The Importance of Residual Renal Function in Peritoneal Dialysis Patients

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Increased peritoneal clearance can compensate for reductions in renal solute removal in patients receiving peritoneal dialysis (PD); however, there is abundant evidence to suggest that renal rather than peritoneal clearance contributes to clinical outcomes. We review the evidence investigating the impact of residual renal function (RRF) and peritoneal solute clearances on survival and quality of life in PD patients. We also provide a comparison of the relative contribution of RRF and peritoneal clearance to patient survival. In addition, mechanisms of survival benefit in patients with preserved renal function, factors contributing to RRF decline, and interventions that may limit the progressive loss of RRF are discussed.

Key words
Residual renal function, survival, quality of life

Introduction

The adequacy of peritoneal dialysis (PD) therapy is generally measured by total urea clearance (Kt/V_{urea}), which consists of both renal and peritoneal urea clearances. According to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative guideline recommendations for peritoneal dialysis adequacy, anuric and non-anuric PD patients should both maintain a minimum total weekly Kt/V_{urea} of 1.7 (1). As renal function progressively declines on dialysis therapy, patients become more dependent on peritoneal clearance for maintenance of that target. To achieve adequate weekly solute clearance, the dose of PD therapy must be increased to compensate for reductions in renal solute removal. Although increased peritoneal clearance may enhance small-solute elimination, there is a wealth of evidence to suggest that renal function rather than peritoneal clearance influences clinical outcomes in non-anuric PD patients.

This article reviews clinical trial data on the influence of residual renal function (RRF) and peritoneal clearances on patient survival and quality of life. The effects of incremental changes in renal and peritoneal clearance on survival, factors that may contribute to RRF decline, and methods of preserving RRF are also detailed.

Discussion

Impact of RRF on survival

The contribution of RRF to the survival of PD patients was first noted in an observational study in the 1990s (2). The authors found that higher RRF and total Kt/V were associated with a reduced risk of death. Several subsequent studies compared the effects of peritoneal and renal clearances on PD patient survival (3–8). The authors consistently identified an inverse relationship between higher RRF and relative risk of death (Table I); however, there were no associations between peritoneal clearance and survival in most of the trials. Those observations suggested that, as a predictor of survival, renal function was more important than the dose of PD therapy. That finding was consistent in the studies despite differences in patient characteristics, PD modality, and selection of covariates for multivariate analyses.

Although RRF has been associated with improved patient outcomes, it is unclear whether baseline renal function or the rate of decline of RRF is the best indicator of survival. In a prospective observational study of 270 Taiwanese PD patients with urine volumes exceeding 100 mL daily, Liao and colleagues (9) evaluated the impact of baseline RRF and its rate of decline on survival, death-censored technique survival, and combined patient and technique survival. Patients were stratified into "slow," "intermediate," and "fast" groups according to the measured rate of

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TABLE I Contribution of residual renal function to survival

Reference	*Pts (n)*	*Measure (1 mL/min)*	*Relative risk reduction (%)*
Maiorca *et al.*, 1995 (2)	68	GFR	48
Diaz–Buxo *et al.*, 1999 (3)	2686	CCr	12
Rocco *et al.*, 2000 (4)	1446	CCr	40
Szeto *et al.*, 2000 (5)	270	GFR (CCr)	35
Bargman *et al.*, 2001 (6)	601	GFR	24
Termorshuizen *et al.*, 2003 (7)	413	GFR	12
Rumpsfeld *et al.*, 2009 (8)	2434	GFR	7

Pts = patients; GFR = glomerular filtration rate; CCr = creatinine clearance.

RRF decline. The authors found that a fast rate of RRF decline was independently and significantly associated with worse patient and technique survival. Rate of RRF decline was a more powerful predictor of survival than baseline RRF.

Impact of RRF on quality of life

A few studies have examined the effects of renal function on quality of life (QOL) in PD patients. A single-center retrospective analysis of 105 prevalent PD patients in Korea evaluated the effects of demographic, clinical, and dialysis treatment parameters on health-related QOL (HRQOL) and depression (10). The authors found that lower renal Kt/V_{urea} but not peritoneal Kt/V_{urea} (pKt/V) was independently associated with both depression and lower scores on the kidney dialysis component of the Kidney Disease Quality of Life short form.

