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https://escholarship.org/uc/item/2qt9378j

Journal

Cardiorenal Medicine, 9(2)

ISSN

1664-3828

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Publication Date

2019

DOI

10.1159/000494808

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Peer reviewed

Review

Individualized Hemodialysis Treatment: A Perspective on Residual Kidney Function and Precision Medicine in Nephrology

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Keywords

Hemodialysis · Residual kidney function · Precision medicine · Incremental hemodialysis · Twice-weekly hemodialysis · Patient-centered outcome · Individualized treatment

Abstract

Background: Residual kidney function (RKF) is often expected to inevitably and rapidly decline among hemodialysis patients and, hence, has been inadvertently ignored in clinical practice. The importance of RKF has been revisited in some recent studies. Given that patients with end-stage renal disease now tend to initiate maintenance hemodialysis therapy with higher RKF levels, there seem to be important opportunities for incremental hemodialysis by individualizing the dose and frequency according to their RKF levels. This approach is realigned with precision medicine and patient-centeredness. ***Summary:*** In this article, we first review the available methods to estimate RKF among hemodialysis patients. We then discuss the importance of maintaining and monitoring RKF levels based on a variety of clinical aspects, including volume overload, blood pressure control, mineral and bone metabolism, nutrition, and patient survival. We also review several potential measures to protect RKF: the use of high-flux and biocompatible membranes, the use of ultrapure dialysate, the incorporation of hemodiafiltration, incremental hemodialysis, and a low-protein diet, as well as general care such as avoiding nephrotoxic events, maintaining appropriate blood pres-

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CardioRenal Medicine

Cardiorenal Med 2019;9:69–82

DOI: 10.1159/000494808

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sure, and better control of mineral and bone disorder parameters. ***Key Message:*** Individualized hemodialysis regimens may maintain RKF, lead to a better quality of life without compromising long-term survival, and ensure precision medicine and patient-centeredness in nephrology practice.

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Introduction

Residual kidney function (RKF), even at such a low level that is usually observed among patients with end-stage renal disease (ESRD), substantially contributes to fluid balance and clearance of uremic toxins [1]. Due to its continuous nature, RKF has additional advantages over hemodialysis in mitigating dynamic changes in body fluid and facilitating the removal of middle molecules and protein-bound solutes [2–6]. RKF also plays a role in endocrine functions such as the production of erythropoietin and the activation of vitamin D [7]. Greater RKF among hemodialysis patients has been correlated with better nutritional status and lower mortality [7–11]. Additionally, patients with substantial RKF have a better quality of life in terms of social function, mental health, and cognitive function [7].

While routinely evaluated among patients on peritoneal dialysis in clinical practice, RKF has been underappreciated among hemodialysis patients. Rather, the adequacy of hemodialysis has been the primary focus of both research and clinical practice, since RKF was believed to go through inevitable rapid decline after the initiation of hemodialysis [12–14]. However, the application of high-dose dialysis failed to show a survival benefit in the Hemodialysis (HEMO) study [15] and the deterioration rate in RKF among hemodialysis patients treated with high-flux biocompatible dialysis membranes and ultrapure dialysates was reported to be similar to that among peritoneal dialysis patients [16]. Therefore, we believe it is time to reevaluate the clinical importance of RKF among hemodialysis patients and to incorporate RKF levels in the management of hemodialysis patients. Indeed, a recent study revealed that plasma concentrations of secreted solutes (i.e., hippurate, phenylacetylglutamine, indoxyl sulfate, and p-cresol sulfate) can be well controlled by twice-weekly hemodialysis in patients with RKF [2]. Given that patients with ESRD now tend to initiate maintenance hemodialysis therapy with higher RKF levels, there seem to be important opportunities for incremental hemodialysis by individualizing the dose and frequency according to their RKF levels. This approach is realigned with precision medicine and patient-centeredness.

