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.

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.
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$^2$ or l/week/1.73 m$^2$ 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], β₂-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$^2$. 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 uncontrolled 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 ± 2.5, 2.5 ± 4.8, and 1.9 ± 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-associated 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...
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 Schiff [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 patients 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 regimen 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 m², 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 protein intake in the ACEI group was 1.3 g/kg/day, while the usual intake in the nondiabetic population is 0.8 g/kg/day. 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.
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 enal-april) 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 blockade 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, β-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].

**Nephrototoxic 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 m² 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 primary 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.

References

1 van der Wal WM, Noordzij M, Dekker FW, Boeschoten EW, Krediet RT, Korevaar JC, Geskus RB; Netherlands Cooperative Study on the Adequacy of Dialysis Study Group (NECOSAD): Full loss of residual renal function causes higher mortality in dialysis patients; findings from a marginal structural model. Nephrol Dial Transplant 2011;26:2978–2983.

2 Shemin D, Bostom AG, Laliberty P, Dworkin LD; Residual renal function and mortality risk in hemodialysis patients. Am J Kidney Dis 2001;38:85–90.

3 Suda T, Hiroshige K, Ohta T, Watanabe Y, Iwamoto M, Kanegae K, Ohntani A, Nakashima Y; The contribution of residual renal function to overall nutritional status in chronic haemodialysis patients. Nephrol Dial Transplant 2000;15:396–401.

4 Termorshuizen F, Korevaar JC, Dekker FW, van Manen JG, Boeschoten EW, Krediet RT; NECOSAD Study Group: The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. Am J Kidney Dis 2003;41:1293–1302.

5 Schwartz GJ, Haycock GB, Edelmann CM Jr, Spitzer A; A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 1976;58:259–263.

6 Counahan R, Chantler C, Ghazali S, Kirkwood B, Rose F, Barratt TM; Estimation of glomerular filtration rate from plasma creatinine concentration in children. Arch Dis Child 1976;51:875–878.

7 Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D; A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–470.

8 Cockcroft DW, Gault MH; Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.

9 Kjaergaard KD, Jensen JD, Peters CD, Jespersen B; Preserving residual renal function in dialysis patients: an update on evidence to assist clinical decision making. NDT Plus 2011;4:225–230.

10 Hoek FJ, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT; Estimation of residual glomerular filtration rate in dialysis patients from the plasma cystatin c level. Nephrol Dial Transplant 2007;22:1633–1638.

11 Ahmadi F, Rahmani F, Lessan-Pezezhiki M, Azmandian J; Utility of cystatin C-derived equations for evaluation of residual renal function in peritoneal dialysis patients. Ren Fail 2015;37:50–56.

12 Bargman JM, Thorpe KE, Churchill DN; CANUSA Peritoneal Dialysis Study Group: Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. J Am Soc Nephrol 2001;12:2158–2162.

13 Steubl D, Hettwer S, Dahinden P, Luppa P, Rondak IC, Regenbogen C, StockKF, Renders L, Heemann U, Roos M: C-terminal agrin fragment (CAF) as a serum biomarker for residual renal function in peritoneal dialysis patients. Int Urol Nephrol 2015;47:391–396.

14 Zhong H, Zhang W, Qin M, Gou Z, Feng P; Validation of cystatin C-based equations for evaluating residual renal function in patients on continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 2016, Epub ahead of print.

15 Davenport A; Measuring residual renal function in dialysis patients: can we dispense with 24-hour urine collections? Kidney Int 2016;89:978–980.

16 Wong J, Sridharan S, Berdeprado J, Vilar E, Viljoen A, Wellsted D, Farrington K; Predicting residual kidney function in hemodialysis patients using serum β-trace protein and β2-microglobulin. Kidney Int 2016;89:1090–1098.

17 Shafl T, Michels WM, Levey AS, Inker LA, Dekker FW, Krediet RT, Hoekstra T, Schwartz GJ, Eckfeldt JH, Coreij J; Estimating residual kidney function in dialysis patients without urine collection. Kidney Int 2016;89:1099–1110.

18 Vilar E, Boltiador C, Wong J, Viljoen A, Machado A, Uthayakumar A, Farrington K; Plasma levels of middle molecules to estimate residual kidney function in haemodialysis without urine collection. PLoS One 2015;10:e0143813.

