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REVIEW

Is incremental hemodialysis ready to return on the scene? From empiricism to kinetic modelling

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Abstract Most people who make the transition to maintenance dialysis therapy are treated with a fixed dose thrice-weekly hemodialysis regimen without considering their residual kidney function (RKF). The RKF provides effective and naturally continuous clearance of both small and middle molecules, plays a major role in metabolic homeostasis, nutritional status, and cardiovascular health, and aids in fluid management. The RKF is associated with better patient survival and greater health-related quality of life, although these effects may be confounded by patient comorbidities. Preservation of the RKF requires a careful approach, including regular monitoring, avoidance of nephrotoxins, gentle control of blood pressure to avoid intradialytic hypotension, and an individualized dialysis prescription including the consideration of incremental hemodialysis. There is currently no standardized method for applying incremental hemodialysis in practice. Infrequent (once- to twice-weekly) hemodialysis regimens are often used arbitrarily, without knowing which patients would benefit the most from them or how to escalate the dialysis dose as RKF declines over time. The recently heightened interest in incremental hemodialysis has been hindered by the current limitations of the urea kinetic models (UKM) which tend to overestimate the dialysis dose required in the presence of substantial RKF. This is due to an erroneous extrapolation of the equivalence between renal urea clearance (Kru) and dialyser urea clearance (Kd), correctly assumed by the UKM, to the clinical domain. In this context, each ml/min of Kd clears the urea from the blood just as 1 ml/min of Kru does. By no means should such kinetic equivalence imply that 1 ml/min of Kd is clinically equivalent to 1 ml/min of urea clearance provided by the native kidneys. A recent paper by Casino and Basile suggested a variable target model (VTM) as opposed to the fixed model, because the VTM gives more clinical weight to the RKF and allows less frequent hemodialysis treatments at lower RKF. The potentially important clinical and financial implications of incremental hemodialysis render it highly promising and warrant randomized controlled trials.

Keywords End-stage renal disease · Incremental hemodialysis · Initiation of dialysis · Residual renal function · Twice-weekly hemodialysis · Urea kinetic modelling

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Introduction

During the upcoming decade about 1 million people in the US are expected to make the transition to dialysis therapy [1]. The majority of dialysis patients are currently treated with a fixed dose thrice-weekly hemodialysis (HD) (3HD/wk) regimen irrespective of whether they are starting dialysis therapy (incident) or have been receiving dialysis for some time (prevalent) and without consideration for their

residual renal function (RKF) [2]. Although the regulatory agencies might consider this HD regimen as "standard of care" and "adequate requirement", it is by no means perfect [2]. The 3HD/wk regimen has been assumed, until recently, almost as a dogma in the dialysis community [3, 4]. Historically, however, HD started with two treatment sessions per week in the 1960s and 1970s, but by the early 80s the HD frequency had increased to 3HD/wk [5]. Incredibly, the 3HD/wk schedule has been widely accepted worldwide without ever undergoing any randomized controlled trial (RCT) to examine whether less frequent HD treatments would be inadequate or harmful [6].

Over the past 30 years, major trials of HD adequacy, modality (nocturnal, home or in-center) and frequency (daily HD) have been anchored to 3HD/wk regimens as the gold standard, including the HEMO Study that failed to prove survival advantages of a higher HD dose [4]. Interestingly, a recent RCT suggested that more frequent (more than 3HD/wk, such as daily) HD may provide patient outcome benefits [7]. Owing to this background, it is easily understandable why a HD frequency of less than 3HD/wk is rarely prescribed in Europe (currently in only 5.2% of all patients in Europe [8]), and even much less so in the US and Canada (probably less than 1% [9]). In contrast to Europe and the US, a recent study reported that 26% of the Chinese dialysis populations are treated using a 2HD/wk schedule [10], which may be the result of socioeconomic conditions, including less access to dialysis therapy and inadequate resource availability.

Incremental HD

The optimal regimen for incident patients is not known. It is plausible that the routine practice of fixed-dose 3HD/wk in incident patients with substantial RKF may be harmful, contributing to an accelerated loss of RKF [11, 12]. Incremental HD is based on the simple idea of adjusting its dose according to the metrics of RKF. Indeed, most patients initiating dialysis have some degree of RKF, often a residual renal urea clearance (Kru) of >3 ml/min and a urine output (UO) of >500 ml/day. Given the importance of RKF preservation in conservative therapy, it seems a contradiction to ignore the contribution of RKF in incident HD patients. What is important to note is that the challenge of preserving RKF or UO in HD patients has never been taken seriously. Clinical practice guidelines generally advise against less than a3HD/wk schedule as inferior. These guidelines do not recommend an incremental transition from less to more frequent HD over time, while, ironically, according to most peritoneal dialysis (PD) guidelines, PD dose should be adjusted upwards parallel to the decline in RKF, the preservation of which is a high priority target in PD [6, 13].

