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Preservation of Residual Kidney Function in Hemodialysis Patients: Reviving an Old Concept for Contemporary Practice

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Abstract

Residual kidney function (RKF) may confer a variety of benefits to patients on maintenance dialysis. RKF provides continuous clearance of middle molecules and protein-bound solutes. Whereas the definition of RKF is variable across studies, inter-dialytic urine volume may emerge as a pragmatic alternative to more cumbersome calculations. RKF preservation is associated with better patient outcomes including survival and quality of life, and is a clinical parameter and research focus in peritoneal dialysis (PD). We propose practical considerations to preserve RKF especially in newly transitioned (incident) hemodialysis (HD) patients: (1) Periodic monitoring of RKF in HD patients through urine volume and including residual urea clearance with dialysis adequacy and outcome markers such as anemia, fluid gains, minerals and electrolytes, nutritional status and quality of life. (2) Avoidance of Nephrotoxic agents such as radiocontrast dye, non-steroidals, and aminoglycosides (3) More rigorous hypertension control and minimizing intradialytic hypotensive episodes. (4) Individualizing the initial dialysis prescription with consideration to an incremental/infrequent approach to HD initiation (e.g. twice-weekly) or PD, and (5) Considering lower protein diet especially on non-dialysis days. Since RKF appears associated with better patient outcomes, it requires more clinical and research focus in the care of HD and PD patients.

Index Words

residual kidney function; end-stage renal disease; incremental hemodialysis

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Introduction and Background

Residual kidney function (RKF) may confer many benefits to patients with end-stage renal disease on maintenance dialysis including associations with better patient survival and health-related quality of life. These benefits are thought to be related to better volume control and greater solute clearance. RKF contributes to overall clearance, and can account for significant differences in dialysis requirements. Studies have reported the predictors of RKF, and its impact on patient outcomes and dialysis dosing in peritoneal dialysis (PD). However, despite nearly half of all patients in the U.S initiating dialysis with an estimated glomerular filtration rate of >10 mL/min/1.73m^2, of which 90% are treated by hemodialysis[1, 2], there are few studies examining the associations of RKF on outcomes in the hemodialysis (HD) patient.

The majority of hemodialysis patients initiate dialysis with a relatively intense thrice weekly dialysis regimen of 3 to 4 hours per session, with little individualization of prescription based on RKF or other patient factors. Why is there a paucity of literature on the impact of RKF in hemodialysis? One reason may relate to the difficulties of accurate inter-dialytic urine collection from HD patients, with less than 5% of HD patients having measured RKF[3]. Another potential reason is the long-held notion that RKF declines rapidly in HD compared to PD patients leading to a nihilistic view on RKF preservation. Most studies have observed a faster RKF decline in conventional (thrice-weekly) HD compared to PD attributed to intra-dialytic hypotension and intermittent abrupt volume depletion[3-6]. However, the use of online hemodiafiltration, high-flux biocompatible membranes and ultrapure water for dialysate may decrease the risk of declining RKF in hemodialysis,[7-10] and an incremental HD initiation with infrequent (once to twice-weekly) HD upon transition to dialysis may preserve RKF longer (see below).

In this review article, we first outline the importance and advantages of RKF in dialysis. We provide a narrative overview of the known predictors of loss of RKF and summarize methods to measure RKF in hemodialysis. Finally, we provide clinical considerations to preserve RKF in hemodialysis patients.

The Importance of Residual Kidney Function

The benefits of RKF are hypothesized to be mediated by improved control of volume, minerals and electrolytes, less inflammation and greater clearance of protein-bound solutes and middle molecules. Hemodialysis is applied only intermittently, while native kidney function is continuous. For this reason, even a small amount of residual function reduces plasma levels of solutes cleared poorly by hemodialysis, such as low molecular weight proteins like β_2-microglobulin[11-13] and protein-bound solutes[14]. A re-analysis of the Canada-USA peritoneal dialysis study (CANUSA), shed light on the important contribution of RKF to patient survival in PD patients[15]. In this multi-center prospective cohort study, 601 peritoneal dialysis patients were studied, and a 12% decrease in relative risk of death was observed for each 5 L/week per 1.73m^2 increment in estimated glomerular filtration rate (eGFR). A 36% decrease in the relative risk of death was observed for each 250mL increment of urine volume. Neither peritoneal creatinine clearance nor net peritoneal

ultrafiltration was associated with patient survival, and the study concluded that peritoneal and native renal clearance cannotassume equivalence. RKF as an independent predictor of survival in patients treated with PD has been reported in several additional prospective, multi-center cohort studies[16-18], and a secondary analysis of a randomized controlled trial[19]. Given the observational nature of these studies, interpretation of results is limited by lack of a standard RKF definition, and confounding due to covariates such as co-morbid disease, age, and general patient health status.

