

# Advances in Understanding and Management of Residual Renal Function in Patients with Chronic Kidney Disease

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## Key Words

Residual renal function · Peritoneal dialysis · Hemodialysis · Chronic kidney diseases

## Abstract

**Background:** Residual renal function (RRF), defined as the ability of native kidneys to eliminate water and uremic toxins, is closely correlated with mortality and morbidity rates among patients receiving either peritoneal dialysis (PD) or hemodialysis (HD) via continuous clearance of middle-sized molecules and protein-bound solutes. Therefore, preserving RRF is considered to be one of the primary goals in managing patients with end-stage renal disease (ESRD). **Summary and Key Messages:** In this article, we provide a review on the understanding and management of RRF in patients on dialysis. RRF may be estimated and measured by calculating the mean 24-hour urine creatinine level and urea clearance. Currently, several middle-sized molecules are reported but rarely used in practice. Many risk factors such as original renal diseases, dietary intake, and nephrotoxic agents impair RRF. Targeting such factors may halt the decline in RRF and offer better outcomes for patients on PD or HD. Except for in PD patients, RRF is a powerful predictor of survival in HD patients. RRF requires more clinical and research attention in the care of patients with ESRD on dialysis.

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## Introduction

Residual renal function (RRF) in patients with end-stage renal disease (ESRD) receiving peritoneal dialysis (PD) or hemodialysis (HD) therapy is defined as the ability of the native kidneys to eliminate water and uremic toxins. RRF is a powerful prognostic indicator, and preservation of RRF is associated with better survival, lower morbidity, and greater quality of life in patients with ESRD on PD or HD [1–4]. Thus, preserving RRF is considered to be one of the primary goals in managing patients with ESRD. The aim of this review is to offer an assessment and update of the current understanding and management of RRF in patients on dialysis.

## Measurements of RRF

RRF may be estimated and measured. However, an optimal method for measuring RRF has not been established. The glomerular filtration rate (GFR) is widely used as an indicator for kidney function. Formulas based on the serum creatinine level are clinically used to estimate the GFR before initiation of renal replacement therapy. The Schwartz formula [5] and more rarely the Counahan-Barratt equation [6] are used in children. The Modifica-

tion of Diet in Renal Disease (MDRD) equation [7] and the Cockcroft-Gault formula [8] are used in adults. Unfortunately, these methods are rarely performed when measuring RRF in patients on dialysis, due to the elimination of creatinine by dialysis.

The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guidelines advocate measuring RRF by calculating the mean 24-hour urine creatinine level and urea clearance scaled on a patient's body surface area and expressed as ml/min/1.73 m<sup>2</sup> or l/week/1.73 m<sup>2</sup> for both PD and HD patients. The time of collecting 24-hour urine is crucial; from PD patients who are in stable condition, 24-hour urine can be collected on a random day, but from HD patients, some clinicians advocate collecting urine in the entire interdialytic interval because of these patients' hemodynamic instability [9].

Since accurately quantifying RRF from urine is arduous, there is a clinical need to develop alternative methods of assessing RRF based on serum testing. Recently, middle-sized molecules such as cystatin C [10, 11],  $\beta_2$ -microglobulin [12], and C-terminal agrin fragment [13], which are resistant to being eliminated by regular dialysis, have been reported by many groups as indicators of RRF [14–18]. More recently, serum bicarbonate [19], *p*-cresyl sulfate and indoxyl sulfate [20], and uric acid [21] have also been claimed to be predictors of RRF. However, the accuracy and reliability of these methods are controversial, and more clinical work is needed to verify them. In addition, exogenous markers such as iohexol, inulin, iothalamate, and EDTA are reported in references but rarely used in practice, because their use is labor intensive and time consuming [22–24].

### Benefits from RRF for PD or HD Patients

Both PD and HD are effective therapeutic options for patients with ESRD. Despite the improvement in techniques for dialysis, patients on PD or HD experience suboptimal outcomes. Due to the fact that loss of RRF is associated with left ventricular hypertrophy, uncontrolled hypertension, and increased erythropoietin requirements [25–28], many studies suggest that RRF is an extremely important determinant of mortality and morbidity in patients on either PD or HD [27, 29].

