Peritoneal Dialysis

CKJ Review

Strategies for preserving residual renal function in peritoneal dialysis patients

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Abstract

Although there have been many advancements in the treatment of patients with chronic kidney disease (CKD) over the last 50 years, in terms of reducing cardiovascular risk, mortality remains unacceptably high, particularly for those patients who progress to stage 5 CKD and initiate dialysis (CKD5d). As mortality risk increases exponentially with progressive CKD stage, the question arises as to whether preservation of residual renal function once dialysis has been initiated can reduce mortality risk. Observational studies to date have reported an association between even small amounts of residual renal function and improved patient survival and quality of life. Dialysis therapies predominantly provide clearance for small water-soluble solutes, volume and acid-base control, but cannot reproduce the metabolic functions of the kidney. As such, protein-bound solutes, advanced glycosylation end-products, middle molecules and other azotaemic toxins accumulate over time in the anuric CKD5d patient. Apart from avoiding potential nephrotoxic insults, observational and interventional trials have suggested that a number of interventions and treatments may potentially reduce the progression of earlier stages of CKD, including targeted blood pressure control, reducing proteinuria and dietary intervention using combinations of protein restriction with keto acid supplementation. However, many interventions which have been proven to be effective in the general population have not been equally effective in the CKD5d patient, and so the question arises as to whether these treatment options are equally applicable to CKD5d patients. As strategies to help preserve residual renal function in CKD5d patients are not well established, we have reviewed the evidence for preserving or losing residual renal function in peritoneal dialysis patients, as urine collections are routinely collected, whereas few centres regularly collect urine from haemodialysis patients, and haemodialysis dialysis patients are at risk of sudden intravascular volume shifts associated with dialysis treatments. On the other hand, peritoneal dialysis patients are exposed to a variety of hypertonic dialysates and episodes of peritonitis. Whereas blood pressure control, using an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and low-protein diets along with keto acid supplementation have been shown to reduce the rate of progression in patients with earlier stages of CKD, the strategies to preserve residual renal function (RRF) in dialysis patients are not well established. For peritoneal dialysis patients, there are additional technical factors that might aggravate the rate of loss of residual renal function including peritoneal dialysis prescriptions and modality, bio-incompatible dialysis fluid and over ultrafiltration of fluid causing dehydration. In this review, we aim to evaluate the evidence of interventions and treatments, which may sustain residual renal function in peritoneal dialysis patients.

Keywords: biocompatible dialysate ACEI; peritoneal dialysis; residual renal function

Importance of RRF in peritoneal dialysis

Peritoneal dialysis technique survival varies throughout the world, depending upon access to transplantation and haemodialysis, and centre practices [1]. Besides loss of patients to transplantation, peritonitis remains the commonest cause for transfer to haemodialysis in many countries [2], and due to the relatively high turnover of peritoneal dialysis patients, it was only in the 1990s that reports of

the importance of maintaining residual renal function (RRF) started to appear [3]. Maiorca *et al.* reported a 50% reduction in mortality in peritoneal dialysis (PD) patients with RRF [4]. These encouraging results were supported by later larger prospective observational studies, with Diaz-Buxo *et al.*, reporting that residual renal creatinine clearance (CrCl) was strongly associated with PD patient survival, whereas peritoneal clearance did not affect outcome. Moreover, they observed in their cohort of some 2686 PD patients, a dose response association between RRF and PD patient survival, with each CrCl 5 L/week/1.73 m² increase in renal creatinine clearance associated with a 10% decrease in mortality, whereas there was no association between peritoneal CrCl and mortality [5].

Similarly, Rocco *et al.* reported that for each 10 L/week/1.73 m² increase in renal CrCl there was a 40% reduced risk for death and also that for each increase in weekly renal Kt/Vurea of 0.1 there was a 12% reduction in the risk for death from a multicentre prospective cohort study of 1446 prevalent PD patients [6]. Once again there was no effect of peritoneal solute clearances on survival. These findings were not limited to North America or Europe [7, 8], with observational reports from Hong Kong [9] and Turkey also confirming that for every 1 mL/min increase in residual GFR mortality risk reduced by 35–47% [10, 11]. These studies emphasized the fact that the residual renal clearance may have greater beneficial effects than comparable peritoneal small solute clearance and as such these clearances are not simply equivalent. This led to the reanalysis of the CANUSA study [12], the landmark multicentre prospective cohort of 680 incident PD patients in Canada and USA, which reported that for each increment of residual renal GFR of 5 L/week/1.73 m² there was a 12% reduction in the risk for death and that for each 250 mL increase in urine volume there was a 36% decreased risk for death. Once again neither peritoneal small solute clearances nor peritoneal ultrafiltration volume were associated with patient survival. Subsequent secondary analysis of ADEMEX study additionally confirmed an advantage for RRF on mortality [13]. This cornerstone multicentre prospective randomized controlled trial of 965 Mexican PD patients, reported that for each increase in

