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The spectrum of kidney dysfunction requiring chronic dialysis therapy: Implications for clinical practice and future clinical trials

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Abstract

Staging to capture kidney function and pathophysiologic processes according to severity is widely used in chronic kidney disease or acute kidney injury not requiring dialysis. Yet the diagnosis of "end-stage kidney disease" (ESKD) considers patients as a single homogeneous group, with negligible kidney function, in need of kidney *replacement* therapy. Herein, we review the evidence behind the heterogeneous nature of ESKD and discuss potential benefits of recasting the terminology used to describe advanced kidney dysfunction from a monolithic entity to a disease with stages of ascending severity. We consider kidney *assistance* therapy in lieu of kidney replacement therapy to better reconcile all available types of therapy for advanced kidney failure including dietary intervention, kidney transplantation, and dialysis therapy at varied schedules. The lexicon "kidney dysfunction requiring dialysis" (KDRD) with stages of ascending severity based on levels of residual kidney function (RKF)—that is, renal urea clearance—and manifestations related to uremia, fluid status, and other abnormalities is discussed. Subtyping KDRD by levels of RKF could advance dialysis therapy as a form of kidney *assistance* therapy adjusted based on RKF and clinical symptoms. We focus on intermittent hemodialysis and underscore the need to personalize dialysis treatments and improve characterization of patients included in clinical trials.

1 | INTRODUCTION

The current classification system for kidney disease is based on an anatomic or structural component (glomerular or tubular), a functional component (glomerular filtration rate [GFR] and urine output), and a temporal component (acute or chronic).[1,2] When chronic kidney disease is diagnosed, severity is classified in five stages based on the level of kidney function, defined by GFR.[3] A diagnosis of acute kidney injury is stratified by changes in GFR and urine output.[4] However, the level of endogenous kidney function in end-stage kidney disease (ESKD) has received little attention.

ESKD, also referred to as chronic kidney disease Stage 5 requiring dialysis (CKD Stage 5D), denotes the presence of a single, final stage of kidney failure accompanied by clinical signs and symptoms for which chronic dialysis therapy is required to sustain life.[5] Indeed, when a diagnosis of ESKD is considered, the primary focus properly shifts from GFR to clinical and biochemical domains inclusive of volume overload and impaired solute clearance.[5] Notwithstanding the primary importance of clinical manifestations in the decision of initiating chronic dialysis therapy, disregarding endogenous kidney function—predominantly when hemodialysis (HD) is prescribed—is a lost opportunity for recognizing the diversity of this "last stage" disease and, with that, a lost opportunity to personalized care. We performed a scoping review of the literature pertaining to the management of ESKD with intermittent HD. We submit that ESKD is a mix of different levels of advanced kidney dysfunction with

overlapping manifestations. In this regard, the potential to refine the diagnosis of ESKD into subtypes, each with different levels of endogenous kidney function and potential therapeutic implications, is discussed.

2 | ESKD IS A MULTIFACETED ENTITY

In advanced kidney diseases, clinical manifestations of volume overload and uremia resulting from impaired solute clearance can involve any organ system in the body (Figure 1). In isolation, each kidney disease-related clinical manifestation is non-specific[6]; before GFR reaches very low levels (usually <10 ml/min/1.73 m^2), these manifestations are treated with dietary and pharmacologic interventions. ESKD encompasses any combination of kidney disease-related clinical manifestations that are typically more severe and can no longer be managed with diet and medications.[7] To date, a specific GFR value for initiating dialysis in the absence of symptomatic kidney failure has not been established.[8] Furthermore, participants in the IDEAL study, a randomized clinical trial of late versus early dialysis initiation, did not have longer survival benefit when dialytic therapy was started at GFR levels >7 ml/min/1.73 m^2.[9]