19 Chang TI, Kang EW, Kim HW, Ryu GW, Park CH, Park JT, Yoo TH, Shin SK, Kang SW, Choi KH, Han DS, Han SH; Low serum bicarbonate predicts residual renal function loss in peritoneal dialysis patients. Medicine (Baltimore) 2015;94:e1276.

20 Yuaene L, Meijers BK, Vanreentrergthum Y, Eve neuropel P; Serum concentrations of p-cresyl sulfate and indoxyl sulfate, but not inflammatory markers, increase in incident peritoneal dialysis patients in parallel with loss of residual renal function. Perit Dial Int 2015;35:492.

21 Hsieh YP, Yang Y, Chang CC, Kor CT, Wen YK, Chiu PF, Lin CC; U-shaped relationship between uric acid and residual renal function decline in continuous ambulatory peritoneal dialysis patients. Nephrology (Carlton) 2015, Epub ahead of print.

22 Swan SK, Halstenson CE, Kasiike BL, Collins AJ; Determination of residual renal function with iohexol clearance in hemodialysis patients. Kidney Int 1996;49:232–235.

23 Sterner G, Frenny B, Månsson S, Ohlsson A, Prütz KG, Almén T; Assessing residual renal function and efficiency of hemodialysis – an application for urographic contrast media. Nephron 2000;85:324–333.
The importance of residual kidney function for patients on dialysis: a critical review. Am J Kidney Dis 2009;53:1068–1081.

Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, Barre PE: Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int 1995;47:186–192.

Shafi T, Jaar BG, Plantinga LC, Fink NE, Lopez-Menchero R, Miguel A, Garcia-Ramon JH, Parekh RS, Powe NR, Coresh J: Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. Am J Kidney Dis 1966; 7: 60–68.

Lewis D, Reith C, Baigent C, Landray MJ; Studer WG, Tomson C, Agodoa L, Tesar V, Levin A, Wong J, Vilar E, Davenport A, Farrington K: Preservation of residual kidney function in patients with planned initiation of peritoneal dialysis. Perit Dial Int 2011;31:313–319.

Menon MK, Naimark DM, Bargman JM, Vas SI, Oreopoulos DG: Long-term blood pressure control in a cohort of peritoneal dialysis patients and its association with residual renal function. Nephrol Dial Transplant 2001;16: 2207–2213.

Menon MK, Naimark DM, Bargman JM, Vas SI, Oreopoulos DG: Long-term blood pressure control in a cohort of peritoneal dialysis patients and its association with residual renal function. Nephrol Dial Transplant 2001;16: 2207–2213.

Feldman HI, Matsuo S, Raicu S, Kes P, Hamzić-Mehmedbašić A: The effect of preserved residual renal function on left ventricular structure in non-urinary peritoneal dialysis patients. Kidney Blood Press Res 2015;40: 500–508.

Koo HM, Doh FM, Kim CH, Lee MJ, Kim EJ, Han JH, Han JS, Ryu DR, Oh HJ, Park JT, Han SH, Yoo TH, Kang SW: Changes in echocardiographic parameters according to the rate of residual renal function decline in incident peritoneal dialysis patients. Medicine (Baltimore) 2015;94:e427.

Bammens B, Evenepoel P, Verbeke K, Vanrenterghem Y: Removal of middle molecules and protein-bound solutes by peritoneal dialysis and relation with uremic symptoms. Kidney Int 2003;64:2238–2243.

Pérez Fontán M, Remón Rodríguez C, Borrás Sans M, Sánchez Álvarez E, da Cunha Naveira M, Quiroz Ganga P, López-Cañiño B, Rodríguez Suárez C, Rodríguez-Carmona A: Compared decline of residual kidney function in patients treated with automated peritoneal dialysis and continuous ambulatory peritoneal dialysis: a multicenter study. Nephron Clin Pract 2014;128:352–360.

Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT; NECOSAD Study Group: Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. J Am Soc Nephrol 2004; 15:1061–1070.

Mathew AT, Fishbane S, Obi Y, Kalantar-Zadeh K: Preservation of residual kidney function in hemodialysis patients: revising an old concept. Kidney Int 2016;90:262–271.

Moist LM, Port FK, Orzl SM, Young EW, Ostbye T, Wolfe RA, Hulbert-Shearon T, Jones CA, Bloembergen WE: Predictors of loss of residual renal function among new dialysis patients. J Am Soc Nephrol 2000;11: 556–564.