In hemodialysis patients, understanding of the important contribution of RKF on patient survival is emerging, although studies remain limited. Shemin et al reported a prospective single center observational study of 114 hemodialysis patients where RKF was associated with a lower risk for mortality (OR 0.44; 95% CI 0.24 to 0.81, p=0.008) [20]. In the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD), 740 incident HD patients were followed prospectively and data of RKF was collected. For each 1-unit increase in renal Kt/V urea, the study reported a 66% decrease in relative risk of mortality[5]. A prospective study of 1,191 patients initiating HD and 609 patients initiating PD found that a full loss of RKF was associated with a 1.5 times higher risk of mortality than patient with RKF, with no significant difference in the effect of RKF between PD and HD patients [21]. Finally, in a recent longitudinal cohort of 5,686 patients initiating maintenance HD, higher RKF at one year after initiating dialysis was associated with better patient survival, with a linear association between mortality and both renal urea clearance and urine volume[22]. This observation may extend the findings of the CANUSA study to HD patients. It should be noted that in these observational studies, the effect of RKF on better outcomes may be residually confounded by patient co-morbidities. In addition, patients with higher levels of residual renal function may be earlier in the disease process of kidney failure, resulting in observed “improved” survival through a lead-time bias.

The survival benefit associated with RKF in both HD and PD patients is likely closely tied to advantages in fluid management. In both HD and PD, chronically volume overloaded dialysis patients are at high risk for hypertension, left ventricular hypertrophy and congestive heart failure[23-25]. In peritoneal dialysis patients, RKF and urine volume maintenance reduces exposure to dextrose, preserves the peritoneal membrane and reduces hyperglycemia and weight gain. In HD patients, RKF allows for lower ultrafiltration volumes during each dialysis session, resulting in less intra-dialytic hypotension and myocardial stunning [26, 27]. Recurrent myocardial stunning with hemodialysis has been shown to predict chronic heart failure, cardiovascular events and mortality[28, 29].

In addition to advantages in survival and fluid management, RKF has a number of other associations in both HD and PD patients. In the CHOICE study (Choices for Healthy Outcomes in Caring for End-Stage Renal Disease), 734 incident hemodialysis patients in the United States were followed prospectively for one year[30]. The self-reported presence of greater than 250mL per day urine output was associated with a better quality of life (as measured by a validated questionnaire) and lower C-reactive protein and interleukin-6 levels compared to those with less than 250 mL per day of urine output. Additional studies have also demonstrated associations between RKF and reduced inflammatory markers [31, 32]. While the exact pathophysiologic mechanism is unclear, the kidney may play a role in

handling of cytokines, with reduced clearance of pro-inflammatory cytokines such as tumor necrosis factor[33] and IL-1[34] observed in nephrectomized rats. RKF has also been associated with better quality of life[35] and this may be related to less fluid and dietary restrictions in patients with RKF on dialysis. RKF is also associated with better ESRD patient nutritional status [36] and control of phosphorus and anemia [3018, 37, 38]. For example, in the CHOICE study, patients with urine output had 12,000 units/week lower EPO requirements when compared to patients with no urine output. This large difference in EPO requirement may be a finding specific to this United States cohort in the late 1990's, as mean weekly EPO doses were lower in Europe and Japan[39] and such high doses are not currently used in the United States. While RKF appears to associate with better patient outcomes, it remains unclear if it is protective or simply indicates better overall health status. Further prospective studies of the predictors of RKF decline, and the effect of RKF on patient outcomes is required to understand if preservation of RKF can modify patient outcomes.

Prospective studies have also assessed the association of higher dialyzer urea clearance on patient survival, both with and without the presence of RKF. In the National Cooperative Dialysis study, patients with creatinine clearances < 3mL/min had benefits when maintaining lower blood urea nitrogen concentrations[40]. In a subgroup analysis of the HEMO study, patients with dialysis vintage of 3.7 years or longer(most of whom were presumed to have little RKF), benefitted from receipt of the high flux dialysis membrane[41]. In the Frequent Hemodialysis Network (FHN) trial, patients were randomly assigned to frequent in-center hemodialysis or conventional thrice weekly hemodialysis. Two thirds of patients in the study were anuric, and frequent HD patients had a significantly higher weekly standard Kt/V compared to conventional HD patients[42, 43]. Frequent HD patients had a lower composite outcome of patient mortality and left ventricular hypertrophy compared to conventional thrice weekly HD patients. In contrast, in the FHN Nocturnal trial, approximately half of patients had urine volume >500 mL per day, and a higher mortality was observed in the frequent nocturnal HD group[44-46]. Overall,a higher dialyzer urea clearance and removal of uremic toxins may be of benefit in patients with little or no RKF. However, this gain may be attenuated in patients with significant RKF[47].