Notwithstanding advances in GFR assessment, current estimates of GFR by endogenous filtration markers may yield inaccurate ascertainment of GFR in advanced kidney failure where protein intake might be low, overestimation of RKF.[10] Moreover, without GFR cutoffs, the diagnosis of ESKD is heavily subjective, with thresholds for what is considered medically refractory uremic signs and symptoms varying between physicians and patients. While patients with ESKD have common patterns of clinical presentation, such as impaired exercise tolerance or physical limitations in activities of daily living, how ESKD is manifested has wide heterogeneity. Patients deemed to have ESKD span the spectrum from being seemingly asymptomatic with mild volume overload for GFR 6 ml/min/1.73 m^2, to significant volume overload at GFR as high as 12 ml/min/1.73 m^2. Registry data show that patients are diagnosed with ESKD when their GFR is anywhere between 4 and 15 ml/min/1.73 m^2; when dialysis is started, half have a GFR > 9 ml/min/1.73 m^2, and >90% have eGFR ≥5 ml/min/1.73 m^2.[11] Thus, ESKD is an umbrella term for a heterogeneous group of patients with advanced kidney diseases with very different

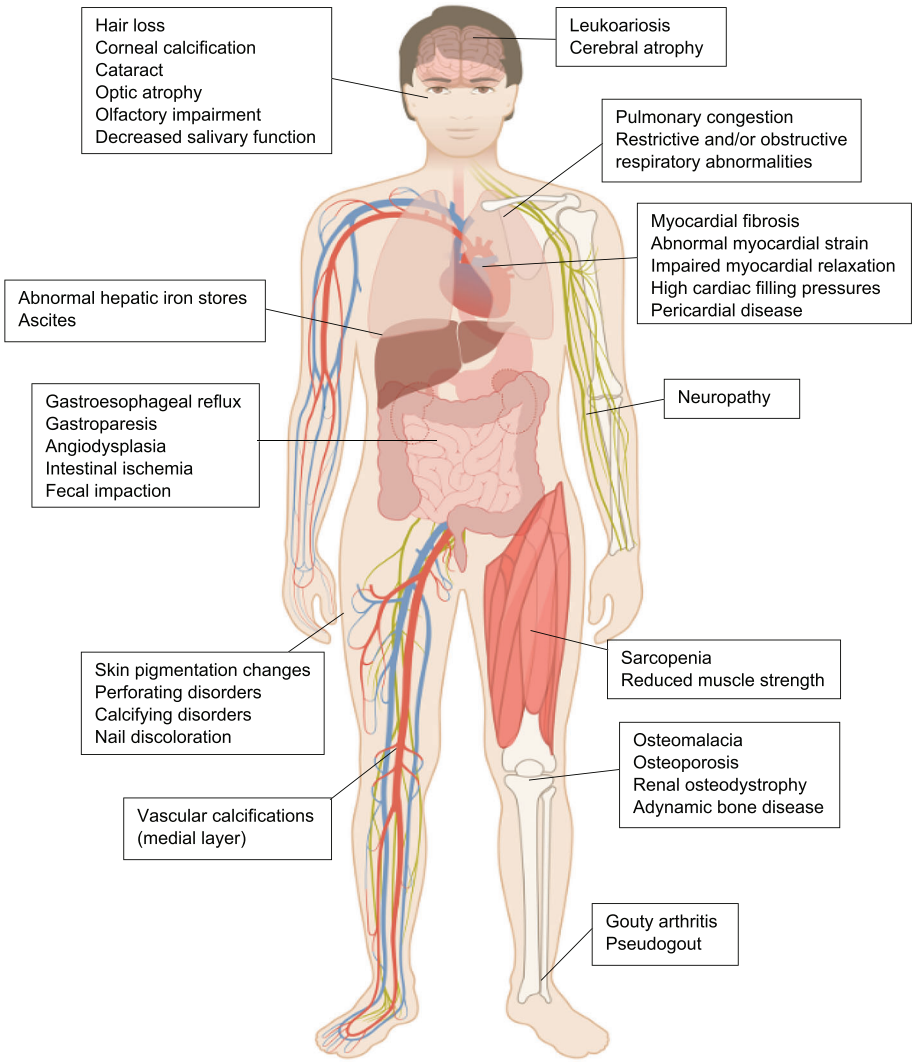

FIGURE 1 The syndrome of kidney dysfunction requiring dialysis. Kidney dysfunction requiring dialysis is a complex entity with pathophysiologic changes that can involve any organ system. Patients present with a wide spectrum of clinical manifestations which are nonspecific and of severity modulated by coexisting illnesses

levels of residual kidney function (RKF) and clinical manifestations (Figure 2).