Obi Y, Rhee CM, Mathew AT, Shah G, Streja E, Brunelli SM, Kovesdy CP, Mehrotra R, Kalantar-Zadeh K: Residual kidney function decline and mortality in incident hemodialysis patients. J Am Soc Nephrol 2016, Epub ahead of print.

Wong J, Vilar E, Davenport A, Farrington K: Incremental haemodialysis. Nephrol Dial Transplant 2015;30:1639–1648.

Wang AY, Lai KN: The importance of residual renal function in dialysis patients. Kidney Int 2003;64:2238–2243.

Herget-Rosenthal S, von Ostrowski M, Kribben A: Definition and risk factors of rapidly declining residual renal function in peritoneal dialysis: an observational study. Kidney Blood Press Res 2012;35:233–241.

Shin SK, Noh H, Kang SW, Seo BJ, Lee IH, Song HY, Choi KH, Ha SK, Lee HY, Han DS: Risk factors influencing the decline of residual renal function in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 1999;19:138–142.

Coronel P, Pérez-Flores I, Calvo N, Martinez-Villasescua M, Cigarrán S: Impact of cardio-vascular events on residual renal function during the first year of peritoneal dialysis. Perit Dial Int 2007;27:454–456.

Kang JS, Jang HR, Lee JE, Park YJ, Rhee H, Seong EY, Kwak IS, Kim YJ, Lee DW, Lee SB, Song SH: The bacterial colonization in tunnelled cuffed dialysis catheter and its effects on residual renal function in incident hemodialysis patients. Clin Exp Nephrol 2016;20:294–301.

Lui SL, Zhi D, Cheng SW, Ng F, Hui PC, Yip T, Lo WK: Effects of Astragalus membranaceus-based Chinese Medicine formulae on residual renal function in patients on peritoneal dialysis. Perit Dial Int 2015;35:595–597.

Iest CG, Vanholder RC, Ringoir SM: Loss of residual renal function in patients on regular haemodialysis. Int J Artif Organs 1989;12: 159–164.

Haynes R, Staplin N, Emberson J, Herrington WG, Tomson C, Agodoa L, Tesar V, Levin A, Lewis D, Reith C, Baigent C, Landray MJ; SHARP Collaborative Group: Evaluating the contribution of the cause of kidney disease to prognosis in CKD: results from the Study of Heart and Renal Protection (SHARP). Am J Kidney Dis 2014;64:40–48.

Patel N, Hu SI: Preserving residual renal function in dialysis: what we know. Semin Dial 2015;28:250–258.

Park J, Ahmadi SF, Streja E, Molnar MZ, Flegel KM, Gillen D, Kovesdy CP, Kalantar-Zadeh K: Obesity paradox in end-stage kidney disease patients. Prog Cardiovasc Dis 2014;56:415–425.

Kazmi WH, Gilbertson DT, Obrador GT, Guo H, Pereira BJ, Collins AJ, Kausz AT: Effect of comorbidity on the increased mortality associated with early initiation of dialysis. Am J Kidney Dis 2005;46:887–896.

Johnson DW, Wong MG, Cooper BA, Branelly P, Bullone I, Collins JF, Craig JC, Fraenkel MB, Harris A, Kesselhurst J, Li J, Lutton G, Pilmore A, Tiller DJ, Harris DC, Pollock CA: Effect of timing of dialysis commencement on clinical outcomes of patients with planned initiation of peritoneal dialysis in the IDEAL trial. Perit Dial Int 2012;32:595–604.
63 Pertosa G, Grandaliano G, Gesualdo L, Schode Fijter CW, ter Wee PM, Donker AJ: The decrease in residual renal function in new peritoneal dialysis patients. Perit Dial Int 2003;23:276–283.

64 Misra M, Vonstone JC, Moore HL, Prowant B, Nolph KD: Effect of cause and time of dropout on the residual GFR: a comparative analysis of the decline of GFR on dialysis. Kidney Int 2001;59:754–763.

65 Tam P: Peritoneal dialysis and preservation of residual renal function. Perit Dial Int 2009;29(suppl 2):S108–S110.

66 Hakim RM: Clinical implications of biocompatibility in blood purification membranes. Nephrol Dial Transplant 2000;15(suppl 2):2–16.

67 Kim S, Oh J, Kim S, Chung W, Ahn C, Kim SG, Oh KH: Benefits of biocompatible PD fluid for preservation of residual renal function in incident CAPD patients: a 1-year study. Nephrol Dial Transplant 2009;24:2899–2908.