More than 300,000 patients are treated with PD worldwide. RRF declines over time in PD patients, which contributes to the overall health and well-being of patients. In the CANUSA (Canada-USA Peritoneal Dialysis)

study, a 12% lower risk of death was observed with each increase in estimated GFR of 5 liters/week/1.73 m<sup>2</sup>. Similar results are reported by the groups of Diaz-Buxo and Rocco, as well as many other groups. Numerous studies have demonstrated that RRF – but not peritoneal solute clearance or peritoneal ultrafiltration volume – was correlated with improved quality of life, reduced inflammation, and survival in PD patients. Furthermore, anemia, blood pressure, hypervolemia, left ventricular hypertrophy, inflammation, malnutrition, mineral and bone metabolism, and phosphorus control are all reported to be associated with RRF in PD patients [28, 30–33]. Preserving RRF offers multiple benefits to patients undergoing PD, including easier management of uremic toxicity and hypervolemia, better control of several complications of chronic kidney disease (CKD), less stringent dietary restrictions, and improved quality of life [1, 28, 34, 35].

RRF is a powerful predictor of survival in PD patients, and similar evidence is emerging for HD patients [2, 29, 36, 37]. Unfortunately, RRF is difficult to assess and was measured in less than 5% of HD patients [38]. In a US single-center study of 114 prevalent HD patients, the presence of any urine output (>100 ml/day) was associated with a 65% lower risk of death during the subsequent 2-year period [2]. Among 740 incident participants in the NECOSAD, a 56% lower mortality was noted for each increase of 1 per week in renal urea Kt/V during a median follow-up of 1.7 years [36]. Wong et al. [16] showed that 1 ml/min of residual renal urea clearance resulted in greater survival benefits than 1 ml/min of HD urea clearance, which may be ascribed to greater removal of middle-sized molecules and improved volume control by native kidneys [29]. Obi et al. [39] reported that a decline in RRF during the first year of dialysis had a graded association with all-cause mortality among incident HD patients. Most of the HD centers start patients on thrice-weekly HD without consideration of RRF. Recently, emerging evidence has suggested that RRF may be better preserved by initiating less frequent and shorter dialysis sessions rather than standard HD [40].

### Risk Factors for and Management of RRF in PD or HD Patients

The primary goals for nephrologists managing patients with ESRD are to lower mortality and improve the life quality. In dialyzed patients, preservation of RRF is associated with better survival, lower morbidity, and greater quality of life [41, 42]. When dialysis is initiated,

management of RRF remains extremely important. Original renal diseases, the dialysis modality, dialysis biocompatibility, catheter-related infections, medication, obesity, infection, cardiovascular events, as well as some uncontrollable factors including ethnicity, age, and gender are all critical influences on RRF [38, 43–51].

#### *Original Renal Diseases and Comorbidity*

The underlying causes of renal disease often have an important impact on CKD progression. Iest et al. [52] reported that the decline in RRF was more rapid in diabetic nephropathy than tubulointerstitial diseases. However, this observation was not confirmed by Moist et al. [38] from the University of Western Ontario. Recently, one report showed that the annual rate of decline in RRF was  $3.8 \pm 2.5$ ,  $2.5 \pm 4.8$ , and  $1.9 \pm 3.6$  for patients with cystic kidney disease, diabetic nephropathy, and glomerulonephritis, respectively [53]. Another group from Hong Kong reported that patients with proteinuric kidney diseases lost RRF faster than the others [28, 43].

Except for original renal diseases which influence RRF, comorbidity may also contribute to the decline in RRF. Cardiovascular diseases including renal artery stenosis and chronic heart failure, obesity, and hyperuricemia all are risk factors with regard to preservation of RRF [28, 54–56].

#### *Time of Initiating Dialysis*

The time of initiating dialysis for ESRD patients varies greatly around the world. It was once considered that the earlier dialysis was started, the better the life condition and expectancy achieved. However, a single randomized controlled trial, the Initiating Dialysis Early and Late (IDEAL) study, demonstrated that earlier dialysis initiation (at an estimated creatinine clearance of 10–14 ml/min) did not reduce mortality compared to later initiation (estimated creatinine clearance of 5–7 ml/min) [57]. Therefore, it cannot be predicted exactly when it is best to initiate dialysis with regard to the rate of decline in RRF.