RRF of CrCl 10 L/week/1.73 m² was associated with an 11% decrease in mortality, and an increase in renal Kt/Vurea of 0.1 a 6% decrease in mortality. More recently, additional studies from the Netherlands, Sweden, Australia and New Zealand have all confirmed the importance of RRF on mortality in PD patients (Table 1) [14–16]. In addition these studies all reported additional benefits for patients with preserved RRF, ranging from improved quality of life to reduced inflammatory markers [14, 15].

Although the evidence from these large observational and interventional trials is strongly weighted to an association between preservation of residual renal function and improved patient survival, they do not prove a causal effect. One potential confounder to all these studies is one of lead-time bias, in that patients with greater residual renal function may have initiated dialysis at a relatively earlier time than those with lower residual renal function. Similarly, some patients with CKD may have been started on peritoneal dialysis after an episode of acute kidney injury, followed by some recovery of RRF.

Measurement of residual renal function

Simply estimating RRF by measuring urine volume is inaccurate in patients with CKD [17]. Although the clearance of inulin, isotopes and radiocontrast agents ([51]chromium ethylenediaminetetra-acetic acid (EDTA) and iothalamate) are more accurate for determining residual renal function in patients with CKD than urine collections [18], these add costs and are impractical for routine clinical practice. As such, most centres use 24-h urine collections, and as urinary urea falls in CKD and underestimates inulin clearance, and conversely the relative ratio of tubular secreted to glomerular filtered creatinine increases urinary creatinine [19, 20], current guidelines advocate calculating the mean of creatinine and urea clearance, and then normalizing clearance to a body surface area of 1.73 m² [21]. However dialysis patients may suffer from sarcopenia, and as such changes in body composition [22, 23].

However, both urea and creatinine are influenced by dietary protein intake, particularly meat, and creatine production depends upon both hepatic synthetic function

Table 1. Summary of studies reported beneficial of RRF on mortality

Reference (year)	Study design	Number, characteristics and modality of subjects	Measurement of RRF	RR or OR of mortality per increase of RRF (CI or P-value)
Maiorca *et al.* (1995) [4]	3-year prospective single centre	Prevalent 68 CAPD and 34 HD	GFR 10 L/week/1.73 m²	0.4 (P < 0.001)
Diaz-Buxo *et al.* (1999) [5]	1-year prospective single centre	Prevalent 2686 CAPD or CCPD	Renal CrCl 10 L/week/1.73 m²	0.89 (P = 0.003)
Rocco *et al.* (2000) [6]	7-month prospective multicentre	Prevalent 1446 CAPD or CCPD	Renal CrCl 10 L/week/1.73 m²	0.6 (0.4–0.8)
Szeto *et al.* (2000) [10]	3-year prospective single centre	Prevalent 270 CAPD	GFR 1 mL/min/1.73 m²	0.65 (0.45–0.94)
Ates *et al.* (2001) [11]	3-year prospective single centre	Incident 125 CAPD	GFR 1 mL/min/1.73 m²	0.53 (0.31–0.92)
Bargman *et al.* (2001) [12]	2-year prospective multicentre	Prevalent 680 CAPD	GFR 5 L/week/1.73 m² Urine volume > 250 mL/day	0.88 (0.83–0.94) 0.64 (0.51–0.8)
Paniagua *et al.* (2002) [13]	2-year multicentre randomized controlled	Incident 965 CAPD	Renal CrCl 10 L/week/1.73 m² Renal Kt/V 0.1 unit	0.89 (P = 0.01) 0.94 (P = 0.01)
Termorshuizen *et al.* (2003) [14]	3-year prospective multicentre	Incident 413 CAPD	GFR 1 mL/min/1.73 m²	0.88 (0.79–0.99)
Chung *et al.* (2003) [15]	2-year retrospective	Incident 117 CAPD	GFR 1 mL/min/1.73 m²	0.79 (0.62–0.99)
Szeto *et al.* (2004) [3]	5-year prospective single centre	Prevalent 270 CAPD	GFR 1 mL/min/1.73 m²	0.8 (0.73–0.88)
Rumpsfeld *et al.* (2009) [16]	3-year retrospective	Incident 2434 CAPD or APD	GFR 10 L/week/1.73 m²	0.93 (P = 0.01)