Predictors of Loss of Residual Kidney Function

The identification of factors that affect RKF in advanced chronic kidney disease has been well established in both the literature and clinical practice. The Kidney Disease Outcomes Quality Initiative (KDOQI) has published guidelines establishing several risk factors for decline in GFR in patients with chronic kidney disease, such as age, race, blood pressure and proteinuria[48]. However, less is known about the recognition and study of these factors upon transition to dialysis therapy. Patient demographics, co-morbid disease and characteristics of dialysis treatment have all been studied, but much of the existing literature is limited by small sample size, retrospective study designs, and lack of standardized definition of RKF (see Table 1 for more details).

Although generally non-modifiable in nature, an understanding of the patient demographics and co-morbid disease that predict decline in residual kidney function could provide prognostic value. In an analysis of USRDS data, a study of 2211 incident dialysis patients

observed female gender and non-white race to be associated with loss of RKF at 1 year (defined as <200mL/24 hours of urine) [3]. However, another report found male race predicted faster RKF decline[49]. Presence of diabetes, poorly controlled hypertension, left ventricular hypertrophy, coronary artery disease and congestive heart failure have all been associated with a faster decline in RKF in dialysis patients [3, 5, 49-53]. Presence of proteinuria upon initiation of dialysis has also been associated with a faster rate of RKF decline [5] and this association was found to occur after the first 6 months of dialysis initiation.

Whereas many of the same factors contribute to the loss of GFR in all incident dialysis patients, there are unique features of PD versus HD which impact RKF. In a review article by Nongnuch et al, PD patients with diabetes were noted to have a faster rate of decline of RKF compared to non-diabetics[54]. In PD patients, automated PD has been associated with a more rapid decline in RKF as compared to continuous ambulatory PD in some retrospective studies[55, 56], but not in a more recent prospective study [5]. Recurrent episodes of peritonitis also contribute to a more rapid decline in RKF in incident PD patients[53]. While the use of biocompatible PD solution was associated with patient survival and preservation of RKF in observational studies[57, 58], a recent randomized controlled trial of 118 incident PD patients found no difference in RKF as measured by 24 hour urine volume after 1 year of follow-up [59].

In HD patients, intra-dialytic hypotension during the first three months of dialysis is associated with RKF decline, as calculated from the mean urea and creatinine clearance from inter-dialytic urine collections[5]. Several treatment-related factors including intra-dialytic hypotension, bio-incompatible dialysis membrane and higher frequency of treatments are associated with RKF decline. While frequent dialysis may reduce intra-dialytic ultrafiltration volumes and myocardial stunning, Daugirdas et al[46] recently reported that in the Frequent Hemodialysis Network Daily and Nocturnal Trials, comparing the effects of assignment to six compared with three-times-per-week hemodialysis on follow-up RKF, frequent nocturnal hemodialysis appears to promote a more rapid loss of RKF. In both trials, baseline RKF was inversely correlated with number of years since onset of ESRD. In the frequent dialysis group, urine volume had declined to zero in 52% and 67% of patients at months 4 and 12, respectively, compared with 18% and 36% in controls.

In another study by Zhang et al [60] in a dialysis center in Shanghai, the investigators examined 30 HD patients who initiated with twice-weekly HD for 6 months or longer and 55 patients who were started and maintained on thrice-weekly HD treatment. Whereas the clinical outcomes were similar between the two groups, the percent of patients with RKF loss was significantly lower in the twice-weekly compared with the thrice-weekly group, especially during the first year of HD initiation. The multivariate analysis showed that male gender, HD frequency, URR and intradialytic hypotension episode were associated with RKF loss. The odds ratio of RKF loss for each additional HD treatment per week was 7.2 suggesting that thrice-weekly HD during the first year of dialysis therapy was association with 7-times higher likelihood of loss of RKF than twice weekly HD. Finally, cellulose acetate or cuprophane dialysis membranes (compared to bio-compatible membranes) are predictive of loss of RKF in some [6, 61, 62], but not all[3, 63] studies.

Measurement of Residual Kidney Function

In PD, the measurement of RKF is well established. Clinical management of PD patients is informed by studies and guidelines which have historically defined peritoneal dialysis adequacy using total solute clearance (native kidney + dialysis). In PD patients, a 24-hour urine collection can be used to measure RKF, since GFR remains stable and blood urea and creatinine concentrations generally do not vary. Since PD is a continuous dialysis modality, residual kidney function estimates can be easily added into the overall estimation of solute clearance. In HD patients, however, there is no validated methodology to measure RKF. Studies and guidelines of adequacy have historically included only solute clearance achieved by hemodialysis. Native kidney GFR may vary over the dialysis cycle [64], and thus accurate estimation of residual kidney function requires collection of urine for the entire inter-dialytic period, usually 44 hours or 2 days, although the conventional 24 hr collection may be pursued as well.