#### *Dialysis Techniques*

The decline in RRF is reported to be as diverse as 0.18–0.33 ml/min/month in HD patients and 0.05–0.30 ml/min/month in PD patients during the first year of dialysis. It has been concluded that HD patients lose RRF more rapidly than PD patients [43, 58–61], who have better hemodynamic stability [62–64]. A single-center experience showed a survival advantage for 35 patients initiating PD therapy and transferring to HD therapy for PD-associat-

ed complications compared to a matched cohort of 64 incident HD-only patients [65]. These results suggest that use of PD as an initial dialysis modality represents a promising strategy for dialysis patients to maximize the early benefits from PD [25].

For PD patients, a difference in RRF decline between the continuous ambulatory form (CAPD) and intermittent ambulatory PD (APD) has been reported. Although Hiroshige et al. [66] and Hufnagel et al. [67] reported a more rapid decline in RRF among patients on APD, several other small trials found no difference between the two modalities [68]. More recently, registry data from the NECOSAD showed a higher risk with APD, particularly in the first year of treatment [69]. The high glucose dialysate and pressure instability in APD therapy are the two major causes leading to earlier loss of RRF [59, 70]. Despite this, the incidence of peritonitis may increase the rate of decline in RRF [71]. It is to be noted that the effect of aminoglycoside (AG) antibiotic treatment for peritonitis on RRF is not clear.

Traditional PD solutions are rich in glucose degradation products (GDPs), which have been demonstrated to be associated with higher serum levels of advanced glycation end products and progressive renal injury [72]. Modifying the peritoneal dialysate by raising pH, reducing glucose, and using non-lactate fluids as a buffer was thought to lessen the adverse effects of conventional PD solutions. This concept is supported by the Euro-Balance Trial, where a neutral-pH, low-GDP lactate solution showed better preservation of RRF than the traditional PD solution [73]. Results from Kim et al. [74] confirmed these findings. In their study, a total of 91 PD patients were included, and the results showed that the residual GFR declined less in those dialyzed with neutral-pH, low-GDP solution than in those dialyzed with the conventional dialysate. However, the beneficial effects on RRF were mixed in a greater number of later studies and trials [75–78]. Yohanna et al. [79] systematically reviewed 11 trials in which 643 patients were included. They reported that the use of a neutral-pH, low-GDP solution resulted in better preserved RRF after various study periods. No significant difference was found in peritoneal ultrafiltration or dialysate-to-plasma creatinine ratio. The conclusion is that the use of a neutral-pH, low-GDP solution results in better preservation of RRF. However, whether the biocompatible solutions can benefit the long-term clinical outcomes of patients cannot be predicted at present [79–81].

The metabolites of icodextrin are high-molecular-weight molecules which may increase plasma osmotic

pressure and preserve the plasma volume and renal perfusion [82]. Icodextrin 7.5% is a dialysis solution containing an isoosmolar glucose polymer with greater ultrafiltration capacity than the 22.7 g/l glucose dialysate [83], and it is typically used for the long day dwell period with APD or the nighttime dwell for CAPD patients. Chang et al. [84] conducted a multicenter, prospective, randomized controlled open-label trial and found that icodextrin solution preserves the residual urine volume better than glucose solution. However, Davies et al. [83] found a contrary effect, and some other studies showed no effect at all [85–88].

In HD, repeated exposure of blood to the dialysis membrane is harmful to RRF [54]. Many studies have shown that the biocompatible polysulfone dialysis membranes used in HD slow the decline in RRF [89, 90]. In a prospective randomized study of cellulose versus high-flux polysulfone dialyzers, the rate of RRF loss was reduced in the latter group. One prospective case-control study reported that the biocompatible polysulfone group had a slower rate of decline in creatinine clearance and urine volume than the cellulose membrane group over the first 3 months, which persisted over the next 12 months [56]. However, these results were not replicated in a smaller but prospective and randomized study by Caramelo et al. (see the comment on this study by Schiffli [91]). The benefits from the biocompatible membrane for RRF are mainly due to the attenuation of inflammatory insults during HD [62, 63, 92]. Compared with CAPD patients, McKane et al. [93] showed there was no difference as to the rate of decline in RRF in HD patients using the polysulfone membrane. The effect of the use of ultrapure water in dialysis on RRF is controversial [93, 94]. Therefore, more large randomized controlled trials are needed to further evaluate the effect of biocompatible membranes and ultrapure dialysis fluid on RRF.

