

DISCLOSURES

J.S.D. owns stock in Biogen Inc. (Cambridge, MA).

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See related articles, "TWEAK-Fn14 Signaling Activates Myofibroblasts to Drive Progression of Fibrotic Kidney Disease," and "Stat3 Controls Tubulointerstitial Communication during CKD," on pages 3639–3652 and 3690–3705, respectively.

Preserving Residual Kidney Function in Hemodialysis Patients—Back in the Spotlight

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The importance of residual kidney function (RKF) is well established in peritoneal dialysis (PD). RKF has been shown to contribute to better solute clearance, uremic toxin removal,

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volume control, and control of phosphate and mineral metabolism and is associated with less anemia and inflammation. Patients on PD with substantial RKF have better dietary intake and nutrition status, less cardiac hypertrophy and dysfunction, and a lower degree of vascular calcification. Most importantly, RKF associates with better overall survival, cardiovascular outcomes, and quality of life.¹ Reanalysis of data from the Canada and United States Study showed that RKF but not PD dose predicted the overall survival of patients on PD, suggesting that the two components of clearance are not equivalent.²

The importance of RKF is also becoming increasingly recognized in the hemodialysis population. For example, over a 2-year follow-up period, Shemin *et al.*³ showed that every 1 ml/min per 1.73 m² higher baseline RKF reduced the adjusted risk of death by 56%. The Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study, including 734 patients on incident hemodialysis from 81 clinics in the United States, used self-reported urine output as an estimate of RKF and found that a higher rate of urine output at baseline was associated with better quality of life, lower inflammation, and lower erythropoietin use.⁴

Several studies have explored the effects of longitudinal changes of RKF or RKF at 1 year in relation to clinical outcomes of patients on hemodialysis. In the Netherlands Cooperative Study of Dialysis (NECOSAD), a complete loss of RKF was associated with a 50% increase in the adjusted risk of all-cause mortality compared with the risk in those still retaining some degree of RKF.⁵ In the CHOICE Study, self-reported urine output >250 ml/d at 1 year of follow-up but not at baseline was independently associated with a lower all-cause mortality rate,⁴ implying that a reduction in urine volume with time on dialysis may be of greater significance than urine volume at dialysis initiation in predicting a higher mortality in patients on hemodialysis. These findings are consistent with data on patients on PD reporting an association between more rapid loss of RKF and higher mortality.⁶

In this issue of the *Journal of the American Society of Nephrology*, Obi *et al.*⁷ add important information about patients on hemodialysis with respect to associations between hard outcomes and both RKF after 1 year of hemodialysis and changes in RKF over 1 year. In a longitudinal cohort of 6538 patients on incident hemodialysis, the amount of residual renal urea clearance (KRU) present after 1 year of dialysis was associated with survival. For example, compared with subjects with KRU of 3–6 ml/min per 1.73 m² at 1 year, those with KRU of 1.5–3 or <1.5 ml/min per 1.73 m² showed approximately 1.4- or 1.9-fold increases, respectively, in the risk of all-cause mortality. This analysis was done using a model adjusted for baseline KRU, demographic and clinical parameters (including comorbidities), single-pool Kt/V (spKt/V), body mass index, normalized protein catabolic rate, and nine biochemical variables.⁷

The rate of decline of KRU over 1 year was also associated with mortality in the study reported by Obi *et al.*⁷ Patients with more rapid annual declines in KRU had higher risks of all-cause mortality, and the association persisted after adjusting for a wide range of potential confounders and was present across a wide range of baseline KRU values. After adjusting for age, sex, race, ethnicity, comorbidities, and spKt/V, patients having a KRU decline rate of >6 or 3–6 ml/min per 1.73 m² per year had two- or 1.25-fold higher risk, respectively, of all-cause mortality compared with the reference group, in which the annual rate of KRU decline was 1.5 ml/min per 1.73 m². An association between a rapid decline in KRU (defined as >3 ml/min per 1.73 m² per year) and all-cause mortality was observed, even after adjusting for baseline age, sex, race, ethnicity, diabetes, presence or absence of baseline heart failure, hemoglobin, serum albumin, and phosphorus; these factors may confound the relationship between loss of RKF and adverse clinical outcomes.⁷

In their study, Obi *et al.*⁷ performed a sensitivity analysis, where they used urine volume per day as another index of RKF. Findings were quite similar to those analyzing RKF in terms of KRU. A more rapid annual decline in urine volume (defined as >600 ml/d per year) was associated with higher mortality risk, and having better preserved urine volume at 1 year was associated with better survival.