The measurement of RKF in dialysis has benefits to consider in both patients and physicians. Although a complete assessment of dialysis adequacy comprises more than just urea clearance, accurate calculation of total solute removal aids physicians in the assessment of dialysis adequacy and dosing of dialysis. For hemodialysis patients with significant RKF, there is a potential for reduction in the duration and frequency of dialysis with an associated better quality of life[65]. For peritoneal dialysis patients, the burden of dialysis can be reduced by adjusting volumes of dialysate and frequency of exchanges in patients with significant RKF. If urea-based methods of RKF are used, inclusion into urea kinetic modelling provides a more accurate assessment of dietary adequacy, including urea generation rate and normalized protein catabolic rate (nPCR), also known as normalized protein nitrogen appearance.

There are several methods by which to measure RKF in dialysis, including estimated GFR (eGFR), residual renal urea clearance (KRU), urine volume, and newer biomarkers. The classic “ideal” molecule to measure glomerular filtration rate (GFR) has the hall mark characteristics of constant generation, free filtration, no metabolization and no secretion or reabsorption. Urea and creatinine are commonly used to estimate GFR. However, creatinine is secreted in the tubule and residual creatinine clearance overestimates the true GFR, especially at low GFR levels. Conversely, urea is passively reabsorbed in the tubule leading to residual urea clearance underestimating the true GFR. KRU can be used as a surrogate to estimate dietary protein intake, and is the preferred RKF measurement method of KDOQI [66]and the International Society of Peritoneal Dialysis[67]. The recommendation for use of KRU to measure RKF is founded on the intrinsic underestimation of renal urea clearance and inherent protection provided to the patient when dosing dialysis. KRU can be calculated by:

$$KRU(mL/min)=\frac{\text{urinary urea (mg/dL)} \times \text{urinary volume (mL)}}{\text{collected time (min)} \times [0.9 \times \text{serum urea (mg/dL)}]}$$

Since serum levels of urea fluctuate in hemodialysis, the Daugirdas approach[68] uses pre-dialysis urea concentrations. It should be noted that KRU (or combined urea and creatinine

clearance) while practical and widely utilized, measures only small-molecule solute clearance, while residual kidney function also contributes to convective clearance of middle-molecules.

Another proposed method of RKF measurement is eGFR, as recommended by the European Best Practice Guidelines for hemodialysis[69]. The eGFR can be calculated by taking the average of the urea and creatinine clearance (GFR = [$C_{creatinine}$ + C_{urea}]/2). Urine volume has been used as a measure of RKF in several observational studies and does correlate with patient outcomes at a population or study cohort level[3, 15, 30]. Urine output alone should not be used on its own to guide clinical management, however when urine output is paired with other important markers of dialysis adequacy such as limited fluid gains, appropriate nutritional status, and controlled phosphate and potassium status, it could be considered a pragmatic alternative to the more cumbersome KRU measurements[70]. Newer markers such as serum cystatin C [71, 72], β_2-microglobulin[73] and B-trace protein[73, 74] have been used to develop estimating equations for RKF with better accuracy and precision than the conventional Modification of Diet in Renal Disease (MDRD) formula or equations using urea and creatinine[73], whereas the accuracy of Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for RKF is not well studied but likely not much better. However, kinetic studies of cystatin C suggest that at low levels of kidney function it may not be a good marker of GFR[75]. Recent studies found that pre-dialysis β_2-microglobulin levels may provide superior estimates of RKF than cystatin C[73, 76]. Studies to refine of the use of blood-based kidney function markers in dialysis patients are needed, as this would prevent the need for urine collections and facilitate more widespread use of incremental dialysis. At present, since more conventional markers such as urea are used to measure dialysis clearance, it is unclear how to incorporate these new biomarkers for residual renal clearance into clinical practice. Iohexol[77] has also been studied to measure RKF. While this method conveniently uses a blood sample taken pre-dialysis with no urine collection, it requires infusing an exogenous substance in the blood and has technical limitations when measuring very low GFRs. Radioisotopes can also be used to measure GFR, and urinary clearance methods may be preferable to plasma with advancing degrees of kidney disease[78].

The measurement of RKF in hemodialysis patients may provide important benefits. However, care must be taken when including RKF into the overall calculation of solute clearance. Dialyzer urea clearance is confounded by dietary protein intake, physical activity and body composition, and cannot be directly combined with measurements of residual kidney function. RKF contributes little to no clearance during the relatively short period of time that hemodialysis occurs. The effects of RKF are most prominent in the long inter-dialytic period with reduction in the pre-dialysis serum urea nitrogen level. KRU provides more efficient clearance than hemodialysis since it is continuous in nature; thus simply adding time-averaged KRU to time-averaged dialysis urea clearance will underestimate the effect of KRU. The European Best Practice Guidelines (EBPG) recommend using eGFR, with Casino and Lopez's kinetic estimate of time-averaged clearance [79] to relate renal and dialysis clearance through the 'equivalent renal urea clearance' (EKR). EKR represents the total continuous equivalent of urea clearance (dialysis + native kidneys), from which RKF can be subtracted. An important caveat to the EBPG guideline recommendation is that EKR is based on KRU and not eGFR. EKR has also been questioned because it does not fully