and muscle mass and physical activity, and changes in intestinal bacteria flora alter urea and creatine gastrointestinal losses [24]. As such, these factors add potential confounders when reviewing serial measurements of RRF from CKD5d patients over time.

The commonest method for estimating creatinine remains the colourimetric Jaffe-based reaction. In kidney disease, chromogens accumulate which can interfere with this assay [25], and as such creatinine estimations vary between laboratories. Enzymatic methods of creatinine measurement, which are less affected, are more reliable. In addition to these technical aspects which affect measurement of RRF, urine volumes and urinary urea, creatinine and protein vary in 24-h urine collections in CKD patients not only consequent upon hydration status but also on patient compliance with completeness of the collection [25]. Although 24-h urine collections remain the standard method to determine RRF in clinical practice, there is not only inter-patient and interlaboratory variation but also intrapatient variability (Figure. 1).

The effect of the original cause of kidney disease on loss of residual renal function in the PD patient

The original cause of kidney disease can certainly have an impact on CKD progression, for example, most CKD5d patients with antiglomerular basement membrane disease initiate dialysis virtually anuric whereas children with nephronophthisis may be polyuric. Haynes et al. reported an annual rate of decline in residual renal function of 3.8 ± 2.5, 2.5 ± 4.8 and 1.9 ± 3.6 mL/min/1.73 m^2 for patients with cystic kidney disease, diabetic kidney disease and glomerulonephritis, respectively [26], and Liao et al. also noted that PD patients with diabetic nephropathy had a more rapid progressive loss of RRF [27]. However, these observations were not supported by USRDS data [28], although this study may have been confounded by including haemodialysis patients and so introducing other factors such as repeated intradialytic hypotensive episodes [29]. More recently, another study from Hong Kong reported that patients with proteinuric renal diseases were more likely to have a faster loss of RRF [30], as were those with peripheral and cardiovascular disease [31] and patients initiating PD with less RFF [30]. Loss of RRF in

Fig. 1. Bland Altman plot showing variation in glomerular filtration rate calculated from sequential 24 h urine collections in 100 peritoneal dialysis patients.

returning kidney transplant patients may vary with centre practices, in terms of immunosuppressive policy and reducing or stopping these medications when starting PD.

As underlying primary renal disease, and baseline GFR at PD initiation appear to have a major effect on determining loss of RRF, these factors should be considered when designing prospective interventional studies designed to preserve RRF.