Of note, in the study by Obi *et al.*,⁷ 29% of the subjects with baseline RKF measurement were found to have either maintained or increased RKF after 1 year of hemodialysis. Whether the increase was genuine or caused by measurement error was uncertain, but these subjects seemed to have fewer comorbidities, including diabetes and heart failure, and were also found to have a higher spKt/V, higher values of serum albumin, and lower values for ultrafiltration rate during dialysis and for normalized protein catabolic rate. An increase in KRU during the observation period had a beneficial effect on outcomes. Patients with a 3-ml/min per 1.73 m² per year increase in KRU showed a 39% lower adjusted risk of all-cause mortality. The associations remained significant after controlling for baseline ultrafiltration rate and its annual change. Whether RKF may be affecting outcome *via* an effect on volume control and ultrafiltration rate or whether the outcomes effect is caused by enhanced removal of uremic solutes requires additional elucidation.

The study by Obi *et al.*⁷ has the strength of analyzing both baseline and 1-year KRU and urine volume data, thus reducing lead time bias that might otherwise have partially explained a better outcome associated with higher baseline RKF indices in some other reports. However, several important limitations of this study are worth noting. First, the study was observational and cannot prove causality. Second, the risk of some degree of selection bias remains in that subjects with little or no RKF were probably less likely to have 24-hour urine collection and may have been excluded from the analysis. Third, there is some suggestion that the rate of decline in RKF is not constant over time and may be particularly rapid during the first 90 days

of dialysis initiation.⁸ Averaging the decline over a full 1-year period may underestimate the rate of decline of RKF within the first 90 days, which may be an especially important or vulnerable period. Fourth, unlike the NECOSAD, which used a structural marginal model adjusting for time-dependent covariates,⁵ this study adjusted only for baseline covariates without taking into account their changes over time.⁷ Fifth, RKF was estimated using KRU⁹ (that is, from the residual renal clearance of a very small solute: urea) and thus, did not measure residual native clearance of potentially important middle molecules or protein-bound uremic solutes.

Urea clearance alone may underestimate RKF, because urea is passively reabsorbed in the proximal renal tubules. However, serum creatinine is secreted by the tubules and may overestimate RKF. The average of renal urea and creatinine clearance may be preferred to KRU as an estimate of RKF,¹⁰ because the ratio of creatinine to inulin clearance at very low values of RKF is highly variable.¹¹ Twenty-four-hour urine collection may not be reliable, because the amount of urine produced varies depending on the timing of collection in relation to the hemodialysis session. Urine volume, KRU, and GFR measured by inulin clearance all increase during the interdialytic period and are the highest on the last day of the interdialytic period.¹¹ Sampling clearance over part of the interdialytic period may, therefore, under- or overestimate RKF, depending on the time of collection in relation to the dialysis session. Thus, ideally, urine volume and RKF should be estimated by collecting urine throughout the entire interdialytic period. van Olden *et al.*¹¹ showed that the overestimation of GFR by creatinine relative to inulin clearance was 0.26 ± 0.60 ml/min if urine collection was done on the last day of the interdialytic period compared with 1.35 ± 1.69 ml/min if urine collection was done on the first day ($P < 0.05$). Similar to the data by van Olden *et al.*,¹¹ another earlier report also suggested that collection of urine on the last day before a dialysis session was rather reproducible, although it may overestimate GFR slightly, and thus, a more practical way to estimate RKF in daily clinical practice.¹² A recent study suggested that serum levels of β -trace protein and β 2-microglobulin may have potential in estimating RKF in patients with $KRU > 2$ ml/min per 1.73 m²,¹³ and this novel approach merits additional investigation and validation.

Given the importance of RKF and its decline, we need better understanding of factors that predict loss of RKF in patients on hemodialysis. Many studies in this area have been limited because of small sample size, retrospective design, and the different definitions of RKF that were used. Consistent with a previous report by Moist *et al.*,¹⁴ Obi *et al.*⁷ found that women, non-Hispanic white ethnicity/race, and the presence of background comorbidities, including diabetes and heart failure, were associated with more rapid loss of RKF. Laboratory parameters associated with a more rapid loss of RKF included higher baseline serum levels of creatinine, phosphate, or intact parathyroid hormone and higher degrees of serum iron saturation. Contrary to the findings by Moist *et al.*¹⁴ and the NECOSAD,¹⁵ in which a lower body mass index

was associated with a slower rate of decline in RKF, in the data from Obi *et al.*,⁷ a higher body mass index was not detrimental and was, in fact, associated with a reduced rate of decline in RKF. The reason for this discrepant finding is not clear. The NECOSAD suggested that proteinuria and the occurrence of intradialytic hypotension might be predictors of more rapid loss of RKF,¹⁶ but these factors were not evaluated in the data reported by Obi *et al.*⁷