68 Bajo MA, Pérez-Lozano ML, Alar-Vizcaino P, del Peso G, Castro MJ, Gonzalez-Mateo G, Fernández-Perpén A, Aguilara A, Sánchez-Villanueva R, Sánchez-Tomero JA, López-Cabrera M, Peter ME, Passlick-Deetjen J, Selgas R: Low-GDP peritoneal dialysis fluid (‘balance’) has less impact in vitro and ex vivo on epithelial-to-mesenchymal transition (EMT) of mesothelial cells than a standard fluid. Nephrol Dial Transplant 2011;26:282–291.

69 Krediet RT: Peritoneal dialysis: from bench to bedside. Clin Kidney J 2013;6:568–577.

70 Cho KH, Do JY, Park JW, Yoon KW, Kim YL: The effect of low-GDP solution on ultrafiltration and solute transport in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 2013;33:382–390.

71 Pajek J, Kveder R, Bren A, Gucsek A, Bucar M, Skobnera A, Waniweski J, Lindholm B: Short-term effects of bicarbonate/lactate-buffered and conventional lactate-buffered dialysis solutions on peritoneal ultrafiltration: a comparative crossover study. Nephrol Dial Transplant 2009;24:1617–1625.

72 Yohanna S, Alkatheeri AM, Bramble SK, McCormick B, Iansavitchous A, Blake PG, Jain AK: Effect of neutral-pH, low-glucose degradation product peritoneal dialysis solutions on residual renal function, urine volume, and ultrafiltration: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2015;10:1380–1388.

73 Kooman JP, Cornelis T, van der Sande FM, Leunissen KM: Is the effect of low-GDP solutions on residual renal function mediated by fluid state? An enigmatic question which still needs to be solved. Perit Dial Int 2016;36:239–242.

74 Wang J, Zhu N, Yuan W: Effect of neutral pH and low-glucose degradation product containing peritoneal dialysis solution on residual renal function in peritoneal dialysis patients: a meta-analysis. Nephron 2015;129:155–163.

75 Breborowicz A, Pawlaczuk K, Polubinska A, Górna K, Wieslander A, Carlsson O, Tam P, Wu G: Effect of peritoneal dialysis on renal morphology and function. Nephrol Dial Transplant 2006;21:3539–3544.

76 Williams JD, Topley N, Craig KJ, Mackenzie RK, Pischetsrieder M, Lage C, Passlick-Deetjen J; Euro Balance Trial Group: The Euro-Balance Trial: the effect of a new biocompatible peritoneal dialysis fluid (balance) on the peritoneal membrane. Kidney Int 2004;66:408–418.

77 Hartmann J, Fricke H, Schiffl H: Icodextrin increases technique survival and low-glucose degradation product-containing peritoneal dialysis solution in patients treated with automated peritoneal dialysis. Am J Kidney Dis 2002;39:862–871.

78 Wolfson M, Piraino B, Hamburger RJ, Morton AR; Icodextrin Study Group: A randomized controlled trial to evaluate the efficacy and safety of icodextrin in peritoneal dialysis. Am J Kidney Dis 2002:40:1055–1065.

79 Takatori Y, Akagi S, Sugiyama H, Inoue J, Kojo S, Morinaga H, Nakao K, Wada J, Makino H: Icodextrin increases technical efficiency in peritoneal dialysis patients with diabetic nephropathy by improving body fluid management: a randomized controlled trial. Clin J Am Soc Nephrol 2011;6:1337–1344.

80 Hartmann J, Fricke H, Schiff H: Biocompatible membranes preserve residual renal function in patients undergoing regular hemodialysis. Am J Nephrol 1997;30:366–373.

81 McCarthy TF, Jenson BM, Squillace DP, Williams AW: Improved preservation of residual renal function in chronic hemodialysis patients using polysulfone dialyzers. Am J Kidney Dis 1997;29:576–583.

82 Schiff H: Choice of dialysis membrane does not influence the outcome of residual renal function in haemodialysis patients. Nephrol Dial Transplant 1995;10:911–912.
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Kidney Dis 2016;2:187–196
DOI:10.1159/000449029

92 Smeyby LC, Widereoe TE, Balstad T, Jarstad S: Biocompatibility aspects of cellophane, cellulosic acetate, polycrylonitrile, polysulfone and polycarbonate hemodialyzers. Blood Purif 1986;1(4):93–101.