In a recent report from the Kidney Disease Improving Global Outcomes (KDIGO) Consensus Conference on kidney disease nomenclature, substitution of ESKD with "kidney failure" with descriptions of symptoms, signs, and treatment was put forward.[12] Guiding principles of the conference were that the revised nomenclature should be patient-centered and precise. Discontinuation of the use of the term "end-stage" was proposed because it causes fear of the unknown, provokes undue trauma, implies impending death, and is obsolete. Patients and care partners perceived the term "kidney failure" as less objectionable, although it still prompted concerns. Of note, participants wanted more clarity about the severity of disease and prognosis, including quantitative descriptions, with the understanding that they would need to learn the meaning of the descriptions.[12] Beyond the important dimension of psychological impacts of disease terminology on healthcare consumers, its heuristic effects on the practice of conventional HD therapy has to be considered.

3 | CONVENTIONAL HD THERAPY AS KIDNEY REPLACEMENT THERAPY

In many countries, conventional HD prescription consists of thrice-weekly HD targeting urea clearance metrics of single pool Kt/V (spKt/V) ≥1.20 and urea reduction ratio ≥65%.[13] This prescription is synonymous to kidney *replacement* therapy, a terminology that signifies complete substitution of kidney function with dialytic therapy. Indeed, conventional HD therapy was validated in clinical trials that involved solely prevalent HD patients with dialysis vintage >2 years and virtually no RKF (patients were excluded if residual renal urea clearance was >1.5 ml/min/35 L of urea volume distribution)[14,15]; this was then extrapolated as "optimal" dialysis dose to all dialysis patients, including those found at the beginning of needing dialytic therapy and who have RKF. Thus, while conventional HD therapy can provide life-sustaining replacement of kidney function in those who have lost RKF, some patients, at least temporarily, would do well with less intensive dialytic therapy in the form of *assistance* therapy to complement underlying levels of ongoing RKF.

In the context of dialysis therapy intensity, it is important to recall studies that compared conventional in-center HD with more intensive forms of HD, that is, short frequent HD and nocturnal HD.[16,17] Unlike the HEMO study, many patients included in the Frequent Hemodialysis Network (FHN) trials—72% in the Nocturnal Trial and 34% in the Daily Trial—had substantial RKF (i.e., urine output >200 ml/day), with an average urine volume, renal urea clearance, and renal creatinine clearance of 760 ml/day, 2.3 ml/min, and 4.7 ml/min in the Nocturnal Trial; and 430 ml/day, 1.2 ml/min, and 2.7 ml/min in the Daily Trial.[18] The FHN trials showed, in the patient population included in both trials, that an intensified HD therapy could introduce risks related to more vascular access complications, more infections, faster loss of residual renal function, and more patient and care partner burden, with equivocal effects on death.[19–21] Barring the endeavor of recent FHN trials comparing short frequent HD or nocturnal frequent HD with conventional thrice-weekly HD,[16,17] no randomized controlled trial examined whether less-frequent HD treatments would be inadequate or harmful. In the rapidly changing landscape of healthcare delivery with the ever-growing recognized importance of personalized treatments, clinical trials that investigate the effectiveness and safety of personalized HD with less frequent HD vs conventional HD are sorely needed.

4 | KIDNEY ASSISTANCE THERAPY

We have considered the term kidney *assistance* therapy (KAT) in lieu of kidney replacement therapy, akin to device terminology (i.e., left ventricular assist device) used in patients with advanced heart failure.[22] KAT would better reconcile all available types of therapy for advanced kidney failure including dietary intervention, kidney transplantation, and dialysis at varied schedules.[23] Dietary interventions have an important role in preventing or delaying dialysis initiation yet

