The number of patients with end-stage renal disease continues to increase worldwide, but the 5-year survival probability for patients on dialysis remains low. Preservation of residual renal function (RRF) is widely recognized to be important in the pre-dialysis setting, but now, its benefit for health and quality of life in people on dialysis has been well established. Preservation of RRF has consistently been shown to improve circulating levels of inflammatory markers, middle molecule clearance, blood pressure, and other markers of dialysis adequacy. Residual renal function has also been associated with improved survival on dialysis. This article reviews strategies for preserving RRF in patients on dialysis to improve long-term survival in this population.

Key words
Residual renal function, biocompatibility, hemodialysis, survival

Introduction
The number of patients with end-stage renal disease (ESRD) continues to increase worldwide; in the United States alone, more than 500,000 patients have ESRD (1). Mortality rates in ESRD patients have improved since the end of the 1980s, but the 5-year survival probability for incident dialysis patients remains at 0.39 (1). Preservation of residual renal function (RRF) is widely recognized to be important in the pre-dialysis setting, but now, its benefit for health and quality of life in people on dialysis has been well established. In peritoneal dialysis (PD) and hemodialysis (HD) patients alike, RRF reduces the need for dietary and fluid restrictions. In addition, RRF is associated with improved clearance of middle molecules, lower circulating levels of inflammatory markers, reduced blood pressure, improved hemoglobin and phosphorus control, and reduced left ventricular hypertrophy (2–4). Among PD patients, lower RRF also confers a higher risk of peritonitis. In one study of 204 patients on continuous ambulatory PD (CAPD), the time to a first episode of peritonitis was longer and the risk of peritonitis was less [19% decrease for every 1 mL/min of glomerular filtration rate (GFR)] in those with higher RRF (5).

Preservation of RRF has also been shown to have a mortality benefit both in HD and in PD. Benefits in mortality were first noted in the PD literature. In the CANUSA study, an increase of 0.1 unit in weekly Kt/V urea was associated with a 5% decrease in the relative risk of death (6). However, the same relationship was not shown in the ADEMEX study (7) or in a randomized controlled trial of CAPD patients in Hong Kong (8), in which no mortality benefit was shown with an increased total (renal + peritoneal) Kt/V above 1.5 – 1.7. The benefit was clarified in a relook at the CANUSA trial (9), in which each 5 L/1.73 m² increase in weekly residual GFR was noted to be associated with a 12% decrease in the relative risk death (0.88; 95% confidence interval: 0.83 to 0.94). No significant contribution to survival was observed for peritoneal GFR or ultrafiltration, indicating that the benefit came solely from RRF. The Netherlands Cooperative Study on the Adequacy of Dialysis 2 (10) found similar results. Each increase of 1 mL/min in residual GFR was associated with a 12% reduction in mortality, but peritoneal GFR had no effect on survival. A fairly recent study of 270 new PD patients found that the rate of RRF decline was an even stronger predictor of survival than was baseline RRF at the start of dialysis (11). In that 4-year study, those with the most rapid rate of decline had the worst survival and the highest technique failure.

A mortality benefit from RRF has now been shown in HD patients as well. In the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease study (12), 734 incident HD patients were prospectively followed, with urine output (UOP) assessed by
questionnaire. Baseline UOP was not associated with improved survival, but 1-year UOP conferred lower all-cause mortality (hazard ratio: 0.70; 95% confidence interval: 0.52 to 0.93; \( p = 0.02 \)), lower epoetin use, and improved quality of life.

Given the number of benefits of RRF, strategies have to be developed to preserve residual GFR for patients starting dialysis. The present review discusses the potential roles of dialysis modality, selection of solution, and other factors in the preservation of RRF for patients on dialysis.

Discussion

Modality and solution selection

Many studies have shown that RRF is lost more rapidly in patients performing HD than in those performing PD (13–15). The largest of those studies, by Moist et al. (13), examined more than 20,000 dialysis patients randomly selected from the U.S. Renal Data System database to look at risk factors for loss of RRF (defined as <200 mL urine output in a 24-hour period). They found that patients treated with PD had a risk of RRF loss 65% lower than that for patients on HD [adjusted odds ratio (AOR): 0.35; \( p < 0.001 \)]. This difference has been speculated to possibly be related to HD with bioincompatible membranes and standard dialysis water, resulting in an inflammatory response and more rapid RRF loss.