account for the more efficient nature of continuous renal clearance, since other more toxic solutes are removed to a greater extent by continuous than intermittent clearance[80]. Depner et al describe a method to combine residual kidney function and dialyzer clearance, by converting residual kidney function to an equivalent intermittent clearance akin to dialysis Kt/V[81]. KDOQI guidelines recommend using KRU to measure RKF, and the 'standard clearance'(stdK), developed by Leypoldt et al, to relate renal and dialysis clearance[82]. The stdK is "the continuous clearance that maintains the blood urea nitrogen at a constant value equal to the average pre-dialysis urea nitrogen" [66]. Since both stdK and KRU are continuous, they can be added to determine a patient's total urea clearance. It should be noted that since Std Kt/V is modeled by using mean pre-dialysis urea rather than time-averaged urea, KRU should be downsized to approximately 70% when added to std Kt/V delivered by hemodialysis[83]As a fixed volume model, stdK has come under some scrutiny as it underestimates stdKt/V in the setting of fluid removal. A newer equation has been developed by Daugirdas et al for $stdK_dt/V$ that includes a correction factor for the contribution of fluid removal.

Use of RKF to guide incremental dialysis dosing

Traditionally, dosing of peritoneal dialysis has been guided by successive measures of total clearance (KRU and dialysis clearance), with incremental increases in peritoneal dialysis dosing as RKF falls over time. A recent review by Wong et al outlines the current lack of adjustment of initial hemodialysis prescription by most HD units. The current paradigm for hemodialysis initiation differs from peritoneal dialysis initiation, with most patients in the United States initiating a standardized thrice-weekly regimen, and few or no measurements of RKF to guide initial dialysis dosing[84]. While this uniform approach remains the standard of care, the initiation of an abrupt thrice-weekly hemodialysis in patients with significant RKF has come under recent scrutiny. Twice-weekly hemodialysis is associated with slower decline of RKF [85] and better patient quality of life [86]. Twice-weekly hemodialysis may also prolong longevity of arterio-venous fistulae, and curb financial costs. Furthermore, there are still important uncertainties about the optimal GFR level for HD initiation[15, 87]. Understanding of the possible associations of twice-weekly hemodialysis initiation on RKF preservation and patient outcomes requires further prospective studies[47].

Current guidelines for hemodialysis adequacy recommend an incremental approach to hemodialysis. The minimum session single pool Kt/V can be reduced in patients with KRU of > 2mL/min/1.73m^2, but twice weekly HD is not recommended unless KRU> 3 mL/min/1/73m^2. This recommendation is based on the ability to attain a spKt/V of >1.2, and a weekly stdKt/V of > 2.2 with conventional hemodialysis treatment times of 4 hour or less[66]. See Table 2 for additional details. Serial measurements of native kidney clearance are important in this setting, to avoid under-dosing of hemodialysis as RKF is lost over time. KRU can be cumbersome to calculate, especially when required serially to monitor RKF and appropriately dose dialysis. Consideration can be given to a more practical approach of monitoring of total urine volume combined with other important markers of adequacy such as anemia and fluid gains [70]. Clinical worsening of any of these adequacy parameters could guide a change in dialysis frequency from two to three times per week. Patients initiating an incremental approach to hemodialysis should be regularly counselled to avoid the

psychological difficulties associated with increasing dialysis frequency and/or time as RKF declines. Finally, economic issues should be considered, and use of incremental dialysis may vary by country based on bundled versus sessional reimbursement[88]. To gain wide acceptance of incremental or individual hemodialysis among health care providers, periodical evaluation of residual kidney function may need to be reimbursed to the extent which compensate the burden of urine collection and evaluation. Whereas novel and pragmatic approach to the transition to hemodialysis, incremental hemodialysis requires further study to understand the association with patient outcomes, and is the topic of a number of on-going trials.

Considerations to Preserve RKF in Hemodialysis Patients

RKF contributes to overall clearance in both PD and HD patients, with associated better patient survival and quality of life. Clinical management and research efforts should consider a focus on strategies to preserve residual kidney function. Based on a critical literature review and our group's expertise, we suggest the following considerations for the preservation of RKF in all patients newly initiated on hemodialysis . See also Table 3 and Figure 1.

1. *Measurement and Monitoring*: Using KRU and/or total urine output, RKF should be measured in all patients initiating hemodialysis, and then monthly to quarterly in patients with significant RKF of > 0.5L/day, or if clinical decision making will be affected by RKF (i.e contrast-enhanced CT scans, incremental dialysis dosing). We proposed significant RKF as defined by >0.5 L/day of urine output (on non-dialysis days), based on recent expert recommendations[70]. While urine volume should not replace formal KRU calculations, when combined with other markers of dialysis adequacy such as anemia, fluid gains, phosphorus/potassium control, nutritional status and health-related quality of life, it could provide a practical and simplified assessment of dialysis adequacy. RKF should be monitored every month or at least quarterly in the first year of hemodialysis for selected patients with significant RKF, and subsequently every quarter to 6 months until the urine volume is < 100mL/day or KRU is <2mL/min/1.73m^2.