The Netherlands Cooperative Study on the Adequacy of Dialysis also assessed QOL in PD patients (7). This prospective, multicenter cohort study of incident PD patients analyzed associations between renal and peritoneal clearances and various parameters of the Kidney Disease Quality of Life short form. The authors found a positive association between residual glomerular filtration rate and all dimensions of the Kidney Disease Quality of Life short form. Most associations were statistically significant. However, no statistically significant associations were observed between peritoneal creatinine clearance and QOL for any of the parameters measured. In fact, peritoneal clearance negatively influenced several parameters. Overall, those data suggest that the benefits of RRF extend beyond improved survival to include subjective measures of patient health, and that those benefits are more important than the dose of PD therapy.

Mechanisms by which RRF affects clinical outcomes

Potential mechanisms for better patient outcomes with preserved RRF include better fluid removal and blood pressure control, enhanced clearance of middle molecular weight toxins such as β_2-microglobulin, better clearance of inflammatory mediators, preserved erythropoietin synthesis in response to hypoxia, increased vitamin D synthesis, and lower peritonitis rates (1). In addition, higher RRF may be an indicator of less advanced end-stage renal disease, suggesting that patients with preserved of renal function have fewer comorbidities and better overall health and QOL.

Impact of peritoneal clearance on survival

Studies conducted in the mid-1990s suggested that higher total Kt/V is associated with improved survival among PD patients (2,11). However, the authors of those studies did not separate the contributions of renal and peritoneal clearance to survival, leading many readers to assume that high targets for PD clearance led to better patient outcomes. The results of subsequent studies that examined individual associations between renal and peritoneal clearances and survival showed that RRF—and not peritoneal clearance—predicts survival (3–8). Excessively high targets for weekly pKt/V may result in an increased burden of therapy, diminished QOL, an inability to achieve weekly targets as anuria develops, and unnecessary transfers from PD to HD therapy as a result of technique failure (12). It has therefore been necessary to identify a maximum threshold for peritoneal solute clearances above which no survival benefit is observed.

Rumpsfeld and colleagues (8) found a relationship between baseline pKt/V and survival in a retrospective observational cohort study of 2434 incident PD patients in Australia and New Zealand. Multivariate regression analyses performed using continuous pKt/V values and pre-specified categorical pKt/V values (<1.45, 1.45 – 1.69, 1.70 – 2.00, and >2.00, with 1.70 – 2.00 as the reference range) found a nonlinear trend toward worse survival in patients with a pKt/V

above and below the reference range. However, the difference was statistically significant only for patients with a pKt/V less than 1.45 ($p = 0.003$). The authors concluded that baseline pKt/V was a nonlinear independent predictor of survival in incident PD patients. The study had multiple limitations, including a retrospective study design, potential confounding by differences in baseline RRF between the subgroups, and an inability of the authors to account for the effects of subsequent changes in PD dose on the survival of participants.

An analysis of participants on continuous ambulatory PD (CAPD) in the ADEMEX (Adequacy of Dialysis in Mexico) trial—a prospective, randomized, multicenter controlled study—found no benefit of increasing peritoneal clearance on survival (12). The average pKt/V of participants was 1.62 in the control group and 2.13 in the intervention group. The authors speculated that peritoneal clearances may have been too high to detect a survival benefit. Another multicenter randomized controlled trial of 320 incident CAPD patients in Hong Kong (13) showed no differences in survival between three groups of patients (target pKt/V: 1.5 – 1.7, 1.7 – 2.0, and >2.0). Despite the lack of an effect of pKt/V on survival, the authors found that the group of patients randomized to peritoneal clearances ranging from 1.5 – 1.7 had more adverse outcomes associated with inadequate dialysis.

Overall, the data suggest a survival benefit for increasing the pKt/V at clearances below 1.7; however, the effect of peritoneal solute removal on survival appears to plateau at higher levels of clearance. The findings that, in contrast to RRF, PD dose does not contribute to better outcomes was reflected in the 2006 revision of the Kidney Disease Outcomes Quality Initiative recommendation for weekly pKt/V, which was reduced to 1.7 from 2.0 (1).

Impact of peritoneal clearance on survival in anuric PD patients

Data about the impact of peritoneal clearance on survival in anuric PD patients are limited. The results of four observational studies in anuric patients are conflicting, but suggest that increasing the peritoneal clearance may have a positive impact on survival at pKt/V values up to 1.7 (14–17). The studies differed with respect to sample sizes, trial design, definition of anuria, and selection of covariates for analysis. Because most of the enrolled participants were receiving CAPD, the results may not be directly applicable to automated PD (APD) patients.