How to Calculate Residual Kidney Urea Clearance

Although RKF can be deduced simply based on self-reported urine volume, this does not precisely reflect RKF, partly because the urine volume is affected by many clinical factors such as fluid intake, diuretics, renal concentrating ability, and serum levels of urea and glucose. Hence, residual renal urea clearance (CL_{urea} or Kru) remains to be the practical method for estimating RKF among hemodialysis patients because renal CL_{urea} can be incorporated into urea-based dialysis adequacy (i.e., Kt/V_{urea}).

However, estimating renal CL_{urea} has been challenging in clinical practice because it requires formal urea kinetic modeling using a specific software (i.e., Solute-Solver®) to obtain the time-averaged serum urea nitrogen concentration during a urine collection [17]. There are some alternative methods such as an average of the pre- and postdialysis serum urea nitrogen concentrations, Jindal and Goldstein's equation, or multiplying a factor of 0.9 against

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Table 1. Available equations to estimate RKF

Study [Ref.]	Feature	Pros	Cons
Formal urea kinetics			
Daugirdas et al. [17]	Formal urea kinetics using a Web-based software (Solute-Solver®) available at www.ureakinetics.org	The most precise method; applicable to various conditions	Requires detailed information input on the website
Estimating equations based on urine collection			
Conventional equation (no original literature) [18]	Uses the average of the postdialysis SUN before urine collection and the predialysis SUN after urine collection	–	Overestimates RKF by 10.3% on average [21]
Jindal and Goldstein [19]	Uses different factors for the postdialysis SUN before urine collection and the predialysis SUN after urine collection in thrice-weekly versus twice-weekly hemodialysis	–	Underestimates RKF by 9.9% on average [21]
Daugirdas et al. [20]	A factor of 0.9 is used for the predialysis SUN to estimate the time-averaged concentration during a urine collection	Simple; does not require postdialysis SUN	Overestimates RKF by 4.5% on average, with a larger error with less frequent hemodialysis [21]
Obi et al. [21]	Uses the predialysis SUN, the urea reduction rate, and the duration of urine collection and the interdialytic interval	<5% error in >98% of cases [21]; applicable to various conditions	–
Estimating equations based on serum markers			
Shafi et al. [25]	Uses β-trace protein, $β_2$-microglobulin, and gender	Does not require urine collection	Relatively large errors; assays are not widely available; not suitable for patients with hemodiafiltration
Wong et al. [26]	Uses β-trace protein, $β_2$-microglobulin, creatinine, predialysis SUN, gender, and ethnicity		

SUN, serum urea nitrogen; RKF, residual kidney function.

the predialysis urea, as suggested by Daugirdas (Table 1) [18–20]. However, all methods lead to biased estimation with wide variation in error depending on the duration of the urine collection period and the interdialytic interval. Recently, a new equation where the estimated CL_{urea} agrees well with the formal kinetic model-based values, with <5% error in most clinical scenarios, was presented (Fig. 1) [21]. The European Best Practice Guidelines recommend using the estimated glomerular filtration rate, that is, the mean of urea and creatinine clearance based on the Casino and Lopes kinetic estimate, to be consistent with peritoneal dialysis practice [22, 23].