2. *Avoid or minimize nephrotoxic events*: Similar to the approach in patients with chronic kidney disease, the avoidance of radiocontrast, non-steroidal anti-inflammatory drugs and aminoglycosides are important considerations to preserve RKF in ESRD patients on dialysis. A recent study compared forty-two patients with ESRD on hemodialysis with urine volume > 0.6 L/day who received iodixanol to an age and urine volume-matched cohort of ESRD hemodialysis patients with no contrast exposure. At three months after contrast exposure there was a decline in urine volume in both groups with no statistically significant difference [89]. Similar findings have been noted in PD patients, where only a temporary decrease in RKF was noted after contrast exposure[90]. These studies minimized contrast load, used low-osmolar contrast agents and implemented hydration protocols as appropriate, and demonstrate that with

appropriate preventative strategies the long term effect of radiocontrast on RKF may be minimized.

It is reasonable to assume that the benefits conferred by RKF from a native kidney would be similar to those from a failing renal allograft, suggesting a prolonged low dose immunosuppression regimen in such patients. One study of PD patients used decision analysis to support a patient survival benefit which outweighed the risks of infection and malignancy from long term immunosuppression [91]. Such studies have not yet been conducted in HD patients, and further research in this area is needed.

3. *Control Blood Pressure and Avoid Intradialytic Hypotension*: Whereas intradialytic hypotensive episodes can cause ischemic insults to remnant kidneys and should be avoided or minimized (see below), chronic uncontrolled hypertension is a leading cause of ESRD. Acute worsening of hypertension in the period immediately preceding initiation of HD may lead to acute kidney injury. With initiation of dialysis and control of hypertension there is evidence to suggest some improvement in RKF, presumably through reversal of this acute component of kidney injury [92]. Use of angiotensin-converting enzyme (ACE) inhibition or angiotensin receptor blockade (ARB) is recommended as the agent of choice by some for control of hypertension in patients with substantial RKF. An observational study of incident USRDS dialysis patients observed an independent effect of ACE inhibition in lowering the risk of RKF loss, defined as urine volume < 200 mL (OR 0.68; $p<0.001$) [3]. A recent randomized controlled trial of 42 HD patients found that ACE inhibition therapy was associated with greater RKF preservation compared to control, with RKF defined as residual GFR and urine volume [93]. However, another observational study found no difference in use of ACE inhibitors on RKF, defined by residual creatinine clearance [9]. Given the different definitions of RKF utilized in each study, caution should be taken to avoid direct comparison. A recent randomized controlled trial comparing atenolol to lisinopril to control hypertension in hemodialysis patients reported higher risk of the composite endpoint of myocardial infarction, stroke and hospitalization for heart failure or cardiovascular death in the lisinopril group compared to the atenolol group [94]. While this evidence must be weighed carefully when prescribing antihypertensive agents in the general prevalent dialysis population, the subgroup of patients with significant RKF was not specifically examined. KDOQI guidelines currently recommend the agent of choice to control blood pressure as ACE inhibitor or ARB in patients with substantial RKF[66].

The use of diuretics increases sodium and water excretion and improves volume status in dialysis patients with RKF. Unlike the findings observed in PD patients with no observed benefit to RKF with diuretic use [95, 96], diuretic use in HD patients has been associated with maintenance of RKF. In an observational study from the Dialysis Outcomes and Practice Pattern Study (DOPPS), loop diuretic use was associated with lower interdialytic weight gain, lower odds of

hyperkalemia, twice the odds of retaining RKF and a 14% lower cardiac specific mortality [97].

Intra-dialytic hypotension contributes to RKF decline in HD patients, and should be avoided while managing hypertension. In a recent large prospective study, Jansen et al reported intra-dialytic hypotension requiring rescue fluid resuscitation as an independent predictor of RKF decline over a 12 month follow-up period[5]. Bedside management of intra-dialytic hypotension consists of increase in dialysate sodium concentration, reduction in dialysate temperature, pre-dialysis administration of alpha agonists such as midodrine, and patient counselling to reduce inter-dialytic weight gains through salt and fluid restriction. However, current clinical assessment of patient target weight remains crude and likely contributes to overly aggressive ultrafiltration and intra-dialytic hypotension. Several advanced methods of target weight assessments have been studied including biochemical markers such as atrial natriuretic peptide[98-100], cyclic guanidine monophosphate [101, 102], vena cava measurement[103], bioimpedance analysis[104], and blood volume monitoring[105]. However, these techniques require further development and validation before routine use.