93 McKane W, Chandra SM, Tatatsall JF, Greenwood RN, Farrington K: Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. Kidney Int 2002;61:256–265.

94 Schiffl H, Lang SM, Fischer R: Ultrafiltration behavior, fluid loss and residual renal function in new dialysis patients. Nephrol Dial Transplant 2002;17:1814–1818.

95 Kalantar-Zadeh K, Unruh M, Zager PG, Smeby LC, Widerøe TE, Balstad T, Jørstad S: Dialysis initiation, duration and frequency of hemodialysis associates with improvement of chronic renal disease. Modification of Diet in Renal Disease (MDRD) Study. Am J Kidney Dis 2009;53:208–217.

96 Zhang M, Wang M, Li H, Yu P, Yuan L, Hao C, Chen J, Kalantar-Zadeh K: Association of initial twice-weekly hemodialysis treatment with preservation of residual kidney function in ESRD patients. Am J Nephrol 2014;40:140–150.

97 Slinin Y, Greer N, Ishani A, MacDonald R, Olson C, Rutks I, Wilt TJ: Timing of dialysis initiation, duration and frequency of hemodialysis sessions, and membrane flux: a systematic review for a KDOQI clinical practice guideline. Am J Kidney Dis 2015;66:823–836.

98 Thomson BK, Momcic B, Huang SH, Chan CT, Uruquhart BL, Skanes AC, Krahn AD, Klein GJ, Lindsay RM: Frequent nocturnal hemodialysis associates with improvement of prolonged QTC intervals. Nephron Clin Pract 2013;123:74–82.

99 Daugirdas JT, Greene T, Rocco MV, Kaysen GA, Depner TA, Levin NW, Chertow GM, Ornt DB, Raimann JG, Larive B, Kliger AS; FHN Trial Group: Effect of frequent hemodialysis on residual kidney function. Kidney Int 2013;83:949–958.

100 Hwang HS, Hong YA, Yoon HE, Chang YK, Kim SY, Kim YO, Jin DC, Kim SH, Kim YL, Kim YS, Kang SW, Kim NH, Yang CW: Comparison of clinical outcome between twice-weekly and thrice-weekly hemodialysis in patients with residual kidney function. Medicine (Baltimore) 2016;95:e2767.

101 Klahr S, Levey AS, Beck GJ, Caggiula AW, Kaysen GA, Depner TA, Levin NW, Chertow GM, Ornt DB, Raimann JG, Larive B, Kliger AS; FHN Trial Group: Effect of frequent hemodialysis on residual kidney function. Kidney Int 2013;83:949–958.

102 Wang AW, Sea MM, Ip R, Law MC, Chow KM, Lui SF, Li PK, Woo J: Independent effects of residual renal function and dialysis adequacy on actual dietary protein, calorie, and other nutrient intake in patients on continuous ambulatory peritoneal dialysis. J Am Soc Nephrol 2001;12:2450–2457.

103 Szeto CC, Lai KN, Wong TY, Law MC, Leung CB, Yu AW, Li PK: Independent effects of residual renal function and dialysis adequacy on nutritional status and patient outcome in continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1999;34:1056–1064.

104 Jiang N, Qian J, Sun W, Lin A, Cao L, Wang Q, Ni Z, Wan Y, Linholm B, Axesslon J, Yao Q: Better preservation of residual renal function in peritoneal dialysis patients treated with a low-protein diet supplemented with keto acids: a prospective, randomized trial. Nephrol Dial Transplant 2009;24:2551–2558.

105 Menon V, Kopple JD, Wang X, Beck GJ, Collins AJ, Kusek JW, Greene T, Levey AS, Sarnak MJ: Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. Am J Kidney Dis 2009;53:208–217.

106 Ruggenenti P, Perna A, Gherardi G, Garini G, Zoccali C, Salvadori M, Scolari F, Schena FP, Remuzzi G: Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. Lancet 1999;354:359–364.

107 O’Brien RC, Cooper ME, Jerums G, Doyle AE: The effects of perindopril and triple therapy in a normotensive model of diabetic nephropathy. Diabetes 1993;42:604–609.

108 Briet M, Schirren EL: Aldosterone: effects on the kidney and cardiovascular system. Nat Rev Nephrol 2010;6:261–273.

109 Navis G, de Jong P, Donker AJ, van der Hem G, Kliger AS; NEOCSAD Study Group: Predictors of loss of residual renal function in peritoneal dialysis patients. Perit Dial Int 2011;31:53–59.