Nevertheless, 24-h urine collection is labor intensive, and it is difficult for many patients to adhere to its protocol and to collect all their urine during a specified period, which leads to biased estimates of their RKF.
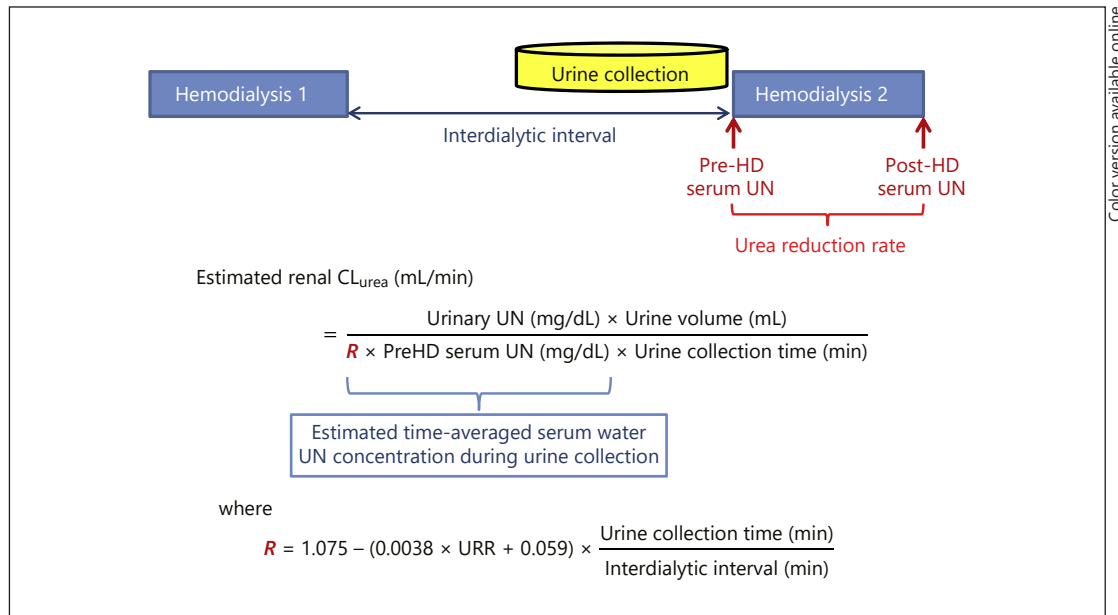
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Fig. 1. How to estimate renal urea clearance (CL_{urea} or Kru). R is a factor for predialysis serum urea nitrogen (UN) to estimate the time-averaged serum water UN concentration during urine collection. The value of 1.075 in R is simply 1/0.93 and results from the need to correct the predialysis urea concentration for serum water. Urine collection is supposed to be completed 1 h before the subsequent dialysis treatment. HD, hemodialysis.

Other Estimation Markers and Their Limitations

There are other methods for estimating RKF using serum filtration markers, such as cystatin C, β_2-microglobulin, and β-trace protein. Serum cystatin C (13.3 kDa) is correlated with RKF among dialysis patients, but its utility is limited because of the large nonrenal clearance of cystatin C exceeding its renal clearance by RKF. β_2-Microglobulin (11.8 kDa) is also removed by high-flux hemodialysis, and its concentration increases in patients with malignancy or inflammation [24]. In contrast, β-trace protein (23–29 kDa) is not removed by conventional low- or high-flux dialysis and shows a steady concentration during the interdialytic period. Some authors suggested dialysis-specific equations using these markers, showing a good correlation with measured RKF [25, 26]. It is useful and convenient to estimate RKF without collecting 24-h urine and to identify those patients with $CL_{urea} \geq 2.0$ mL/min/1.73 m^2. However, the equation was developed with cross-sectional estimation and, hence, was not fully validated for repeated measurements over time. Indeed, in the study by Shafi et al. [25], the equations tended to underestimate the change in clearance over time compared with the change in measured CL_{urea}. β-Trace protein is also significantly removed by convection and, hence, not suitable for estimating RKF among patients receiving hemodiafiltration (HDF) [27].

RKF and the Management of Blood Pressure and Body Fluid Levels

Most hemodialysis patients gain body fluid during the interdialytic period due to very low levels of renal function, and volume control and management have been among the most strenuous tasks for both patients and healthcare providers. Even with the best effort to

restrict patients' intake of salt and fluid and to maximize the ultrafiltration volume, chronic volume overload may occur, leading to progression of hypertension and cardiovascular disease [28, 29]. Several studies have shown a relationship between greater interdialytic weight gain or fluid overload and higher cardiovascular mortality risk [30, 31], and patients with little or no RKF are likely to accumulate more body fluid [32, 33].