The quality of water used for dialysis is subject to standards issued by the Association of the Advancement of Medical Instrumentation. Those standards require that product water used for the generation of dialysate have fewer than 200 colony-forming units per milliliter (notably, the Centers for Medicare and Medicaid Services uses a cutoff of 2000) and that it contain fewer than 2 endotoxin units per milliliter. When subjected to even more rigorous purification, resulting in fewer than 0.1 colony-forming units per milliliter, and fewer than 0.03 endotoxin units per milliliter, the resulting dialysate is considered ultrapure (though still not sterile). Dialysis with synthetic membranes and ultrapure water has been associated with less loss of RRF and rates of RRF decline similar to those seen with PD (16–19). In a 2-year German study, patients were randomized to traditional or to ultrapure HD, with those using ultrapure dialysate having a significantly higher GFR at the end of the study (4.3 mL/min vs. 2.5 mL/min, \( p < 0.05 \)). Furthermore, in a prospective observational study involving nearly 500 patients, CAPD was compared with HD performed using synthetic high-flux membranes and ultrapure water, and no difference in loss of RRF was observed during 2 years of follow-up, despite the CAPD patients being younger and having fewer comorbidities and higher performance scores than the HD patients (16). Unfortunately, despite the demonstrated benefits of ultrapure water, its use is not common in HD centers, and PD remains the preferred modality selection to maintain RRF.

The PD solutions selected may also affect RRF. Many current PD solutions are bioincompatible, with low pH and high levels of glucose that can result in the production of reactive carbonyl compounds and advanced glycation end-products. Those molecules may be absorbed through the peritoneum, causing apoptosis of renal tubular epithelial cells and resultant loss of RRF (20).

Several studies have explored the use of fluids that are more biocompatible and have produced varying results. The Euro-Balance study compared pH-neutral fluid low in glucose degradation products (Balance) with standard PD fluid in a 12-week crossover trial (21). Patients receiving the Balance solution showed lesser cytokine levels, decreased peritoneal ultrafiltration, and both increased urine output and increased RRF. The trial was small, however, and not powered to detect changes in RRF. Another trial, the Balnet study, randomized 91 incident PD patients to Balance solution or to traditional PD solution with 1 year of follow-up (20). A trend toward improved RRF was observed with the Balance solution, but that trend did not reach statistical significance. Furthermore, it must be noted that baseline renal function was significantly higher in the Balance group and that the study was also insufficiently powered to detect differences. Similar results were shown in two other trials of 50 and 93 new PD patients randomized to biocompatible or to standard solution (22,23). The smaller trial noted lower degrees of inflammation that were maintained for 1 year of treatment, but no difference in RRF, ultrafiltration volume, or indices of dialysis adequacy. By contrast, a recent study of Gambrosol Trio, a biocompatible fluid, showed a significantly greater RRF decline in patients using standard solution rather than the Gambrosol (24). The effect was independent of the use of angiotensin converting-enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB).
Although this most recent trial did show a benefit, that benefit has not been replicated, and at the present time, there is no convincing evidence to advocate for the routine use of biocompatible PD solutions for preservation of RRF.

ACEis and ARBs
The ACEis and ARBs have been extensively studied in the non-dialysis population, in whom they have been shown to preserve RRF in a number of chronic kidney disease states (25–27). That relationship holds true for patients on dialysis as well. In a study by Moist et al. (13) mentioned earlier, the authors retrospectively reviewed data from more than 1000 PD patients to determine factors associated with preserved RRF. Among the modifiable risk factors, use of an ACEi in PD patients lowered the risk for RRF loss (AOR: 0.69; \(p = 0.02\)), independent of blood pressure control. In an analysis of HD patients only, this lowered risk approached statistical significance (AOR: 0.71; \(p = 0.06\)).

Use of an ACEi has been further explored in prospective fashion. In a small randomized controlled trial of 60 CAPD patients, the patients were randomized either to 5 mg ramipril or to placebo, with the patients receiving ramipril showing improved RRF at 1 year (adjusted residual GFR: 1.72 mL/min vs. 0.64 mL/min respectively; \(p = 0.03\)); treated patients also had a lower likelihood of anuria (\(p < 0.001\)), with blood pressure control being similar between the groups (28). Another single-center randomized trial of 34 CAPD patients given either 80 mg valsartan or a placebo daily confirmed a slower decline in RRF among treated patients (3.2 ± 0.3 mL/min/1.73 m² vs. 4.3 ± 0.7 mL/min/1.73 m²; \(p < 0.01\)). Blood pressures were the same in both groups over the 2-year study period (29).

In addition to preserving RRF, use of an ACEi or ARB has also been shown to improve mortality among PD patients. In a retrospective analysis of 306 incident PD patients, those who had been treated with ACEi or ARB, or both, for at least 6 months were compared with those who had not, with a 62% reduction being found in the risk of death for the treated group (adjusted hazard ratio: 0.38; \(p < 0.001\)) (30). Throughout the analyzed period, blood pressures were higher in those who had received an ACEi or ARB, suggesting that the survival benefit with was not simply a result of lower blood pressure.

Despite the absence of a large randomized trial to prove the benefits of ACEis or ARBs in the dialysis population, use of these agents in hypertensive dialysis patients is currently recommended by the Kidney Disease Outcomes Quality Initiative because of the consistent benefit shown in retrospective reviews and small randomized controlled trials (31). The guidelines also recommend consideration of the use of these agents in normotensive PD patients in the presence of another indication such as heart failure. The benefit of RRF preservation in normotensive patients is not clear from the existing data, although the known benefits of ACEis and ARBs appear to be independent of BP control. We advocate their routine use.