110 Reyes-Marin FA, Calzada C, Ballesteros A, Amato D: Comparative study of enalapril vs losartan on residual renal function preservation in automated peritoneal dialysis. A randomized controlled study. Rev Invest Clin 2012;64:315–321.

111 Karihaloo A: Anti-fibrosis therapy and dialysis in peritoneal dialysis patients treated with chronic peritoneal dialysis. Adv dialysis treatment 2016;2:187–196.

112 Turner JM: We avoid RAAS inhibitors in PD patients with residual renal function. Semin Dial 2016;29:265–267.

113 Gross O, Schulze-Lohoff E, Epple J, Böker S, Palm S, Christen M, Kostakis K, Stylianou P, Petrasik I, Ergini A, Voskarides K, Dafnis E: Residual renal function in hemodialysis patients: the role of angiotensin-converting enzyme inhibitors in its preservation. ISRN Nephrol 2012;2013:184527.

114 Janssen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT; NECOSAD Study Group: Predictors of the rate of decline of residual renal function in incident dialysis patients. Kidney Int 2002;62:1046–1053.
125 Papakrivopoulou E, Booth J, Pinney J, Davensport A: Comparison of volume status in asymptomatic haemodialysis and peritoneal dialysis outpatients. Nephron Extra 2012;2:48–54.
126 Kim JK, Kim YS, Song YR, Kim HJ, Kim SG, Moon SI: Excessive weight gain during the first year of peritoneal dialysis is associated with inflammation, diabetes mellitus, and a rapid decrease in residual renal function. PLoS One 2015;10:e0139033.
127 Cheng LT, Chen W, Tang W, Wang T: Residual renal function and volume control in peritoneal dialysis patients. Nephron Clin Pract 2006;104:c47–c54.
128 Davies SJ: Preserving residual renal function in peritoneal dialysis: volume or biocompatibility? Nephrol Dial Transplant 2009;24:2620–2622.
129 Medcalf JF, Harris KP, Walls J: Role of diuretics in the preservation of residual renal function in patients on continuous ambulatory peritoneal dialysis. Kidney Int 2001;59:1128–1133.
130 Bragg-Gresham JL, Fissell RB, Mason NA, Bailie GR, Gillespie BW, Wizemann V, Cruz JM, Akiba T, Kurokawa K, Ramirez S, Young EW: Diuretic use, residual renal function, and mortality among hemodialysis patients in the Dialysis Outcomes and Practice Pattern Study (DOPPS). Am J Kidney Dis 2007;49:426–431.
131 Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, Udelson JE, Zannad F, Cook T, Ouyang J, Zimmer C, Orlandi C: Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) Investigators: Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007;297:1332–1343.
132 Hiramatsu T, Hobo A, Hayasaki T, Kahu K, Furuta S: A pilot study examining the effects of tolvaptan on residual renal function in peritoneal dialysis for diabetics. Perit Dial Int 2015;35:552–558.
133 Shemin D, Maaz D, St Pierre D, Kahn SL, Chazan JA: Effect of aminoglycoside use on residual renal function in peritoneal dialysis patients. Am J Kidney Dis 1999;34:14–20.
134 Baker RJ, Senior H, Clemenger M, Brown EA: Empirical aminoglycosides for peritonitis do not affect residual renal function. Am J Kidney Dis 2003;41:670–675.
135 Lui SL, Cheng SW, Ng F, Ng SY, Wan KM, Yip T, Tse KC, Lam MF, Lai KN, Lo WK: Cefazolin plus netilmicin versus cefazolin plus ceftazidime for treating CAPD peritonitis: effect on residual renal function. Kidney Int 2005;68:2375–2380.
136 Weisbord SD, Bernardini J, Mor MK, Hartwig KC, Nicoletta PJ, Palevsky PM, Piraino B: The effect of coronary angiography on residual renal function in patients on peritoneal dialysis. Clin Cardiol 2006;29:494–497.
137 Ahmadi F, Abbazadeh M, Razeghi E, Maziar S, Khoidaki SD, Najafi MT, Lessan-Pezeshki M: Effectiveness of N-acetylcysteine for preserving residual renal function in patients undergoing maintenance hemodialysis: multicenter randomized clinical trial. Clin Exp Nephrol 2016, Epub ahead of print.