In addition, there seems to be a vicious cycle between decreased RKF and intradialytic hypotension, another risk factor for mortality among hemodialysis patients. Intradialytic hypotension occurs due to multiple factors including impaired cardiac function, autonomic neuropathy, and excessive fluid removal. Intradialytic hypotension may result in decreased renal blood flow, which leads to renal ischemia and, eventually, to further loss of RKF [34, 35]. Decreased RKF, in turn, increases the burden of sodium and water retention, resulting in poorer blood pressure control, higher pulse wave velocities, and the progression of left-ventricular hypertrophy [36].

RKF and the Management of Mineral and Bone Disorders

Mineral and bone disorder (MBD) in ESRD patients is characterized by elevated levels of serum calcium, phosphorus, parathyroid hormone (PTH), and alkaline phosphatase, which eventually lead to an increased risk of cardiovascular disease and mortality by promoting vascular calcification. Several studies have investigated the role of RKF in modifying the progression of MBD. In the cross-sectional study by Chen et al. [37], RKF was a risk factor for vascular calcification independent of other established risk factors, such as age, hemodialysis vintage, diabetes, calcium phosphorus byproducts, and C-reactive protein. RKF is also important in modifying the mortality risk associated with serum phosphorus and intact PTH levels among incident hemodialysis patients [38]. In a large administrative cohort of incident hemodialysis patients in the USA, serum phosphorus and all-cause mortality were positively correlated in general, but the risk associated with hyperphosphatemia was higher among patients with greater RKF. Moreover, the association between all-cause mortality and higher PTH levels was observed only among hemodialysis patients with substantial RKF, but not among those with little or no RKF. Thus, RKF not only facilitates better control of phosphate levels but also affects the entire dynamic between phosphorus levels, intact PTH levels, and mortality rate.

RKF and Nutritional Assessment

Protein energy wasting and inflammation, or malnutrition-inflammation-cachexia syndrome, is common and associated with mortality among patients with chronic kidney disease including ESRD [39–41]. Albumin, as a surrogate marker of malnutrition, is an independent predictor of quality of life, hospitalization, and mortality risk [42–46]. Interestingly, in a recent cohort study of incident hemodialysis patients, those with greater RKF showed higher serum albumin levels at baseline and maintained these levels during the follow-up period [47]. Additionally, serum albumin levels tend to increase over 12–18 months after dialysis initiation, which is followed by a gradual but continuous decrease. This initial increase in serum albumin level was observed independently of baseline RKF, suggesting that this increase cannot be fully explained by decreased loss of urinary protein with diminished RKF after dialysis initiation. The initial increase in serum albumin can be attributed to an improved appetite following the removal of uremic toxins, improved protein synthesis, and reduced protein degradation due to the resolution of metabolic acidosis.

The normalized protein catabolic rate (nPCR), a proxy for dietary protein intake among stable hemodialysis patients, has been shown to be associated with the serum albumin level as well as with better survival among hemodialysis patients [42, 48–50]. However, given that the nPCR does not account for urinary urea excretion, protein intake is underestimated with the nPCR among patients with RKF [48]. For example, in a large US cohort of incident hemodialysis patients, the median nPCR with and without accounting for renal urea clearance at baseline was 0.94 and 0.78 g/kg per day, respectively. The median within-patient difference in nPCR was 0.14 g/kg per day and was larger among patients with greater RKF. In addition, the association of the nPCR with survival appeared to be stronger when renal CL_{urea} was accounted for in the calculation of the nPCR. These findings suggest that renal CL_{urea} should be periodically monitored and accounted for when evaluating protein intake using the nPCR among patients with RKF.

RKF and Dialysis Adequacy

Until now, the results from the National Cooperative Dialysis Study (NCDS), published in 1981, have dictated the current treatment paradigm to achieve a minimal delivered dialysis dose of 1.2 per session in single-pool Kt/V or 2.3 per week in standard Kt/V for thrice-weekly hemodialysis patients with little or no RKF [51, 52]. Since RKF also contributes to the small solute clearance, the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend using renal CL_{urea} to measure RKF [18]. Renal CL_{urea}, if present and measured, can be converted into renal standard Kt/V so that it can be added to dialysis standard Kt/V as follows:

$$Renal\ standard\ Kt/V = \frac{Renal\ CL_{urea}\left[mL/min\right] \times 10{,}080\left[min\right]}{V_{Watson}\left[L\right] \times 1{,}000}.$$

A renal CL_{urea} value of 3.0 mL/min in an average dialysis patient is close to a standard Kt/V value of approximately 1.0 per week. Given that the recommended value for standard Kt/V is 2.3, it is suggested that the dialysis frequency may be safely reduced to twice weekly for patients with renal CL_{urea} ≥3.0 mL/min/1.73 m^2 [18].