Factors influencing RRF decline

Numerous clinical trials have investigated the effects of various demographic and iatrogenic variables on the rate of RRF decline. Moist and colleagues (18) conducted an observational cohort study of 1843 U.S. dialysis patients to determine predictors of RRF loss in incident PD and HD patients. Regression analysis incorporated 33 demographic and clinical variables thought to influence the rate of RRF decline. Separate analyses of PD and HD patients were performed to account for differences in factors that may affect RRF decline depending on modality. Significant independent predictors of RRF loss in PD patients included: female sex, non-white race, and history of diabetes or congestive heart failure. Patients receiving angiotensin converting-enzyme inhibitors, calcium channel blockers, or PD rather than HD therapy had reduced odds of RRF loss. The relationship between dialysis modality and risk of RRF decline persisted even after adjustment for confounding variables including age, sex, comorbid conditions, hypertension, medications, and baseline glomerular filtration rate. Interestingly, no difference in the risk of RRF decline was observed for patients receiving APD or CAPD.

Liao and colleagues (9) also conducted a multivariate regression analysis to identify factors that were responsible for loss of RRF in PD patients. Those authors found that the median annual rate of RRF decline was 0.885 mL/min/1.73 m^2. Factors that were independently associated with RRF decline included higher levels of baseline RRF, higher body mass index, history of diabetes and congestive heart failure, use of diuretics, and history of peritonitis and hypotensive events. In accordance with the results reported by Moist and colleagues, no statistically significant association was found between PD modality and rate of RRF decline.

Most of the available data indicate that preservation of RRF and survival are superior for patients receiving PD than for those receiving HD within the first 1 – 2 years of therapy (19–22). The benefits of PD are attributed to better hemodynamic stability and a lack of inflammatory dialyzer reactions. Although most studies support the conclusion that RRF is better preserved in PD, a study by McKane and colleagues (23) found that survival was similar between the PD

and HD modalities when biocompatible dialyzers and ultrapure dialysate water are used during HD.

The results of studies comparing the effects on RRF of CAPD and APD are controversial. A few small nonrandomized studies found superior preservation of RRF with CAPD (24,25). Authors of those trials speculated that the continuous nature of CAPD results in fewer hemodynamic fluctuations, ultimately leading to better-preserved RRF. In contrast to studies that report an advantage of CAPD therapy, two randomized trials and a multicenter study found no difference of RRF decline in APD and CAPD patients (26,27). Overall, there is no conclusive evidence to suggest that there are differences in the effects of APD and CAPD on the rate of decline of RRF.

Several studies have examined the differential effects of biocompatible and conventional dialysates on the rate of RRF decline. Compared with conventional solutions, biocompatible solutions generally have a more neutral pH and contain lower concentrations of glucose degradation products. Those properties may enhance peritoneal membrane viability and preserve RRF. Multicenter randomized controlled trials investigating the effects of biocompatible and conventional PD solutions on the rate of RRF decline have generated conflicting data. The BalNet study (28) found that RRF was better preserved in patients receiving dialysis with biocompatible PD fluids. However, that finding reached only borderline significance. The DIUREST study (29) showed a significantly slower rate of RRF decline in patients receiving biocompatible solutions. The *bal*ANZ study (30) showed a significantly longer time to anuria, but no effect of biocompatible solutions on RRF decline.

Interventions to limit progressive loss of RRF

Progressive loss of RRF may be limited by interventions that target modifiable risk factors for kidney injury. Interventions can consist of using angiotensin converting-enzyme inhibitors or angiotensin receptor blockers to optimize blood pressure and limit proteinuria; minimizing volume depletion to prevent renal ischemia; avoiding the use of nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, aminoglycosides, and contrast media; preventing hypercalcemia; and using biocompatible PD solutions. Loop diuretics are also used in dialysis patients to increase urine output. However, they seem to have no beneficial effect on the rate of RRF decline.

Summary

A preponderance of the available studies demonstrate that renal rather than peritoneal clearance contributes to survival and improved QOL in non-anuric PD patients. Available evidence suggests that survival may be better indicated by the rate of RRF decline than by baseline RRF. The survival advantage conferred by higher levels of RRF can be attributed to factors other than solute clearance that are affected by the preservation of native kidney function. Studies of anuric PD patients have demonstrated a positive impact of increasing peritoneal clearance on survival up to pKt/V values of 1.7; however, as clearances increase above that level, survival tends to plateau. Many factors that may contribute to the rate of RRF decline have been identified; among them are the cause of end-stage renal disease, comorbid conditions, medications, dialysis modality, and the dialysate used. Interventions that address those factors might help to preserve RRF and lead to improved patient outcomes.

Disclosures

All authors are employed by or affiliated with Fresenius Medical Care North America.

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