid decline of residual renal function in patients on automated peritoneal dialysis. *Perit Dial Int* 1996; **16**: 307–315.
78. Hufnagel G, Michel C, Queffeulou G *et al.* The influence of automated peritoneal dialysis on the decrease in residual renal function. *Nephrol Dial Transplant* 1999; **14**: 1224–1228.
79. Rodriguez-Carmona A, Pérez-Fontán M, Garca-Naveiro R *et al.* Compared time profiles of ultrafiltration, sodium removal, and renal function in incident CAPD and automated peritoneal dialysis patients. *Am J Kidney Dis* 2004; **44**: 132–145.
80. Selby NM, Fonseca S, Hulme L *et al.* Automated peritoneal dialysis has significant effects on systemic hemodynamics. *Perit Dial Int* 2006; **26**: 328–335.
81. de Fijter CW, ter Wee PM, Donker AJM. The influence of automated peritoneal dialysis on the decrease in residual renal function. *Nephrol Dial Transplant* 2000; **15**: 1094–1096.
82. Bro S, Bjorner JB, Tofte-Jensen P *et al.* A prospective, randomized multicenter study comparing APD and CAPD treatment. *Perit Dial Int* 1999; **19**: 526–533.
83. Rodriguez AM, Diaz NV, Cubillo LP *et al.* Automated peritoneal dialysis: a Spanish multicentre study. *Nephrol Dial Transplant* 1998; **13**: 2335–2340.
84. Holley JL, Aslam N, Bernardini J *et al.* The influence of demographic factors and modality on loss of residual renal function in incident peritoneal dialysis patients. *Perit Dial Int* 2001; **21**: 302–305.
85. Singhal MK, Bhaskaran S, Vidgen E *et al.* Rate of decline of residual renal function in patients on continuous peritoneal dialysis and factors affecting it. *Perit Dial Int* 2000; **20**: 429–438.
86. Gallar P, Ortega O, Carreno A *et al.* Rate of decline in residual renal function is equal in CAPD and automated peritoneal dialysis patients. *Perit Dial Int* 2000; **20**: 803–805.
87. Nussbaum SR. Pathophysiology and management of severe hypercalcemia. *Endocrinol Metab Clin N Am* 1993; **22**: 343–362.
88. Faller B, Lameire N. Evolution of clinical parameters and peritoneal function in a cohort of CAPD patients followed over 7 years. *Nephrol Dial Transplant* 1994; **9**: 280–286.
89. Medcalf JF, Harris KP, Walls J. Role of diuretics in the preservation of residual renal function in patients on continuous ambulatory peritoneal dialysis. *Kidney Int* 2001; **59**: 1128–1133.
90. Li PK, Chow KM, Wong TY *et al.* Effects of an angiotensin-converting enzyme inhibitor on residual renal function in patients receiving peritoneal dialysis. A randomized, controlled study. *Ann Intern Med* 2003; **139**: 105–112.
91. Suzuki H, Kanno Y, Sugahara S *et al.* Effects of an angiotensin II receptor blocker, valsartan, on residual renal function in patients on CAPD. *Am J Kidney Dis* 2004; **43**: 1056–1064.

92. Davies SJ, Woodrow G, Donovan K *et al.* Icodextrin improves the fluid status of peritoneal dialysis patients: results of a double-blind randomized controlled trial. *J Am Soc Nephrol* 2003; **14**: 2338–2344.
93. Adachi Y, Nakagawa Y, Nishio A. Icodextrin preserves residual renal function in patients treated with automated peritoneal dialysis. *Perit Dial Int* 2006; **26**: 405–407.
94. Ho-Dac-Pannekeet MM, Schouten N, Langendijk MJ *et al.* Peritoneal transport characteristics with glucose polymer based dialysate. *Kidney Int* 1996; **50**: 979–986.
95. Konings CJ, Kooman JP, Gladziwa U *et al.* A decline in residual glomerular filtration during the use of icodextrin may be due to underhydration. *Kidney Int* 2005; **67**: 1190–1191.
96. Lo WK. Effect of PD solutions on patient outcome. *Contrib Nephrol* 2006; **150**: 90–96.
97. le Poole CY, Van Ittersum FJ, Weijmer MC *et al.* Clinical effects of a peritoneal dialysis regimen low in glucose in new peritoneal dialysis patients: a randomized crossover study. *Adv Perit Dial* 2004; **20**: 170–176.
98. Taylor GS, Patel V, Spencer S *et al.* Long-term use of 1.1% amino acid dialysis solution in hypoalbuminemic continuous ambulatory peritoneal dialysis patients. *Clin Nephrol* 2002; **58**: 445–450.
99. Williams JD, Topley N, Craig KJ *et al.* The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. *Kidney Int* 2004; **66**: 408–418.
100. Montenegro J, Saracho RM, Martinez IM *et al.* Long-term clinical experience with pure bicarbonate peritoneal dialysis solutions. *Perit Dial Int* 2006; **26**: 89–94.