Measurement and Estimation of Residual Kidney Function in Patients on Dialysis

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Residual kidney function (RKF) in patients on dialysis is strongly associated with survival and better quality of life. Assessment of kidney function underlies the management of patients with chronic kidney disease before dialysis initiation. However, methods to assess RKF after dialysis initiation are just now being refined. In this review, we discuss the definition of RKF and methods for measurement and estimation of RKF, highlighting the unique aspects of dialysis that impact these assessments.

Key Words: Residual kidney function, Glomerular filtration rate, β-Trace protein, β-2 Microglobulin, Cystatin C

INTRODUCTION

There is a continuum of kidney function throughout the course of acute and chronic kidney disease. At late stages of kidney disease, loss of excretory, endocrine, and metabolic functions of the kidney contribute to signs and symptoms of uremia, requiring replacement of kidney function to preserve health. In patients receiving kidney replacement therapy, the remaining function of the kidney is referred to as the residual kidney function (RKF). In the following sections, we will discuss definition of RKF, relevance of RKF in patients on dialysis, followed by methods for RKF measurement and estimation.

Definition of RKF

RKF is the kidney function in patients receiving kidney replacement therapy for kidney failure. Conceptually, "total kidney function" is the sum of RKF and the function provided by kidney replacement therapy (Fig 1). In principle, it would be optimal to quantify total kidney function as the sum of RKF and function provided by kidney replacement therapy, and to express each component of RKF in the same units used in earlier stages of kidney disease. Although RKF may be present in patients with acute kidney failure and in kidney transplant recipients, we will limit our discussion to patients with chronic kidney failure receiving dialysis. The concept of "total small solute clearance" as a component of total kidney function might be particularly useful for patients with chronic kidney failure during the transition to dialysis. Although these concepts are appealing as a unifying metrics, there are theoretical and methodological challenges to this approach.

Theoretical limitations include the following: First, although it is generally accepted that glomerular filtration rate (GFR) provides the best assessment of the overall kidney function in health and disease, there are important kidney functions in addition to glomerular filtration, including other excretory functions (reabsorption and secretion), and endocrine and metabolic functions. Although the decline in GFR in acute and chronic kidney disease generally parallels the decline in other kidney functions, impairment in other functions may contribute importantly to signs and symptoms of uremia at very low GFR, requiring separate assessment and treatment. For example, deficiencies of hormones produced by the kidney, vitamin D and erythropoietin, can be replaced, ameliorating secondary hyperparathyroidism and anemia. Salt and water retention can be treated by diuretics, ameliorating fluid overload.

Second, although glomerular filtration is the primary mechanism for excretion of many small solutes (molecular weight <500 Da), retention of larger solutes normally excreted by the kidney may also contribute to the burden of illness. In particular, recent attention has focused on solutes that are excreted predominantly by tubular secretion,[1,2] whose serum levels may rise disproportionately to the reduction in GFR. Some of these "secretion markers" are protein-bound and not removed by dialysis to the same extent as urea.[3,4] Other small solutes are considered "sequestered" as they are not in rapid equilibrium with the plasma volume and thus are not efficiently removed by intermittent dialysis. Although dialysis dosing has traditionally focused on urea clearance as a surrogate for all small solute clearance, monitoring the serum levels of secreted and sequestered solutes in addition to filtered solutes may also aid in patient assessment.

Third, methodologically, it may be difficult to reliably quantify the level of GFR at very low values using the same techniques used at higher levels of kidney function. Intermittent dialysis removes some filtration markers, leading to non–steady-state serum concentrations, and endogenous extrarenal elimination of filtration markers by the liver, intestines, or other organs is often not well quantified.

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Notwithstanding these limitations, defining the total small solute clearance for patients treated by dialysis as the sum of small solute clearance provided by glomerular filtration, tubular secretion, and dialysis is essential to provide a basis to personalize the management of uremia treated with dialysis. In addition, the concept of total kidney function can highlight aspects of current therapies that are adequate, such as clearance of urea, and other aspects that need improvement.