Strategies for preserving RRF in patients with progressive CKD

Dietary intervention

Increased protein intake increases both the glomerular filtration rate and increases renal tubular acid excretion in the normal kidney. As hyperfiltration and increased renal tubular work load to maintain acid-base homeostasis have both been proposed as mechanisms for continued renal injury, protein restriction may potentially reduce the rate of loss of RRF. The potential benefits of dietary protein restriction (0.58 g/kg/day versus a normal dietary protein intake of 1.3 g/kg/day) to slow the progression of chronic kidney disease (CKD) were reported in the Modification of Diet in Renal Disease (MDRD) study [32], which demonstrated that a low protein diet had a modest effect when compared with blood pressure control in patients with CKD stages 3–4 (eGFR 25–55 mL/min/1.73 m^2). Follow-up suggested that there may have been a continuing effect, predominantly for those with diabetic kidney disease [33]. In contrast, very low protein diets with keto acid supplements (protein intake 0.28 g/kg/day and ketoacids 0.28 g/kg/day) did not reduce progression in patients with CKD stage 4–5 (eGFR 13–24 mL/min/1.73 m^2) and were associated with increased mortality when compared with those on a low-protein diet [34]. There are limited data in PD patients, although a small single centre trial reported that RRF was better maintained in incident PD patients with a urine output $\geq$800 mL/day or an eGFR $\geq$2 mL/min/1.73 m^2, over 12 months prescribed a low-protein diet with supplemental ketoacids (protein intake 0.6–0.8 g/kg/day with keto acids 0.12 g/kg/day) versus a low- 0.6–0.8 g/kg/day and a high-protein diet group 1.0–1.2 g/kg/day [35]. Reducing dietary protein intake reduces serum creatinine, but how this affects measurement of residual renal function in patients with CKD5d is unknown, as it may increase the ratio of creatinine secreted by the tubule compared to that filtered thus giving a 'higher' creatinine-based estimate of RRF. Similarly it is unknown whether reducing dietary protein intake affects gastrointestinal creatinine loss. In addition, none of these studies assessed dietary sodium or phosphate intake, which are linked to dietary protein ingestion, and lower protein diets supplemented with keto acids would have been expected to contain lower sodium and phosphate content. Thus, although an observational study reporting faster loss of RRF in PD patients with higher dietary protein intake [36] may have been due to greater protein intake, it may have been confounded by higher dietary sodium and phosphate intake.
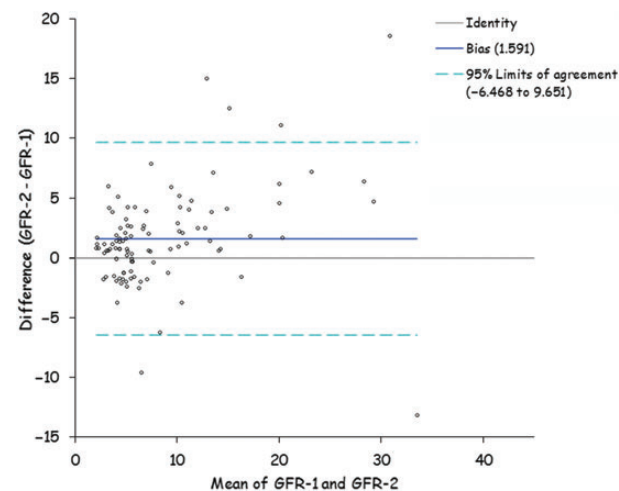
Effects of blood pressure control and RRF

The protective effects of blood pressure control to slow the progression of CKD are the basis of medical management. However, the role of blood pressure control in preserving RRF in PD patients remains inconclusive. Moist et al. reported

no association between blood pressure control and the rate of loss of RRF in their retrospective review of 1032 incident PD patients from the USRDS database [28]. However, this apparent difference with CKD may be confounded by clinicians treating hypertension on one hand, and on the other patients with low blood pressure secondary to cardiac dysfunction, or those patients with hypertensive kidney disease with blood pressures below their autoregulatory range are more prone to episodes of acute kidney injury with more rapid loss of residual renal function [37].

Effects of renin-angiotensin-aldosterone system blockage

Although angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) have been convincingly demonstrated to reduce the rate of progression and proteinuria in CKD patients [38], it is unclear whether they have a benefit in the PD patient [39]. Although ACEIs and ARBs improve survival in patients with chronic heart failure they reduce renal function [40], and similarly in PD patients, any potential benefit may be abrogated by an increased risk of hypotension and acute kidney injury [41]. The results of observational studies have been mixed, with a large retrospective study from USRDS on incident and prevalent PD reporting ACEIs had a protective effect on RRF [28], whereas a study of 160 incident PD patients from Australia, and 451 from the Netherlands showed no benefit [36, 42], although more diabetics were treated with ACEIs in the latter study. A recent observational study reported a small protective effect for ACEIs, but when corrected for other factors showed no statistical advantage for ACEIs [30]. Two small randomized trials have reported better preservation of RRF with ACEIs/ARBs. First, Li *et al.* studied 60 PD patients and reported the rate of decline in RRF over 12 months with ramipril was 2.07 mL/min per 1.73 m^2 versus 3.0 mL/min per 1.73 m^2 for the control group, although there was no difference in RRF between the groups at 3, 6 and 9 months, and the only difference was at the end of the study when a number of patients had dropped out and some had stopped taking ramipril due to side effects. Interestingly, the hazard ratio for anuria was higher in the ramipril-treated group at 3, 6, 9 months, which may be explained by the haemodynamic side effects of ACEIs [43]. Suzuki *et al.* reported on 34 patients randomized to valsartan or other antihypertensives and the ARB group had lower loss of RRF over 2 years from 3.2 ± 0.3 to 4.3 ± 0.7 mL/min/1.73 m^2 compared with 5.9 ± 0.5 to 2.8 ± 0.4 mL/min/1.73 m^2 in the control group [44].