Contrast and other toxins
It is generally recommended that the use of drugs and other nephrotoxins that can worsen renal function in chronic kidney disease be avoided in patients on dialysis as well. Nonsteroidal anti-inflammatories, aminoglycoside antibiotics, and oral phosphate solutions used for colonoscopy preparation are some of the agents to be avoided. Nonsteroidal anti-inflammatory agents, including inhibitors of cyclooxygenase-2, should be used minimally and sporadically, if at all, in dialysis patients with preserved RRF.

Aminoglycoside antibiotics are commonly used in dialysis patients for the treatment of peritonitis and catheter infections. Given their nephrotoxic potential, they should obviously be used with caution. The question is, may they be used at all? One prospective study of 72 PD patients followed for 4 years showed that patients who had received aminoglycosides experienced a more rapid decline in RRF and a lesser UOP (32). Similarly, Shemin et al. (33) reported significantly greater RRF loss in patients using aminoglycoside antibiotics for more than 3 days. However, shorter courses of aminoglycosides appear not to adversely affect RRF in adults or children (33–35). Accordingly, current recommendations from the International Society of Peritoneal Dialysis permit the use of aminoglycosides for empiric gram-negative coverage, but urge their discontinuation once antibiotic sensitivities are known and alternative agents have been identified (36). Ideally, avoidance of peritonitis is the superior course, because peritonitis is also associated with a decline in RRF (37).

Oral phosphate solutions have been associated with acute nephrocalcinosis and chronic renal failure...
in patients with normal baseline renal function (38,39). Because of this risk of worsening renal function, these solutions should be avoided in dialysis patients.

It is interesting to note that, although it would appear appropriate to avoid intravenous contrast agents in dialysis patients, there are no convincing data that use of these agents is associated with a significant impact on long-term RRF. In a study of 36 PD patients receiving intravenous contrast and 36 control PD patients, no difference in RRF or daily UOP was observed (40). However, the patients who received contrast were given 1 L normal saline for gentle pre-hydration. Similar results were found in a study of 10 matched CAPD patients receiving a median 107 mL of hypo-osmolar contrast (41). Those patients received no pre-hydration (but were encouraged to drink 500 mL more), and they did show a temporary decline of RRF post procedure, but no difference in RRF at 30 days or 4 months. A recent prospective trial with 42 ESRD patients on HD also did not show a difference in UOP or RRF when compared with matched controls at 6 months after exposure to contrast (42). There were similar numbers of patients with diabetes in both groups, and again, no pre-hydration or medications were given. Note, however, that the patients in that study who received intravenous contrast underwent HD within 3–5 hours of the contrast being administered.

Although the foregoing studies do not suggest loss of RRF after radiocontrast use, we nevertheless suggest that, if a patient on dialysis requires a contrast study, pre-hydration should be considered, and the lowest possible volume of contrast should be used. Consideration should also be given to performing dialysis as quickly as possible after contrast administration. In the foregoing studies, N-acetylcysteine was not used; based on meta-analysis, there are scant data to recommend its use in the dialysis population (43).

Diuretics have been shown to improve urine output and to allow for liberalized fluid intake in patients on dialysis, translating into improved RRF (44–46). In the previously mentioned study by Liao et al. (11), which showed a strong associated between the rate of RRF decline and survival, use of diuretics was associated with an increased rate of RRF loss. However, a causal link is not clear, because worsened RRF might have necessitated the use of diuretics. Use of diuretics would then be a consequence of the loss of RRF rather than a factor responsible for its decline. Given the existing data, diuretics should be used to prevent the need for aggressive ultrafiltration, but care should be taken to avoid hypotension.

**Summary**

Residual renal function has consistently been shown to improve circulating levels of inflammatory markers, middle molecule clearance, blood pressure, and other markers of dialysis adequacy and survival on dialysis. Given those benefits, strategies are required to maintain RRF in dialysis patients. In maintaining RRF, PD is superior to HD. Patients on HD can preserve RRF just as PD patients do, provided that the HD uses synthetic membranes and ultrapure dialysis water (although this practice is not standard). Biocompatible PD solutions may affect RRF, but the data are insufficient to recommend routine use of such solutions at this time. Use of ACEis and ARBs has consistently been shown to result in better preservation of RRF and improved survival. Unless contraindicated, these agents should be used routinely in dialysis patients with RRF. Caution should be exercised in the use of nonsteroidal anti-inflammatories, oral phosphate solutions, and prolonged aminoglycoside antibiotics. Despite known nephrotoxic potential, intravenous contrast agents have not been associated with loss of RRF in either PD or HD patients, but these agents should still be used with caution.

**Disclosures**

The authors have no financial conflicts of interest to disclose.

**References**

25 Andersen S, Tarnow L, Rossing P, Hansen BV, Parving HH. Renoprotective effects of angiotensin II receptor blockade in type 1 diabetic patients with


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