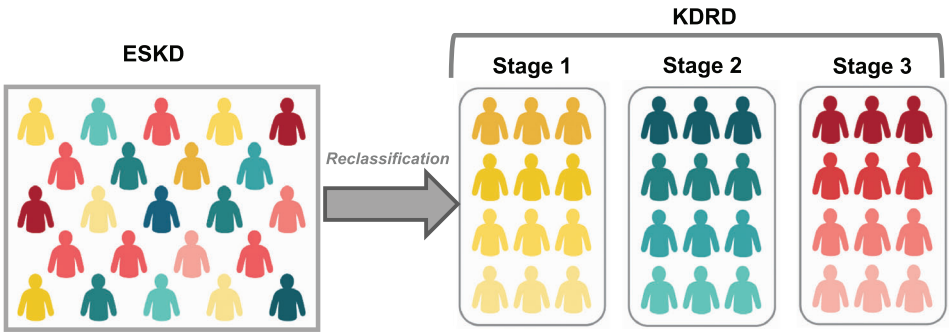

FIGURE 2 Theoretical illustration of patient heterogeneity at diagnosis of kidney dysfunction requiring dialysis. In a cross section of patients diagnosed with end-stage kidney disease (ESKD), wide differences in clinical manifestations, endogenous kidney function, and prognosis exist. ESKD clusters a spectrum of advanced kidney diseases requiring kidney assistance therapy subsumed under one disease entity. A change in the approach to diagnosis and treatment of ESKD to kidney dysfunction requiring dialysis (KDRD) with subgroups of syndrome stages along the continuum of kidney function loss could unravel a wider underlying patient population spectrum

it remains significantly underused. Research showed that a patient-centered plant-dominant low-protein diet (PLADO), of 0.6–0.8 g/kg/day composed of >50% plant-based sources, could be the centerpiece of a conservative and preservative kidney failure management strategy that challenges the prevailing dialysis-centered paradigm.[24] Based on the type of KAT selected, clinical management of advanced kidney failure may be categorized into kidney dysfunction requiring dietary intervention (KDRDt), kidney dysfunction requiring transplantation (KDRT), and kidney dysfunction requiring dialysis (KDRD). Importantly, KAT can be combined in the form of diet and dialysis (KDRDtD).[25–27] In a prospective multicenter randomized controlled study, Brunoli et al. assigned Italian uremic patients, age ≥70 years with GFR 5 to 7 ml/min and without diabetes, to a vegan diet (35 kcal; proteins, 0.3 g/kg body weight daily) supplemented with keto-analogues, amino acids, and vitamins ($n = 56$) or dialysis initiation ($n = 56$).[28] At 1 year, the observed survival rates (intention to treat analysis) were 83.7% (95% confidence interval [CI] [74.5, 94.0]) in the dialysis group and 87.3% (95% CI [78.9, 96.5]) in the diet group (log-rank test for noninferiority, $p < 0.001$; for superiority, $p = 0.6$); the difference in survival was −3.6% (95% CI [−17, +10]; $p = 0.002$); and the hazard ratio for hospitalization was 1.50 for the dialysis group (95% CI [1.11, 2.01]; $p < 0.01$). The authors concluded that supplemented very low protein diet was effective and safe for postponing dialysis treatment in elderly patients without diabetes.[28]

5 | THE SPECTRUM OF KIDNEY DYSFUNCTION REQUIRING DIALYSIS

A large body of research shows that patients receiving dialysis therapy experience a wide array of general symptoms of the uremia syndrome (dyspnea, faintness/dizziness, nausea, and appetite loss); neuromuscular problems (muscular ache and extremity numbness); and skin problems (dry, itchy skin)[29–31]; often in the form of symptom clusters.[32] A few cross-sectional studies showed that the severity of gastrointestinal and cardiopulmonary symptoms increased with length of time on dialysis and those with urine output <100 ml/day had more electrolyte imbalances and higher burden of unpleasant symptoms within symptom clusters.[31,33] Assessed with validated instruments, physical decline, frailty, and cognitive impairment also directly correlate with dialysis vintage.[34–36] Pathologic changes in the cardiovascular (e.g., myocardial fibrosis, pulmonary hypertension, valvular calcifications, and medial vascular calcification)[37–42]; cerebrovascular (cerebral atrophy, leukoaraiosis, and cerebral white matter water content)[43,44]; and gastrointestinal (liver iron content)[45] systems similarly worsen over time.