Unexpectedly, RRF improved after ARB administration and was higher at 6 months than prior to starting ARBs, suggesting that some patients had regained RRF after an acute decline which had initiated starting PD treatment. Neither study showed any effect of ACEI/ARB on proteinuria. A small prospective trial showed no difference between ARBs and ACEIs on RRF [45].

More recently, a systematic review from the Cochrane library reported that ACEIs or ARBs may provide some protection in preserving RRF in PD patients, but did not reduce proteinuria. However, as the number of studies and quality of studies, in terms of potential confounders was markedly limited, no recommendation that ACEIs/ARBS should be the antihypertensive agents of choice for PD patients could be made [46]. On the other hand ACEIs/ARBs did not increase serum potassium, although the combination of ACEIs and ARBs may potentiate hyperkalaemia and oliguria in PD patients [47].

The effect of loop diuretics on RRF

In clinical practice, diuretics are commonly prescribed to PD to aid volume control, but hypovolaemia may lead to acute kidney injury and loss of RRF. Observational studies have either reported no effect on RRF [28, 36], or a loss of RRF [26, 30]. On the other hand, Van Olden *et al.* observed that in the short term, high dose furosemide increased both free water and sodium excretion but without affecting urea or creatinine clearance [48]. In a randomized trial, Medcalf *et al.* compared the effect of 250 mg/day of furosemide over 12 months in 61 incident PD patients [49] and showed that although treatment with furosemide improved fluid balance and increased urine volume and sodium excretion there was no benefit on preserving RRF. As such there is no convincing data that loop diuretics, such as furosemide maintain RRF, whereas they increase urine output and sodium excretion and as such may benefit volume overloaded patients.

Effects of peritoneal dialysis modality and RRF

Around the world, the proportion of patients treated by continuous ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis overnight cyclers (APD) varies markedly. There has been a debate as to whether APD therapy leads to earlier loss of RRF. APD patients are generally exposed to higher glucose dialysates compared with CAPD, and glucose exposure has been reported to be associated with faster loss of RRF [36]. In addition, blood pressure tends to fall when peritoneal dialysate is drained out and then increases during infill, and it has been hypothesized that these changes in blood pressure and cardiac filling could predispose to renal hypoperfusion and earlier loss of RRF [50]. Hiroshige and Hufnagel were the first to report more rapid loss of RRF with APD in small single-centre series [51, 52]. However, others reported no difference between the two modalities in small trials [53, 54] and large observational databases and registries [26, 28, 39, 53, 55] (Table 2). More recently, registry data from the NECOSAD study reported a higher risk for loss of RRF with APD, particularly in the first year of treatment, with an adjusted hazard ratio 2.66 (confidence interval 1.60–2.44) [65]. Apart from the NECOSADS study [65], nearly all of the other studies are potentially confounded by patient selection bias and underlying original kidney disease, as generally the older more comorbid patients were treated by CAPD [54]. APD therapy using high glucose dialysates may potentially increase the risk of hypovolaemic episodes and renal ischaemia, and as such lead to an earlier loss of RRF.

Effects of biocompatible peritoneal fluid and RRF

Conventional peritoneal dialysis fluids are hypertonic and acidic, containing lactate as a base equivalent and glucose degradation products (GDPs). The newer neutral pH, lower GDP PD fluids, may better preserve RRF as they may cause less intraperitoneal inflammation, and so reduce peritoneal ultrafiltration and fluid losses [55]. This concept is supported by a short-term European study which reported greater urine volume and both urinary urea and creatinine clearance with the neutral pH low GDP glucose containing dialysates [66]. These beneficial effects of neutral pH dialysates were confirmed by a number of clinical trials, which reported better preservation of RRF with the less bioincompatible dialysates [66,