One of the major hindrances to the incorporation of RKF into hemodialysis adequacy is the complexity of accounting for the entire function of the remnant kidney. Less frequent hemodialysis treatments may be allowed at lower RKF levels than what is currently suggested given the advantage of RKF over equivalent dialysis urea clearance [53, 54], but the approach to sum up renal and dialysis urea clearance is at least warranted because it assumes the minimum benefit of RKF and because it does not underestimate the potential risk associated with inadequate dialysis. It should be noted that our ability to reduce solute concentrations by intensifying hemodialysis treatment is limited, probably due to the presence of nondialytic solute clearances and/or changes in solute production [55]. Native kidneys provide solute clearance equivalent to or more than that of hemodialysis treatment with the same urea clearance, especially for middle molecules (i.e., β_2-microglobulin) and protein-bound uremic toxins (i.e., indoxyl sulfate and p-cresol sulfate) [2, 56]. RKF also provides other benefits than solute clearance, such as continuous fluid removal, and more preserved endocrine functions. Indeed, there have been studies suggesting that RKF is more strongly associated with survival among ESRD patients than is dialysis adequacy, even with the same amount of small solute clearance [57, 58].

Accordingly, the benefit from hemodialysis treatment may also be attenuated among patients with substantial RKF [56, 58]. In line with this theoretical concept, Wang et al. [59] reported that the association between higher delivered dialysis dose and better survival was

CardioRenal Medicine

Cardiorenal Med 2019;9:69–82

DOI: 10.1159/000494808

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linearly attenuated with greater renal CL_{urea} among incident hemodialysis patients. Furthermore, the Frequent Hemodialysis Network (FHN) group showed contrasting results in their Daily and Nocturnal trials. The FHN Daily Trial mainly consisted of long-term hemodialysis patients, of whom two-thirds were anuric, and daily in-center frequent hemodialysis resulted in reduced left ventricular mass, better control of blood pressure and serum phosphorus, and better long-term survival [60]. On the other hand, the FHN Nocturnal Trial included patients relatively new to dialysis, half of whom had a urine volume of 0.5 L or more, and 6-times-weekly home nocturnal hemodialysis resulted in a steeper RKF decline and higher mortality in the frequent hemodialysis group [11, 61]. Recent studies have suggested potential advantages of incremental hemodialysis for patients with substantial RKF, such as a slower RKF deterioration rate, greater quality of life, longer longevity of the arteriovenous fistula, and lower medical cost [62–65].

RKF and Survival Prediction

A prospective observational study first reported that compared with anuric hemodialysis patients, patients with any RKF at the time of dialysis initiation experienced a 56% lower mortality [9]. The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD-2) investigators also reported that the mortality risk decreased by 56% with every 1.0/week increment in renal Kt/V_{urea} at 3 months after the initiation of dialysis. In a prospective cohort study (the CHOICE study), although the baseline urine output was not associated with better survival, the maintained urine output after 1 year (self-reported, 1 cup or 250 mL/day of urine) was associated with a 30% reduction in adjusted mortality risk [7]. Maintained RKF was also correlated with a better quality of life, a decreased dose of erythropoiesis-stimulating agents, and reduced inflammation. In order to overcome a potential lead-time bias in these studies, Obi et al. [11] examined the annual change in renal CL_{urea} among incident hemodialysis patients and reported a linear association with greater subsequent mortality risk.