Ischemic insults during HD sessions may cause a rapid decline in RRF [58, 60, 61]. Studies have shown that patients initiated with twice-weekly HD experienced better preservation of RRF [95, 96]. More than thrice-weekly HD and extended-length HD during a short follow-up did not improve clinical outcome compared to conventional HD and resulted in a greater number of vascular access procedures (very-low-quality evidence) [97]. More importantly, frequent nocturnal HD can accelerate the decline in RRF, which may be related to a greater tendency towards hypotension and/or increased inflammation associated with prolonged extracorporeal exposure [98, 99]. Hwang et al. [100] enrolled 685 patients from a prospective, multicenter observational cohort including pa-

tients with RRF undergoing twice-weekly HD or thrice-weekly HD and patients without RRF undergoing thrice-weekly HD. Patients with RRF undergoing twice-weekly HD had an increased risk of mortality compared with thrice-weekly HD. Given that the dialysis regimens obviously vary in different areas, it cannot be conclusively decided whether infrequent or incremental HD initiation is better for RRF preservation or not.

#### *Dietary Intervention*

Generally, increased protein intake may increase both glomerular filtration and renal tubular acid excretion and, as a consequence, promote renal injury in patients. Since variable amounts of protein are lost during dialysis, the recommended amount of dietary protein for adult dialysis patients is ~1.2 g/kg body weight of proteins per day, as opposed to nondialysis patients with a GFR <30 ml/min/1.73 m<sup>2</sup>, where 0.6–0.75 g/kg is suggested. Dietary protein restriction (0.58 g/kg/day vs. a normal dietary protein intake of 1.3 g/kg/day), as reported by Klahr et al. [101] in an MDRD study, slows the progression of CKD. Consistent with the fact that nutritional status plays an important role in preserving RRF in both HD and PD patients [3, 102, 103], in a study of 60 incident PD patients who were randomized to protein intakes of 0.6–0.8 g/kg, 0.6–0.8 g/kg + keto acids, and a high-protein diet of 1.0–1.2 g/kg, over 12 months the group receiving 0.6–0.8 g/kg + keto acids did not experience any decline in RRF compared to those in the other groups [104]. However, low protein is often linked to low energy intake and consequently causes malnutrition. An MDRD study showed that a very-low-protein diet + keto acid supplementation (protein intake of 0.28 g/kg/day and keto acids at 0.28 g/kg/day) did not reduce the progression in patients with CKD stages 4–5 and was associated with increased mortality, which may be partly ascribed to poor nutrition [105]. Further investigation is required to clarify the optimal protein intake for the preservation of RRF and clinical outcomes in patients on PD or HD.

#### *Renin-Angiotensin-Aldosterone System Blockade and Blood Pressure Control*

In patients with CKD, use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has been proved to be able to slow the progression of CKD (stages 1–5) via reducing systemic and glomerular pressure, attenuation of inflammation, as well as many other mechanisms [106–114].

For PD patients, a large retrospective study showed that ACEI has a protective effect on RRF [115]. The mean

decline in residual GFR and the probability of anuria over 12 months in an ACEI group were smaller than those in a control group [116]. Similarly, RRF had improved after ARB administration, and was even higher at 6 months than prior to ARB treatment, suggesting that some patients regained RRF after an acute decline. However, there were also some opposite findings [59, 117, 118]. A study comprising 452 incident PD patients by Kolesnyk et al. [117] did not find any benefit with regard to RRF in patients who were treated with ACEIs/ARBs at dialysis initiation. Recently, Zhang et al. [119] systemically reviewed the effect of ACEI and ARB in preserving RRF in PD patients, and found that blocking the renin-angiotensin-aldosterone system (RAAS) with ACEI or ARB may halt the decline in RRF but that there was no effect on proteinuria in PD patients. A recent report by Turner [120] suggests that clinicians should avoid the impulse to stop RAAS inhibitors because of their role in delaying or preventing modality failure in patients on PD.