Table 2. Summary of studies reported effect of dialysis modality on RRF

Reference (year)	Study design	Subject characteristics	Favour CAPD	Details
Hiroshige *et al.* (1996) [51]	6-month prospective	Prevalent 8 NIPD, 5 CCPD, 5 CAPD	Yes	Rate of change of RRF in −0.29 (NIPD) versus −0.34 (CCPD) versus +0.01 (CAPD) mL/min/month
Rodriguez *et al.* (1998) [56]	3-year prospective	Prevalent 25 CAPD, 20 APD	No	
Hufnagel *et al.* (1999) [52]	18-month prospective	Incident 6 NIPD, 12 CCPD, 18 CAPD	Yes	Rate of change of RRF in −0.26 (APD) versus −0.13 (CAPD) mL/min/month
Bro *et al.* (1999) [57]	6-month randomized controlled trial	Prevalent 13 CAPD, 12 APD	No	
Moist *et al.* (2000) [28]	3-year retrospective	Incident 722 CAPD, 310 APD	No	
De Fijter *et al.* (2000) [53]	2-year randomized controlled trial	Incident 13 CCPD, 11 CAPD	No	
Gallar *et al.* (2000) [58]	1-year prospective	Incident 11 CAPD, 9 APD	No	
Singhal *et al.* (2000) [59]	4-year prospective	Incident 211 CAPD, 31 APD	No	
Holley *et al.* (2001) [60]	9-year retrospective	Incident 11 CAPD, 9 APD	No	
Jansen *et al.* (2002) [39]	1-year prospective	Incident 243 PD subjects	No	
Hidaka *et al.* (2003) [61]	6-year prospective	Incident 27 CAPD, 7 APD	Yes	Approximate time to decrease 50% of RRF in CAPD is 15 months versus APD 4 months, P < 0.001
Johnson *et al.* (2003) [36]	6-year prospective	Incident 134 CAPD, 12 APD	No	
Rodriguez-Carmona (2004) [62]	1-year prospective	Incident 53 CAPD, 51 APD	Yes	Hazard ratio of APD versus CAPD = −1.2 (−2.25 to −0.15, P = 0.02)
Rabindranath (2007) [63]	Systematic review of 3 RCT	49 PD subjects	No	
Liao (2009) [27]	10-year retrospective	Incident 188 CAPD, 82 APD	No	
Su *et al.* (2010) [64]	9-year retrospective	Prevalent 140 CAPD, 32 APD	No	
Cnossen *et al.* (2010) [55]	7-year retrospective	Incident 179 CAPD, 441 APD	No	
Balasubramanian *et al.* (2011) [54]	5-year retrospective	Incident 178 CAPD, 13 APD	No	
Michels *et al.* (2011) [65]	3-year retrospective	Incident 505 CAPD, 78 APD	Yes	Higher risk of loss of RRF in APD compared to CAPD in first year of treatment (adjusted hazard ratio 2.66, CI 1.66–4.44)

67]. However, these beneficial effects on RRF were not substantiated by a greater number of later studies and trials [68–76] (Table 3). The most recent randomized prospective trial, which recruited patients who were well matched for original kidney disease and comorbidity, reported no beneficial effect for low GDP neutral pH dialysates on preserving RRF [73]. A recent Cochrane report commented that the number of good quality trials with appropriate patient numbers was somewhat limited. Their meta-analysis reported that overall, although the use of neutral pH low GDP glucose-containing dialysates were associated with increased urine volumes compared to standard dialysates [83], there was no overall statistically significant benefit in terms of maintaining RRF or benefit at 12 or 24 months of treatment, although there was potential benefit after 2 years. As such, with the relatively high turnover of PD patients, the majority of PD patients would not benefit from the prescription of these less bioincompatible dialysates in terms of preserving RRF.

Effects of icodextrin and RRF

Icodextrin 7.5% is a dialysis solution containing an iso-osmolar glucose polymer with greater ultrafiltration capacity than 22.7 g/L glucose dialysates [77] and is typically used for the long day dwell period with APD or the night-time dwell for CAPD patients. As icodextrin decreases extracellular water (ECW) [84], there have been concerns that it may lead to dehydration and loss of RRF [85]. One

randomized study measuring body composition and ECW reported that icodextrin reduced ECW, but also reduced urine output and GFR [85]. Only one small single-centre study reported that icodextrin usage helped preserve RRF [86], whereas five other studies showed no effect [87–91] (Table 4). As such, a recent Cochrane meta-analysis concluded that whereas icodextrin increased ultrafiltration compared with a standard 22.7 g/L glucose exchange, there was no effect on RRF [83]. However, as icodextrin can lead to a reduction in ECW, patients could potentially be at increased risk of dehydration and acute kidney injury, as dehydration is linked to loss of RRF [36].