How to Protect RKF

A tailored dialysis therapy for each patient's characteristics potentially preserves RKF when initiating and maintaining hemodialysis therapy. Here, we discuss several possible methods for preserving RKF that can be selected according to a patient's characteristics.

General Care

Although there are several new strategies that may preserve RKF in hemodialysis patients, it is still important to maintain general principles to protect the residual kidneys, such as avoiding or minimizing nephrotoxic events (i.e., radiocontrast, nonsteroidal anti-inflammatory drugs, and aminoglycosides) [66] as well as appropriate control of blood pressure after initiating dialysis. Intradialytic hypotension may accelerate RKF loss via ischemic insults and can be prevented by sodium and water restriction, dialysate cooling, sodium profiling (which is reserved for short-term use), changing the ultrafiltration profile, and acetate-free HDF [67–70]. Using loop diuretics in hemodialysis patients with considerable RKF can also lower interdialytic weight gain and eventually benefit the preservation of RKF [71]. These measures need to be individualized according to patient conditions. Additionally, lower serum calcium levels, higher serum levels of phosphorus, and intact PTH have been associated with a faster decline in RKF [11, 72]; hence, better control of MBD parameters may result in preserving RKF.

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DOI: 10.1159/000494808

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High-Flux Biocompatible Membrane, Ultrapure Water, and On-Line HDF

Biocompatible dialysis membranes (e.g., polysulfone membrane), when compared to bioincompatible membranes (e.g., cellulose membrane), are associated with the preservation of RKF [73, 74]. In addition, ultrapure dialysate combined with high-flux synthetic membranes is effective in slowing RKF deterioration with lower C-reactive protein and IL-6 levels, when compared to conventional dialysate [75]. Other studies have also reported similar RKF declines between patients on peritoneal dialysis and those treated with hemodialysis utilizing high-flux biocompatible membranes and ultrapure dialysate [16, 76]. On-line HDF, a well-known method that has a greater clearance of β_2-microglobulin than conventional hemodialysis by its convection [77], uses ultrapure dialysate because it requires the dialysate to be directly infused into the extracorporeal circuit. Several studies have shown that RKF or urine volume was more preserved among patients treated with on-line HDF than among those treated with conventional hemodialysis [78, 79]. These observations may be attributed to fewer intradialytic hypotensive episodes and reduced dialyzer-induced systemic inflammation [80].

Incremental Hemodialysis

The core concept of incremental dialysis is the smooth "transition," rather than abrupt "start," from conservative management of chronic kidney disease to dialysis therapy [81]. This approach has been successfully used for peritoneal dialysis patients, not for hemodialysis patients. Additionally, patients on incremental peritoneal dialysis showed a lower decline in RKF, a similar survival rate, and fewer hospitalizations than standard peritoneal dialysis patients [82]. With incremental hemodialysis, dialysis treatment is initiated once or twice weekly – rather than thrice weekly, as in the conventional regimen – if patients have substantial RKF. Then, the hemodialysis frequency is gradually increased in accordance with RKF deterioration. Kalantar-Zadeh and Casino [83] and Kalantar-Zadeh et al. [84] suggested an 11-criteria matrix for successfully implementing twice-weekly hemodialysis in clinical practice, including urine volume and interdialytic fluid gain.

In addition to a better quality of life, lower medical cost, and longer patency of vascular access, several studies have demonstrated that compared to ESRD patients who started hemodialysis therapy at the conventional thrice-weekly frequency, patients managed with incremental hemodialysis showed a slower decline in RKF (Table 2).

Compared to patients on thrice-weekly hemodialysis, twice-weekly hemodialysis patients were shown to have more urine output and reduced hospitalization rates [62]. Also, the rate of RKF decline among patients with twice-weekly hemodialysis was similar to that among patients with peritoneal dialysis [85]. In a retrospective cohort of patients under a hemodialysis regimen in Shanghai, the prevalence of RKF loss was lower among patients treated with twice-weekly hemodialysis than among those treated with thrice-weekly hemodialysis, especially during the first year of dialysis [34]. Additionally, in a longitudinal cohort study of incident hemodialysis patients, those treated with an incremental regimen showed a slower decline in CL_{urea} during the first year of dialysis and similar survival thereafter when compared to those with conventional hemodialysis thereafter [64]. However, among patients with CL_{urea} <3.0 mL/min/1.73 m^2, incremental hemodialysis was associated with an increased mortality risk. Therefore, while incremental hemodialysis may preserve RKF after dialysis initiation, RKF appears to be an important factor that predicts which patients would benefit from an incremental hemodialysis regimen.