Since HD patients are usually dialyzed 3 times a week and only a small part of them need antihypertensive medications, there are few reports of the effects of RAAS blockade on RRF in HD patients. Recently, some investigators reported that the initial HD therapy affected the effect of RAAS blockade on RRF. Xydakis et al. [121] showed in a 1-year randomized controlled open-label study of 42 HD patients that ACEI treatment (with enalapril) was associated with a significantly greater preservation of residual GFR and urine volume, while in another randomized, placebo-controlled study, ARB therapy (with irbesartan) did not achieve any beneficial results [122]. Since blockage of the renin-angiotensin system may increase the risk of intradialytic hypotensive episodes, which possibly causes ischemia-induced kidney damage, additional studies are required to test these medications in HD patients.

Moist et al. [38] showed that the use of calcium antagonists could reduce the risk of RRF loss in adults treated with CAPD. More recently, Roszkowska-Blaim et al. [123] found no effect of calcium antagonists,  $\beta$ -blockers, and loop diuretics on absolute and relative RRF loss in children treated with chronic PD.

#### *Volume Status and Diuretics*

Hypovolemia has been widely accepted as a threat to the preservation of RRF. Observational data from the NECOSAD suggests that the episode of volume depletion is an independent risk factor for RRF loss [124]. However, studies using bioimpedance techniques led to an increased extracellular fluid volume in PD patients [125],

which was closely linked to a rapid decline in RRF [126]. At present there are opposing opinions regarding the best fluid management for patients requiring dialysis. On the one hand, if one aims at minimizing extracellular fluid volume overload and consequent hypertension and left ventricular hypertrophy, it may be detrimental to RRF [124]. On the other hand, keeping patients intentionally 'wet' to maintain RRF may have extracardiac effects [127, 128].

Apart from restricting salt and fluid intake, diuretics play an important role in volume control. In a prospective, open-label, randomized trial, 61 incident CAPD patients were randomly assigned to furosemide treatment (250 mg/day) and no furosemide treatment [129]. The furosemide group had a clinically significantly better preservation of the urine volume at 6 months and 1 year, but there was no effect on the rate of decline in RRF. In contrast, in a DOPPS report including 16,420 HD and PD patients, diuretics were associated with lower interdialytic weight gain, less hyperkalemia, and better preservation of RRF [130].

Tolvaptan, a vasopressin antagonist that used to be utilized for congestive heart failure [131], would be a novel agent for preserving RRF through volume control. In a pilot study, a total of 24 patients after PD initiation were divided into two groups: those who received tolvaptan treatment and those who did not. As a result, the urine volume, renal Kt/V, and renal creatinine clearance levels were consistently decreased in the control group, whereas these parameters were maintained in the tolvaptan group at 6 and 12 months [132].

#### *Nephrotoxic Insults*

For patients on PD, AGs are used to treat peritonitis. It was reported that AG use may be associated with decline in RRF; however, this observation was not replicated by other groups [133–135]. Radiocontrast agents are another group of nephrotoxins which cause a decline in RRF in patients on dialysis [136]. N-acetylcysteine (NAC) is widely used before contrast exposure. In a multicenter, randomized clinical trial to investigate the efficacy and safety of oral NAC for preserving RRF in patients undergoing HD, the GFR in patients receiving NAC was improved, whereas in the control group, a decline of 1.0 ml/min/1.73 m<sup>2</sup> was recorded. After 3 months, the 24-hour urine volume in the NAC group was an average of 137 ml higher than that in the control group. The conclusion is that 3-month treatment with NAC appears to be effective in preserving renal function in patients undergoing HD [137]. Although very little evidence exists on the promo-

tion of a decline in RRF by nephrotoxic regimens, avoidance of such nephrotoxic agents such as nonsteroidal anti-inflammatory drugs, AGs, and radiocontrast agents is still strongly recommended for patients on dialysis, especially PD.

## Conclusion

Preservation of RRF is associated with better survival and less mortality in both PD and HD patients. Therefore, preserving RRF is now considered to be one of the pri-

mary goals in managing patients with ESRD. Risk factors such as comorbid diseases, volume dysregulation, and many others predict a decline in RRF. Although ACEI and ARB treatments exhibit beneficial effects on the preservation of RRF, a better understanding and further investigation into RRF in patients on both PD and HD are required to further improve patient care.

## Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

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