These findings fit with the model of spectrum disorder, in which the clinical and pathophysiologic features of ESKD progress over time. It has been theorized that progressive retention of middle molecules and protein-bound uremic solutes, resulted from the progressive decline in endogenous kidney solute clearance and limited dialytic removal with conventional dialysis treatments, are mechanisms for the accelerated disease processes in dialysis patients.[46–48] Thus, given the heterogeneous nature of clinical manifestations at the time of ESKD diagnosis and the seemingly progressive nature of clinical features associated with ESKD, revising ESKD taxonomy from a single, last-stage connotation to an entity with a measurable range of severity seems warranted.

6 | PARAMETERS TO CONSIDER IN DECONSTRUCTING KDRD

6.1 | Renal urea clearance

Clinical staging presupposes that illness evolves in an identifiable temporal progression of phases, differentiated by clinical presentation and/or specific biochemical markers. In diseases of the kidneys, common biochemical changes are modifications in plasma clearance and excretion of water and uremic solutes.

RKF, the equivalent of GFR in patients receiving dialysis therapy, is the term used to quantify endogenous kidney function, assessed on timed urine collection and expressed as urine volume/day and renal urea clearance (ml/min/1.73 m^2 or ml/min/35 L). The enduring value of renal urea clearance for management of patients with peritoneal dialysis has long been appreciated.[49–51] The prescription of peritoneal dialysis, being inherently of low efficiency compared with HD, takes into account residual renal urea clearance; the intensity of peritoneal dialysis is increased by adjusting volumes of dialysate and frequency of exchanges as the RKF declines.[52] The evidence for the value of renal urea clearance in peritoneal dialysis lends a compelling rationale for renal urea clearance-based classification. Patients with ESKD, found on the continuum of kidney dysfunction and GFR deterioration, could be subtyped based on the common determinant of RKF. Hence, we suggest changing the terminology of ESKD to "kidney dysfunction requiring dialysis" (KDRD) with stages categorized by levels of RKF—that is, residual renal urea clearance—at dialysis initiation and during the natural course of pathology progression (Figure 3).

The perspective of KDRD subtyping by levels of residual renal urea clearance stems from urea kinetic models. The HD prescription is intended to achieve target levels of weekly urea clearance; incorporation of residual renal urea clearance and Kt/Vurea permits adaptations in dialysis schedules.[53–55] Casino and Basile developed a variable target model of urea clearance whereby the weight given by residual renal urea clearance (normalized 35 L urea distribution volume) in weekly urea clearance is higher than in the fixed target model.[56–58] The computation with the variable target model yields a gradual schedule of HD for ranges of renal urea clearance, shown in Figure 3. Several ongoing clinical trials use similar renal urea clearance cut-offs to establish eligibility for study intervention of less frequent HD in the form of once- or twice-weekly HD versus thrice-weekly HD.[59–62]

Use of renal urea clearance has some limitations, because they depend on performing accurate urine collection and the day of urine volume collection (e.g., long vs. short interdialytic period). There is also the potential for intermittent and temporary decline in RKF with intercurrent acute illness.[55,63] For these reasons and pending more

Characterization	Syndrome Stage		
Residual Kidney Function	**Stage 1**	**Stage 2**	**Stage 3**
Renal urea clearance	>4.0 mL/min/35 L	2.0-4.0 mL/min/35 L	<2.0 mL/min/35 L
Hemodialysis (HD) schedule Dialysis dose, spKt/Vurea ≥1.20	**1 HD/week**	**2 HD/week**	**3 HD/week** **4 HD/week**
Clinical Manifestations	Patient-reported symptomatology, Volume overload		
Risk Profile	Preparedness for dialysis initiation, Socioeconomic index		
Additional Markers	Markers of tubular secretory function		

Note: Individual patients' HD regimens must consider uremic symptoms, hyperkalemia, volume management, and quality of life among other parameters.

Abbreviations: HD, hemodialysis; spKt/V, single pool Kt/V.