Low-Protein Diet

A low-protein diet results in a reduced burden of nitrogen, phosphate, and potassium, and is an effective strategy for postponing dialysis initiation for patients with chronic kidney

Table 2. Initial and follow-up RKF in hemodialysis patients

Study [Ref.] (study design)	Year	RKF index (unit)	Groups of interest	Subjects, n	Baseline RKF	Follow-up RKF or decline rate
Vilar et al. [10] (observational)	2009	CL_{urea} (mL/min/1.73m^2)	Incremental high-flux HD	650	3.1±1.9 at 3 M	0.9±1.2 at 60 M
Lin et al. [62] (observational)	2009	CL_{cr} (mL/min)	2/w HD	23	3.4±1.4	0.06/M
			3/w HD	51	4.1±2.0	0.36/M (decline rate)
Teruel-Briones et al. [85] (observational)	2013	rGFR (mL/min/1.73m^2)	2/w HD	61	6.1±2.1	0.18/M
			3/w HD	49	5.4±2.9	0.33/M
			PD	83	7.0±3.2	0.18/M (decline rate)
Caria et al. [91] (observational)	2014	rGFR (mL/min/1.73m^2)	1/w HD combined with low-protein diet (CDDP)	38	7.8±1.9	0.13/M
			3/w HD	30	9.2±4.2	1.53/M (decline rate)
Zhang et al. [34] (observational)	2014	rGFR (mL/min/1.73m^2)	2/w HD	30		34±32 M
			3/w HD	55		21±19 M (time to RKF loss)
Obi et al. [64] (observational)	2016	CL_{urea} (mL/min/1.73m^2)	Incremental HD	351	4.8	CL_{urea} was more preserved by 16% in incremental vs. conventional HD
			Matched patients on conventional HD	8,068	4.6	
Nakao et al. [92] (observational)	2018	rGFR (mL/min)	1/w HD + low-protein low-salt diet	112	3.0±0.7	2.1±0.6 at 12 M
			3/w HD	30	N/A	0.7±0.5 at 12 M
Hartmann et al. [74] (RCT)	1997	CL_{cr} (mL/min)	3/w HD with polysulfone membrane	10		0.37±0.06/M
			3/w HD with cellulose acetate membrane	10		0.50±0.04/M (decline rate)
Jansen et al. [67] (observational)	2002	rGFR (mL/min/1.73m^2)	3/w HD	279	5.9±2.8	Relative decline in rGFR was faster by 20% in HD vs. PD at 6 M
			PD	243	6.4±2.4	
Lang et al. [14] (observational)	2001	CL_{cr} (mL/min)	3/w HD with biocompatible membrane	15	7.6±1.6	1.9
			3/w HD with bioincompatible membrane	15	7.4±1.8	3.6
			CAPD	15	7.4±1.2	0.6 (decrease in CL_{cr} by 6M)
McKane et al. [16] (observational)	2002	CL_{urea} (mL/min/1.73m^2)	3/w HD with high-flux biocompatible membrane and ultrapure water	300	4.2	2.5
			CAPD	175	4.2	2.1 (CL_{urea} at 18 M)
Schiffl et al. [75] (RCT)	2002	CL_{cr} (mL/min)	Ultrapure dialysate	15	7.9±2.0	4.3±1.8 at 24 M
			Conventional dialysate	15	7.9±1.8	2.5±1.8 at 24 M