Relevance to Incident ESRD

ESRD, defined in the United States as chronic kidney failure treated by dialysis or transplantation, is an important public health problem with high prevalence and cost.[5] More than 100,000 patients start dialysis for ESRD in the United States every year but face a grim prognosis.[5] Approximately 20% to 25% of the patients starting dialysis do not survive first year on dialysis and only 50% survive more than 3 years.[5] Despite many advances in the general medical care of the patients, survival on dialysis has improved minimally over the past 3 decades. Reducing this first year risk of death in patients on dialysis is listed as a Healthy People 2020 goal,[6] but appears unlikely to be achieved in the next 3 years. In addition to the high risk of death, quality of life on dialysis also remains dismal with patients experiencing myriad of symptoms, including those from uremia.[7,8]

CLINICAL SUMMARY

- Residual kidney function (RKF) is the kidney function in patients treated with dialysis and "total kidney function" is the sum of RKF plus function provided by kidney replacement therapy.
- "Total small solute clearance" in patients on dialysis is a component of total kidney function and is the sum of small solute clearance by glomerular filtration, tubular secretion, and the dialysis modality.
- Assessment of RKF requires measurement or estimation of glomerular filtration rate from clearance or serum concentrations of filtration markers.
- Estimation of glomerular filtration rate by serum concentrations of low molecular weight proteins is a promising new method to assess RKF without urine collection.

RKF in patients on dialysis is strongly associated with survival. Among patients treated with peritoneal dialysis (PD), reanalysis of 2 studies, the Canada-USA (CANUSA) Peritoneal Dialysis Study[9] and the ADEquacy of PD in MEXico (ADEMEX) trial,[10] highlighted the benefit associated with RKF. Consequently, RKF has been referred to as the "heart" of PD.[11] However, due to the ease of achieving an "adequate" urea clearance by hemodialysis (HD), RKF had long been ignored in patients treated with this modality. Emerging data in the past decade have changed this paradigm. The Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study reported that incident patients on HD with preserved RKF at year 1 after dialysis initiation had a 30% lower risk of all-cause mortality and a 31% lower risk of cardiovascular death.[12] Similar findings were reported by the Netherlands Cooperative Study on Adequacy of Dialysis (NECOSAD)[13] and more recently by a retrospective cohort study of patients treated at a large dialysis organization in the United States.[14,15] The association of higher RKF with improved outcomes in both PD and HD is likely a manifestation of higher solute and fluid excretion in patients with RKF, compared with those without RKF.

Together, these data suggest that presence of RKF in patients on dialysis is an important characteristic that should be factored into dialysis care. However, although more than 1 million people started dialysis in the past decade, no clinical trials have addressed the question of dialysis dosing accounting for RKF.[16] The National Cooperative Dialysis Study (NCDS) and the Hemodialysis (HEMO) Trial, both excluded patients with RKF. More recently, increasing focus on the benefits of RKF and the factors associated with loss of RKF has revived the concept of incremental dialysis where dialysis is prescribed to supplement RKF to reach a prescribed total small solute clearance.[17-21] Key to these proposals is the ability to reliably assess RKF.

METHODOLOGICAL ISSUES IN ASSESSING RKF

RKF is generally assessed by methods used to assess GFR. In principle, GFR is product of the average filtration rate of each nephron times the number of nephrons. "True GFR" cannot be measured directly in humans. Instead, GFR is assessed from clearance measurements or estimated from plasma levels of filtration markers. Both measured GFR (mGFR) and estimated GFR (eGFR) may differ from true GFR because of systematic error (bias) or random error (imprecision), quantifying bias and imprecision is important in comparing GFR measurement and estimation methods. Several aspects of GFR assessment methods have implications for GFR measurement and estimation in patients on dialysis.

First, because of the intermittent nature of dialysis there are hemodynamic perturbations that can affect true GFR. For example, volume overload before dialysis and volume removal during intermittent HD cause variation in true GFR, with lowest levels immediately after dialysis and highest levels before dialysis.[22]

Second, solute clearance by dialysis is not the same as by the kidney. The diffusion coefficients for dialysis membranes and sieving coefficients of the glomerulus are each inversely related to the molecular size of the solute, but the apparent "cutoff" size is higher for the glomerulus than for the dialysis membrane. Small solutes (<500 Da, such as urea [60 Da] or creatinine [113 Da]) are freely filtered by the glomerulus and diffuse through dialysis membranes. Substantial amounts of "middle" molecular weight solutes (500-30,000 Da) are filtered, but are variably removed by dialysis (Table 1). For example, only small