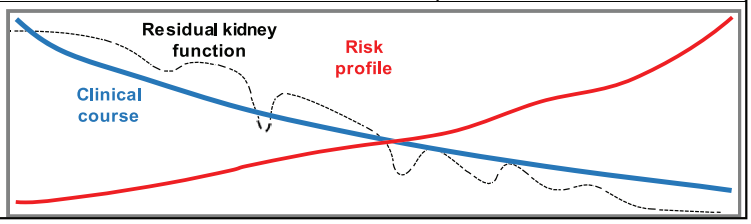

FIGURE 3 A conceptual model for deconstructing kidney dysfunction requiring dialysis

research on HD therapy adjustment by residual renal urea clearance levels, conservative renal urea clearance intervals could be considered for clinical staging. From a treatment standpoint, HD treatments with dialysis spKt/Vurea ≥1.20 can be provided once-weekly until residual renal urea clearance falls to <4.0 ml/min/35 L, and twice-weekly until residual renal urea clearance falls to <2.0 ml/min/35 L.[56–58] More frequent HD in the form of four or five times per week can also be considered. In patients with limited RKF, regimens of frequent HD (i.e., HD more frequent than conventional thrice-weekly HD) have been associated with improved composite outcomes of all-cause mortality and quality of life or all-cause mortality and reduction in left ventricular mass index.[16,64]

6.2 | Clinical manifestations

Renal urea clearance is just one element that can be used to guide dialysis prescription. A series of other clinical dimension ought to be incorporated when individualizing the HD prescription. These include management of volume status and blood pressure control, achieving adequate nutrition, anemia and bone-mineral metabolism control, and tailoring prescription to patient-reported symptomatology and goals of care.[13,65,66] Adjuvant pharmacologic therapies with potassium-binding agents and loop diuretics can facilitate dialytic therapy personalization. Enhanced volume control and sodium excretion with loop diuretics can provide protection from the adverse consequences of fluid overload.[67–69] Moreover, enhanced potassium excretion may allow individuals more dietary freedom, potentially allowing for better nutritional balance, greater protein intake, and prevention of protein energy wasting as well as improving quality of life.

An important objective in the care of patients with advanced kidney dysfunction, apart from conferring adequate solute clearance, is maintaining extracellular volume homeostasis. For patients on HD, a higher interdialytic weight gain is associated with higher ultrafiltration rates and increased mortality, independent of urea clearance.[70–72] The current consensus is that once- or twice-weekly HD is safe for patients with appropriate levels of residual renal urea clearance, as long as interdialytic weight gains do not exceed the upper limit of ultrafiltration rates.[73–75] For illness staging, an ultrafiltration rate scaled to body surface area could be considered.[76] For example, a patient on twice-weekly HD who has a residual renal urea clearance of 3 ml/min/35 L and ultrafiltration rates >13 ml/body surface area/hour, ought to have dialysis three times per week if interdialytic weight gains cannot be reduced with high-dose diuretics.[77] Prescription of diuretics after dialysis initiation can mitigate volume- and solute-related complications. Studies have found that among patients who initiate in-center HD with an active loop diuretic prescription, 46% receive a loop diuretic prescription refill after dialysis initiation; those continued on loop diuretics after the start of dialysis had a significant 7% lower risk for all-cause hospitalization after adjustment for health status.[78] Although renal urea clearance and urine output do not measure the same physiologic and clinical parameters—the former is a clearance and the latter a fluid volume—they are closely correlated.[79]

6.3 | Risk profile

Access to healthcare and social determinants are systemic issues that impact the acuity of dialysis initiation and bear important prognostic information.[80] These factors merit recognition in the categorization scheme (e.g., "planned" or "unplanned" dialysis initiation). Epidemiologic studies can build socioeconomic scores based on, for example, insurance and employment status. Patients with unplanned dialysis initiation and unfavorable socioeconomic score could benefit from more frequent evaluation and healthcare education during the first 3 months of dialysis.