CAPD, continuous ambulatory peritoneal dialysis; CDDP, Combined Diet Dialysis Program; CL_{urea}, residual renal urea clearance; GFR, glomerular filtration rate; rGFR, residual GFR estimated as the arithmetic mean of creatinine and urea clearance; CL_{cr}, creatinine clearance; HD, hemodialysis; M, months; PD, peritoneal dialysis; RCT, randomized clinical trial; RKF, residual kidney function.

disease not on dialysis [86, 87]. Inadequate protein intake may lead to protein wasting, one of the major concerns among dialysis patients, but small retrospective studies of predialysis patients have suggested that even a very-low-protein diet (0.3 g/kg body weight [BW]/day) supplemented with keto/amino acids may not compromise long-term patient safety [88, 89]. In this context, a low-protein diet has been integrated with a less frequent hemodialysis program at the initiation of dialysis, showing significant advantages in RKF protection. Although a low-protein diet has compliance issues and safety concerns for patients on dialysis [90], Caria et al. [91] showed that motivated patients with incident ESRD were closely adherent to the "Combined Diet Dialysis Program," which included a low-protein diet (0.6 g/kg BW/day) combined with once-weekly hemodialysis. Furthermore, the patients enrolled in this program experienced slower declines in RKF, better control of anemia and mineral disorders, and lower hospitalization rates while maintaining a good nutritional status when compared to those who initiated conventional thrice-weekly hemodialysis. Consistent findings were observed in a prospective cohort from Japan [92].

On the other hand, several observational studies have shown that lower serum albumin levels are associated with a steeper RKF decline and higher mortality [11, 46, 48, 93]. Along with the fact that the hemodialysis procedure per se increases net protein catabolism, a low-protein diet may be discouraged because of concerns regarding protein energy wasting [94, 95]. Indeed, many dialysis patients have a protein intake lower than the recommended dietary allowance level (0.8 g/kg BW/day), and a recent randomized clinical trial revealed that high-protein meals during dialysis increase serum albumin levels [50].

However, there are distinct differences between unintentional low protein intake and an intentional low-protein diet. Unintentional low protein intake, as measured in most observational studies, is usually due to appetite loss and/or dysphagia and is strongly associated with the patient's disease condition. It is also accompanied by generalized insufficiency or deficiency of nutrients such as energy and vitamins. In contrast, an intentional low-protein diet, which is a dietary intervention, requires patients to consume high-energy foods, which effectively suppress protein catabolism related to low protein intake [96]. Keto/amino acids and deficient vitamins are also supplemented if indicated. Therefore, a low-protein diet may not necessarily increase the risk of morbidity and mortality even among hemodialysis patients if it allows patients to spend fewer days with restrictions for dialysis treatment.

Nevertheless, it has been practically challenging to adhere to such dietary interventions with low protein and high energy intake [97]. Given the potential risk of protein wasting induced by inadequate energy intake, the implementation of a low-protein diet may be restricted to highly motivated and well-prepared patients, as was done in those studies showing the safety of protein restriction [88, 89]. Therefore, it is yet to be determined whether a dietary intervention including a low-protein diet has beneficial effects by protecting RKF in ESRD.

Future Directions

We propose several strategies for a broad implementation of RKF-based individualized hemodialysis regimens. First, the development of concise and reliable methods for estimating RKF levels is essential, because one of the key barriers is the labor-intensive urine collection. Several methods have been developed for estimating RKF without urine collection, but it remains unclear whether the discrepancies between estimated and actual levels are acceptable for clinical decision-making with regard to such an individualized therapy. Second, simple guides are also necessary in order to identify candidates for individualized therapy and to modify hemodialysis treatment (especially in terms of treatment time and frequency)

according to RKF levels. Urea kinetic modelling is required to obtain precise total CL_{urea} by combining dialysis and residual renal clearance, but the currently available software is not easy enough to use in daily clinical practice. Third, such efforts to individualize hemodialysis treatment should be appropriately acknowledged in the reimbursement system. We believe that these measures, if taken appropriately, would ensure precision medicine and patient-centeredness in nephrology practice.

Disclosure Statement

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