4. *Adjust Hemodialysis Prescription:* Consideration should be given to an individualized approach to the initial hemodialysis prescription in all new ESRD patients, In patients with substantial RKF, initiation of a once to twice weekly HD regimen is associated with a slower decline of RKF[85] and better patient satisfaction[86]. Readjustment of the dialysis prescription, including increasing frequency to thrice weekly, should be guided by decline in RKF and other measures of dialysis adequacy. In patients who are amenable to self-care, a 'PD first' approach is advocated given the current observational data supporting the association of initial PD modality and preservation of RKF [3, 5, 106, 107]. Ultimately, an 'integrative care approach' may provide patients initiating on PD with a survival benefit, as demonstrated in a recent large retrospective analysis. PD patients who transferred to HD when PD-related problems (such as peritonitis or adequacy issues) arose had a higher survival than those maintained on PD [108]. The routine use of high-flux, biocompatible dialyzer membranes and ultrapure water for dialysate in HD patients is recommended, as these strategies are associated with preservation of RKF[7, 9, 109].

5. *Consider Low Protein Diet*: It is important to note that some historical and recent data suggest a low protein diet (0.6 to 0.7 g/kg/day) on non-dialysis days combined with infrequent HD (once to twice a week) may help prolong RKF preservation. Some studies have suggested combination of low to very low protein diet with essential amino-acids or keto-analogues[110, 111112]. If such dietary interventions are attempted, a regular to high protein diet (1.2 g/kg/day) may still be recommended during hemodialysis treatment days, given higher intradialytic catabolic rate and loss of amino-acids during hemodialysis therapy. Indeed high protein meals during hemodialysis treatment can be encouraged if there is no drop in blood pressure [113, 114] while low protein diet on non-dialysis days are maintained.

Conclusions

In maintenance dialysis patients, RKF provides effective and continuous clearance of both small and middle molecules, plays a role in metabolic homeostasis, nutritional status and cardiovascular health, and aids in fluid management. RKF is associated with better patient survival and health-related quality of life in maintenance dialysis patients, although these effects may be residually confounded by patient co-morbidities. Preservation of residual kidney function in HD patients requires a careful approach, including regular monitoring, avoidance of nephrotoxins, gentle control of blood pressure, and a personalized initial dialysis prescription including consideration of incremental hemodialysis. Whereas RKF is established in the management of PD patients, its role in the management and outcomes of HD patients requires more clinical and research focus.

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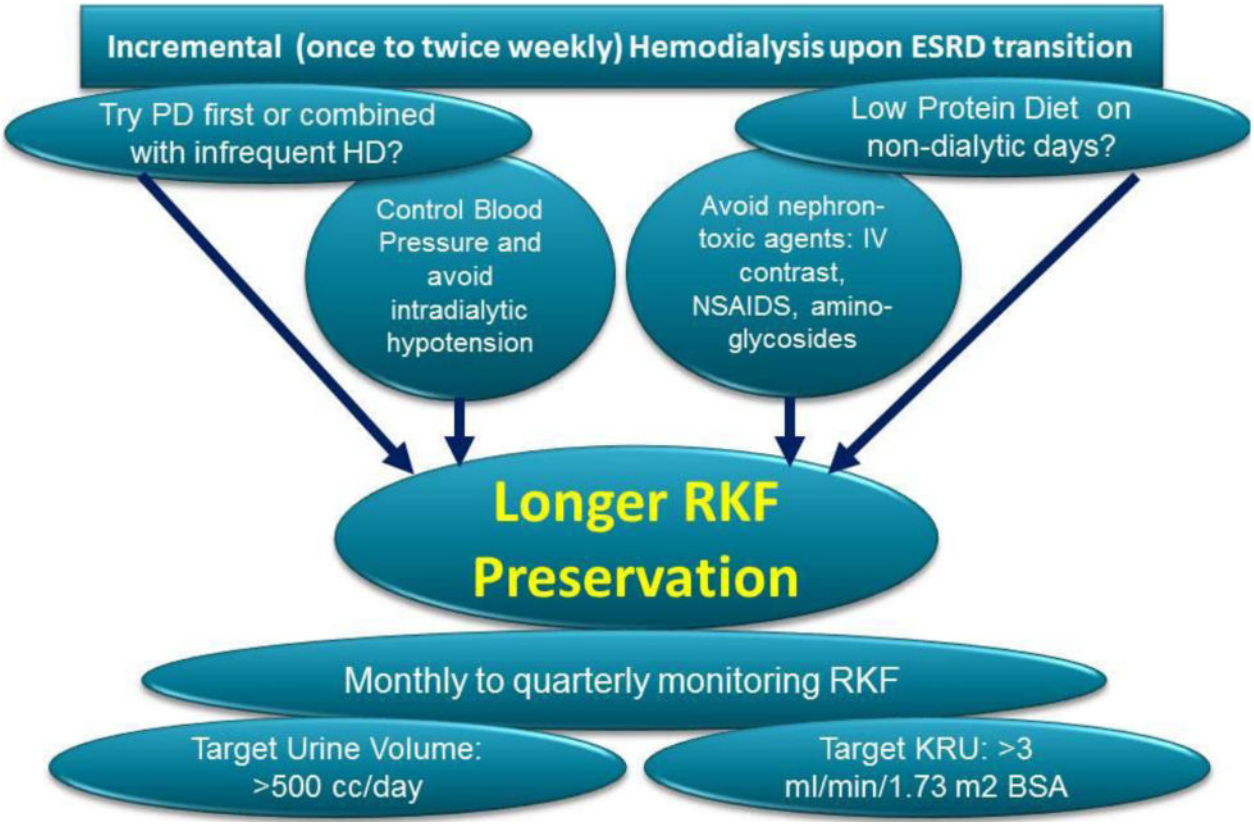