The study by Obi *et al.*⁷ is timely and noteworthy in confirming the importance of maintaining RKF in patients on hemodialysis and the adverse effect of a fall in RKF on survival. There is evidence from the Frequent Hemodialysis Network (FHN) Nocturnal Trial that accelerated loss of RKF may be associated with a frequent nocturnal dialysis schedule, particularly when total weekly dialysis time was > 24 h/wk. Of the subjects randomized to six times weekly frequent nocturnal hemodialysis, 52% and 67% of subjects became anuric at 4 and 12 months, respectively, compared with 18% and 36%, respectively, randomized to a thrice weekly dialysis schedule. Notably, almost all subjects who complied with the prescribed frequent and long hemodialysis schedule became anuric by 1 year. In contrast, the FHN Daily Trial did not find that following the prescribed daily (actually five times per week as delivered) regimen was associated with an accelerated decline in RKF, although results in the FHN Daily Trial were more difficult to interpret, because the numbers of subjects with substantial RKF at baseline in either randomized arm were relatively small.¹⁷ If a frequent and extended dialysis schedule does cause accelerated loss of RKF, the exact mechanism is not clear, but extracellular volume depletion, intradialytic hypotension with dialysis-induced tissue ischemia or dialyzer circuit-induced inflammation, exposure to microbubbles, and/or platelet activation might contribute as risk factors. Thus, it is possible that the potential benefits of frequent and long dialysis schedules may be partially or completely offset by an adverse effect on RKF preservation when such augmented regimens (as delivered with current equipment) are applied to patients who still have substantial RKF.

In recent years, there has been revived interest in a strategy of incremental hemodialysis for patients with substantial RKF, where hemodialysis dose and frequency are tailored on the basis of the amount of RKF.¹⁸ In a separate study, Obi *et al.*¹⁹ have shown that incremental hemodialysis may be a safe treatment strategy for subjects with substantial RKF and allow better preservation of RKF. Thus, in patients with substantial RKF, the use of incremental dialysis might conceivably not only reduce costs and patient burden but also, help maintain the RKF that is apparently so beneficial to a number of clinically relevant patient outcomes. However, there is a note of caution. In the incremental hemodialysis study by Obi *et al.*,¹⁹ incremental hemodialysis (given using a twice weekly schedule) was associated with higher mortality risk among those subjects with baseline $KRU < 3$ ml/min per 1.73 m² or baseline urine volume < 600 ml/d. Thus, it seems that an incremental hemodialysis strategy involving a twice per week schedule may not be

appropriate for all patients and might decrease survival when applied to those who are relatively oliguric or anuric.

Apart from incremental hemodialysis in selected patients, another potential strategy for preserving RKF may include optimal control of BP while avoiding the occurrence of intradialytic hypotension and minimizing the occurrences of both volume depletion and overhydration. The use of diuretics, renin-angiotensin-aldosterone system blockers, or a low-protein diet may also be of benefit in preserving urine volume or RKF. However, none of these strategies have been evaluated in adequately powered randomized trials. A recent multicenter randomized trial in 82 patients on hemodialysis (in which 56 completed the study) failed to show a benefit of an angiotensin receptor blocker in slowing the decline of RKF or urine volume over 1 year of treatment, but the study was underpowered.²⁰ Thus, substantial knowledge gaps remain as to how best to prevent RKF loss in patients on dialysis.

Moving forward, we need to standardize the method of estimating RKF to facilitate monitoring at regular intervals in those patients who still have urine output. Simple, reliable, and cost-effective techniques of estimating RKF will help in the collection of data in this area, so that we can better understand the mechanisms for RKF decline over time. The Kidney Disease Outcome Quality Initiative 2006 guidelines recommended monitoring the course of RKF,⁹ but this is not routinely done in most centers. Given its importance, preservation of RKF should be incorporated as part of the standard of care for patients on hemodialysis and might logically be considered as one measure of dialysis quality. We do need randomized, controlled trials to identify effective therapies that will preserve RKF and also, determine whether better preservation of RKF will translate into better patient outcomes.

DISCLOSURES

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