Effects of volume status and RRF

Intravascular volume depletion has been widely accepted as a cause of loss of RRF in PD patients [36]. However many studies using bioimpedance techniques have reported that PD patients generally have an increased ECW volume [92]. Although faster transporters may be expected to potentially be at greater risk of hypervolaemia due to the more rapid fall in the osmotic glucose gradient, cross-sectional studies have not reported any differences in ECW volume with transporter status in healthy APD outpatients and CAPD outpatients using 7.5% icodextrin [93].

Many clinicians err on the side of volume expansion for PD patients in the belief that this will help maintain RRF. Studies using the less bioincompatible PD dialysates reported lower peritoneal ultrafiltration, and so the question

Table 3. Summary of studies reported effect of biocompatible peritoneal solution on RRF

Reference (year)	Study design	Subject characteristics	Favour balance solution	Details
Feriani et al. (1998) [76]	6-month randomized controlled trial	Prevalent 33 lactate base, 36 bicarbonate base	No	
Coles et al. (1998) [77]	2-month randomized controlled trial	Prevalent 3 arms, 19 lactate base, 20 lactate/bicarbonate, 20 bicarbonate	No	
Tranaeus et al. (2000) [78]	1-year randomized controlled trial	Prevalence 106 CAPD, 70 (bicarbonate/lactate), 36 (lactate)	No	
Rippe et al. (2001) [69]	2-year randomized controlled trial	Prevalent 40 conventional, 40 neutral pH dialysate	No	
Williams et al. (2004) [66]	6-month randomized crossover	Prevalent 86 CAPD subjects	Yes	Renal CrCl and urea clearance increase when using balance solution and decrease when using standard solution
Montenegro et al. (2006) [79]	1-year randomized controlled trial	Incident 36 CAPD, 18 (lactate base), 18 (bicarbonate base)	Yes	GFR decline in lactate base group, but preserved in bicarbonate group
Szeto et al. (2007) [70]	1-year randomized controlled trial	Incident 25 conventional, 25 neutral	No	
Fan et al. (2008) [71]	1-year randomized controlled trial	Incident 61 CAPD or APD for conventional fluid, 57 CAPD or APD for neutral fluid	No	
Choi et al. (2008) [74]	1-year randomized controlled trial	Prevalent, 104 CAPD, 51(neutral), 53 (conventional)	No	
Weiss et al. (2009) [80]	6-month prospective crossover	Prevalent 53 CAPD	Yes	Improvement of GFR when using bicarbonate base solution
Pajek et al. (2009) [74]	6-month prospective crossover	Prevalent 26 CAPD	No	
Haag-Weber et al. (2010) [81]	18-month randomized controlled	Prevalent 69 CAPD, 43 (neutral), 26 (conventional)	Yes	Monthly RRF change faster in conventional group, −4.3% versus −1.5% (P = 0.04)
Bajo et al. (2011) [72]	2-year prospective	Incident 20 standard, 13 balance fluid	No	
Johnson et al. (2012) [73]	2-year randomized controlled trial	Incident 93 conventional, 92 balance fluid	No	
Kim et al. (2012) [82]	2-year randomized controlled trial	Incident 91 CAPD, 48 (balance), 43 (conventional)	Yes	Residual renal function significantly higher in balance solution at the end of study
Cho et al. (2013) [76]	1-year randomized controlled trial	Incident CAPD, 32 (balance), 28 (conventional)	No	

Table 4. Summary of studies reported effect of icodextrin peritoneal solution on RRF

Reference (year)	Study design	Subject characteristics	Favour icodextrin solution	Details
Posthuma et al. (1997) [87]	2-year randomized controlled trial	Prevalent, CCPD, 11 (icodextrin), 10 (lowest glucose)	No	
Plum et al. (2002) [88]	3-month randomized controlled trial	Prevalent, APD, 20 (icodextrin), 19 (2.27% glucose)	No	
Konings et al. (2003) [85]	4-month randomized controlled trial	Prevalent, CAPD and CCPD, 22 (icodextrin), 18 (glucose)	No	GFR significantly decrease in icodextrin treated group, but maintain in control group
Adachi et al. (2006) [86]	2-year retrospective	Prevalence case matched control APD, 10 (icodextrin), 12 (glucose)	Yes	GFR significantly decrease in control group, but maintain in icodextrin treated group
Takatori et al. (2011) [90]	2-year randomized controlled trial	Incident, CAPD and APD, 21 (icodextrin), 20 (glucose)	No	