Figure 1.
Schematic of the Preservation of the RKF in Hemodialysis Patients.

Table 1

Predictors of Loss of Residual Kidney Function on Transition to Dialysis

Predictor	Reference	Effect on RKF	Definition of RKF
Demographics			
Increasing age	Moist 2000	−	UV < 200mL
Female sex	Moist 2000	−	UV < 200mL
Non-white race	Singhal 2000	+	GFR
	Zhang 2014	+	UV <200mL
	Moist 2000	−	UV < 200mL
Co-Morbid Disease			
Diabetes	Moist 2000	−	UV < 200mL
Hypertension	Johnson 2003	−	GFR
Left Ventricular Hypertrophy	Singhal 2000	−	GFR
Congestive Heart Failure	Johnson 2003	−	GFR
Proteinuria	Menon 2001	−	GFR
	Kim 2012	−	GFR
	Moist 2000	−	UV<200mL
	Jansen 2002	−	GFR
Hemodialysis Characteristics			
3 vs 2 times weekly	Lin 2009	−	UV and KCr
6 vs 3 times weekly	Zhang 2014	−	UV < 200mL
Intra-dialytic hypotension	Daugirdas 2013	−	UV, KRU, KCr
Bio-incompatible membrane	Jansen 2002	−	GFR
	Moist 2000	None	UV<200mL
	Zhang 2014	−	UV < 200mL
	Caramelo 1994	None	UV, KCr
	Lang 2001	−	KCr
	McCarthy 1997	−	KRU
	Hartmann 1997	−	UV, KCr

Abbreviations: UV, Urine Volume; GFR, glomerular filtration rate defined by mean of urea and creatinine clearances; KRU, residual urea clearance; KCr, residual creatinine clearance.

Table 2

Using standard clearance (stdKt/V[a]) to relate residual kidney and dialyzer clearance

KRU (mL/min)	KRU (mL/week)	Weekly stdKt/V[b]	Dialyzer stdKt/V[c]
1	10,080	0.25	1.95
2	20,160	0.50	1.70
3	30,240	0.75	1.45

[a] using the Daugirdas method of calculation[83]

[b] contributed by RKF, assuming V=40L

[c] required to obtain stdKt/V of 2.2

Abbreviations: RKF, Residual Kidney Function; UV, Urine Volume; KRU, residual urea clearance; NSAIDS, non-steroidal anti-inflammatories; COX-2, cyclo-oxygnase-2; RAAS, renin-angiotensin-aldosterone system; HD, hemodialysis; PD, peritoneal dialysis.

Table 3

Considerations for Preservation of Residual Kidney Function in Hemodialysis

1. Measure and Monitor RKF	• Measure KRU and/or inter-dialytic UV in all patients initiating hemodialysis • Target KRU > 3mL/min/1.73m^2 and UV> 0.6L/day • Monitor KRU and/or UV every month to every quarter in year 1, then every quarter to every 6 months, until UV <100 mL/day or KRU < 2mL/min/1.73m^2 • Measure and monitor other parameters of adequacy (anemia, fluid gains, phosphate/potassium control, nutritional status and health-related quality of life)
2. Avoid or minimize nephrotoxic events	• Radiocontrast dye • Aminoglycosides • NSAIDS and COX-2 inhibitors • Withdrawal of transplant immunosuppression
3. Control Blood Pressure and Avoid Intradialytic Hypotension	• Control Hypertension • Utilize RAAS blockade and loop diuretics
4. Adjust Hemodialysis Prescription	• Initial dialysis modality (2x weekly HD or PD first approach) • Re-evaluate dialysis dose if RKF or adequacy changes • High-flux, biocompatible dialyzer membranes • Ultrapure water for dialysate • Avoid intra-dialytic hypotension
5. Consider Low Protein Diet	• Low protein diet (0.6 to 0.7 g/kg/day) on non-dialysis and regular to high protein diet (1.2 g/kg/day) on hemodialysis days