6.4 | Protein-bound solutes and tubular secretory function

A more comprehensive, biologic characterization of KDRD requires a departure from the urea-centric approach and incorporation of solutes

that accumulate in much higher concentrations than urea.[46] Interest is growing in measuring tubular secretion of protein-bound solutes to provide insight into kidney disease etiology and improve adverse outcome predictions.[81] For example, hippuric acid, indoleacetic acid, and indoxyl sulfate circulate bound to plasma proteins,[82,83] minimizing effective removal by current dialysis modalities[84,85]; tubular secretion is as an essential mechanism for eliminating these molecules.[86] It has been postulated that the survival advantage in patients with KDRD and RKF is driven by preserved tubular secretory function rather than preserved glomerular filtration function.[49,51] Studies have shown that a decline in kidney function before dialysis initiation is accompanied by an increase in net secretory clearance, possibly reflecting an adaptive response.[87,88] Jhawar et al.,[89] Klammt et al.,[90] and Marquez et al.[91] showed that plasma indoxyl sulfate concentration is greater in anuric patients than those with RKF. Indoxyl sulfate may exert adverse cardiovascular effects by binding to the cytoplasmic aryl hydrocarbon receptor, which acts as a nuclear transcription factor mediating macrophage migration, oxidative stress, and transforming growth factor-signaling.[92] Several variables remain poorly defined when considering measurement of tubular secretory markers such as standardization of testing, correlation with regression of glomerular filtration and disease etiology, and association with clinical outcomes. Further research to address these and other elements of tubular secretory function is needed before its incorporation in clinical decision making.

7 | CLINICAL IMPLICATIONS OF A STAGING MODEL OF KDRD

Staging is particularly useful when it enables the understanding of illness progression from a heuristic perspective and when it guides therapy and estimates prognosis. The formal recognition of KDRD as a collection of heterogeneous kidney diseases with varying degrees of RKF may help eliminate the reluctance to accept alternative dialysis schedules and personalize treatment, to improve patients' quality of life and clinical outcomes.[63,93] Many would argue that, absent clinical practice substantiation from clinical trials and in the present era of using high-performance dialyzers, the frequency of HD treatments is partly driven by payor policy of payment for three HD sessions per week. Yet, we fail to consider that, akin to harmful effects reported with medical overtreatment of other conditions,[94–96] thrice-weekly HD may have detrimental effects in patients who could otherwise have been effectively treated, at least temporarily, with less frequent HD.

New taxonomy could spur research focusing specifically on early stages of KDRD, which is key to identify interventions that will prevent or delay transition to later stages. Importantly, research that will rigorously test the safety and effectiveness of less frequent schedules of HD in earlier stages of KDRD will fill knowledge gaps as to whether once-weekly or twice-weekly HD prevents progression to later stages while preserving or improving patients' survival and/or quality of life.[59,61,62] We note the distribution of individuals across stages of KDRD at the time of dialysis initiation is expected to vary by age, etiology of kidney disease, number, and/or severity of comorbidities, medications, and so forth.[97,98] Developing clinical and biological tools to predict RKF loss would greatly aid dialysis prescription, both for peritoneal dialysis and HD.[99–103] Patients may transition to more advanced stages of KDRD in a gradual or accelerated manner, and in a permanent or temporary fashion, the latter occurring in the setting of an acute illness and (reversible) acute kidney failure.

Another utility for KDRD staging is its potential to optimize research designs. To date, several different interventions tested in clinical trials found no beneficial effects in patients with ESKD treated with HD.[104–107] The reasons for treatment failure are multiple, including true failure of the tested interventions. However, inclusion of patients with different levels of RKF may have masked benefits of the interventions among phenotypic subgroups. As a result, generalization of results and the specific application of conclusions to a particular illness stage are challenging. We anticipate that a refined categorization of patients with KDRD would foster consistency in trial design, execution, and reporting.

8 | CONCLUSIONS

ESKD is a subjective diagnosis of a heterogeneous syndrome that lumps patients with uremic kidney diseases into one disease. The current approach to ESKD contrasts to that in other areas in medicine, where diagnoses and treatments are anchored in a solid understanding of the natural history of illness progression. A different terminology with added classification of ESKD into KDRD with stages that subgroup patients according to the severity of RKF may help clinicians personalize HD prescriptions and spur research to validate syndrome stages and identify risk factors that could predict stage progression, treatment response, and overall prognosis. Future research is necessary to incorporate acuity of dialysis initiation, RKF and socioeconomic index in the management of patients with KDRD; and elucidate the importance of tubular function in order to refine KAT in patients with KDRD of different severities.

CONFLICT OF INTEREST

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