arose as to whether any benefit in maintaining urine volume or RRF was secondary to prevention of dehydration, rather than any effect of the dialysate *per se*. On the other hand, sustained hypervolaemia will result in hypertension, left ventricular hypertrophy [94] and may lead to an increased risk for cardiovascular mortality. In a cross-sectional study of 550 prevalent stable PD patients which defined hypervolaemic status, as ratio of ECW to TBW measured by multifrequency electrical bioimpedance assessments (MFBIA), urine output was lower in hypervolaemic patients [95]. Although MFBIA measures ECW, other causes of ECW expansion include inflammation and hypovolaemia [96]. However, the association between natriuretic peptides and ECW in PD patients suggests that many are volume expanded [97]. McCafferty et al. examined the association of annual measurement of MFBIA and loss of RRF in 237 prevalent PD patients [98] and reported that there were no differences in the change in RRF with respect to absolute or relative changes in ECW/TBW ratio. Importantly, this study showed that maintaining a hypervolaemic state did not preserve RRF, and this needs to be confirmed by a prospective blinded study.

Effects of nephrotoxic insults and RRF

Nephrotoxic agents such as non-steroidal anti-inflammatory drugs, aminoglycoside antibiotics and radio-contrast iodine are recognized to increase the risk of acute kidney

injury in patients with CKD [41]. PD patients are at risk of peritonitis [1], and peritonitis may lead to hypotension and relative hypovolaemia with an increased risk of loss of RFF [30, 36]. In addition, treatment with aminoglycosides might potentially lead to a more rapid loss of RFF, and this was observed by Shemin *et al.* [99]. Nonetheless, several subsequent studies reported that aminoglycoside treatment did not adversely affect RRF compared with other antibiotic regimes [100–102]. Lui *et al.* randomly assigned 102 CAPD patients to once daily intraperitoneal cefazolin and netilmicin versus cefazolin and ceftazidime for 14 days. Although RRF was significantly reduced at Day 14 in the aminoglycoside group, RRF recovered to baseline by 6 weeks [102]. Registry data from Australia did not show any effect of aminoglycosides on the rate of decline of RRF in some 1400 PD patients who had suffered one of more episodes of PD peritonitis [103]. Thus, although once daily short courses of aminoglycoside may cause a transient reduction in RRF, they do not appear to have a discernable adverse long-term effect, when dosages are adjusted to maintain therapeutic and toxic levels avoided. Radiocontrast-induced acute kidney injury is more common in patients with underlying CKD. However, reports from retrospective observational studies have not noted a major effect of contrast exposure on loss of RRF [59,103]. As PD patients generally have an expanded ECW, this may help protect against radiocontrast injury in patients with appropriate periprocedural hydration.

Dittrich *et al.* prospectively investigated the effect of radiocontrast media on RRF in a small number of PD patients and noted that the combination of a reduced volume of non-ionic hypo-osmolar contrast media and oral hydration did not adversely affect RRF after 30 days [104]. Likewise, Moranne *et al.* reported no difference in RRF measured 2 weeks after radiocontrast exposure when PD patients were hydrated with 1 L of 0.9% saline preprocedure compared with PD controls [105]. Although radiocontrast exposure may cause an acute deterioration in RRF with appropriate hydration and minimizing radiocontrast dosage does not appear to have a permanent deleterious effect on RRF.

Conclusion

Preservation of RRF is an important determinant of both PD technique and patient survival. However, loss of RRF is dependent upon the primary renal disease and patient comorbidities and is affected by lead-time bias in terms of when patients initiate PD and also whether starting PD an episode of acute kidney injury, which is then followed by partial recovery of RRF. As there are significant errors in measuring RRF in PD patients, the question arises as to whether the effects of treatments designed to preserve RRF can be truly assessed above the background variation in RRF and patient risk factors. As such, there is little if any current convincing evidence to confirm the effect of strict blood pressure control or support the use of ACEI/ARBs compared with other antihypertensive medicines or less bioincompatible peritoneal dialysates in preserving RRF. Avoidance of dehydration and episodes of acute kidney injury associated with peritonitis appear important in preserving RRF, but on the other hand deliberately keeping PD patients overhydrated, as assessed by bioimpedance [106] does not appear to preserve RRF. Further carefully designed large scale prospective studies are warranted to prove the benefits of drug and other interventions to preserve RRF.

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