Potential benefits of incremental HD

Survival

The body of literature on incremental HD is surprisingly small but of high-quality and fast growing, especially in recent years. There are no RCTs that directly compare standard 3HD/wk with incremental HD. The literature is without exception observational [10, 14–26] (Table 1). As far as survival is concerned, some studies suggest a survival advantage of incremental HD [14, 17, 21], while others report a similar mortality compared to standard HD [19, 23, 26] and a few suggest a higher mortality compared to standard HD [18, 20]. Taken together, the majority of the available studies suggest a non-inferiority of incremental HD related to survival, in that there appears to be no overtly harmful effects on survival by reducing dialysis dose so long as a significant RKF is present. It is important to note that subgroup analyses of a recent study showed a worse survival of incremental versus thrice-weekly HD only when the RKF was lowest, whereas survival was the same or even tended to be better with incremental HD when the RKF was higher [24]. In another study, in incident HD patients with low or moderate comorbid disease, survival was similar for patients initiated on an incremental or conventional HD regimen, whereas it was higher for more frequent HD [26].

Preservation of RKF

The key question is what is RKF in dialysis patients? Traditionally, renal function is expressed as glomerular filtration rate (GFR). The gold standard estimate of GFR is measurement of urinary clearance of inulin [27]. This requires the continuous infusion of inulin so it is impractical for routine clinical use. Although isotopic methods may have greater accuracy in determining GFR, cost and resources limit their use in routine clinical practice, and they also have their own confounders particularly in dialysis patients [28]. Thus, interdialytic urine collection remains the mainstay for measuring RKF in HD patients. In the absence of a mid-dialysis-collection point blood sample, the mean of the post- and pre-dialysis samples is conveniently used to reflect the mean interdialytic blood level. Ideally, urine collection should span the whole interdialytic period rather than just 24 h, since UO and GFR can vary significantly during the interdialytic period [29]. However, in the real world scenario of clinical practice, there is often a trade-off between the ideal and what patients find acceptable and can comply with. As such, many centers opt for a 24-h urine collection, as this is less inconvenient for the patient. The timing of such collections in relation

Table 1 Summary of studies examining the association between infrequent HD and clinical outcomes

References	Cohort description	Exposure (vs. 3HD/wk)	Results
Hanson et al. [14]	Incident HD patients (n = 4888) Prevalent HD patients (n = 10,179)	2HD/wk	Lower adjusted mortality risk in both incident and prevalent HD patients. This association was attenuated after adjustment for RKF at HD initiation (available only in incident patients)
Lin et al. [15]	Prevalent HD patients (n = 74)	2HD/wk	Similar nutritional laboratory parameters. Greater preservation of RKF (without adjustment)
Supasyndh et al. [16]	Prevalent HD patients (n = 142)	2HD/wk	Similar nutritional laboratory parameters and protein intake, but greater energy intake
Vilar et al. [17]	Incident HD patients (n = 650)	2HD/wk	Survival advantage and lower erythropoietin requirements in patients with significant RKF
Stankuviene et al. [18]	Incident HD patients (n = 2428)	1HD/wk 2HD/wk	Higher adjusted mortality (RKF data not available)
Lin et al. [19]	Incident HD patients (n = 639) Prevalent HD patients (n = 673)	2HD/wk	Similar adjusted mortality risk overall as well as subgroups of incident and prevalent patients (RKF data not available)
Elamin et al. [20]	Prevalent HD patients (n = 2012)	2HD/wk	Higher 1-year crude mortality (89% vs. 85%)
Fernandez-Lucas et al. [21]	Incident HD patients (n = 95)	2HD/wk	Greater crude survival. Greater preservation of RKF (without adjustment)
Caria et al. [22]	Incident HD patients (n = 68)	1HD/wk with low protein diet	Greater preservation of RKF (without adjustment)
Zhang et al. [10]	Incident HD patients (n = 85)	2HD/wk	Greater preservation of RKF (without adjustment). Odds ratio for faster RKF loss was 7.2 after adjustment for sex, urea reduction rate and intradyalitic hypotension episodes
Park et al. [23]	Incident HD patients (n = 927)	2HD/wk	Comparable results to 3HD/wk initiation for health-related quality of life, RKF and all-cause mortality
Obi et al. [24]	Incident HD patients (n = 23,645)	2HD/wk	Greater preservation of RKF. Higher mortality after the first year of dialysis in patients with the lowest RKF
Obi et al. [25]	Incident HD patients (n = 6538)	2HD/wk	Graded association of RKF decline during the first year of dialysis with all-cause mortality
Mathew et al. [26]	Incident HD patients (n = 50,756)	2HD/wk	Comparable results to 3HD/wk initiation for modelled mortality risk in selected patients with adequate RKF and reasonable general health

HD hemodialysis; *1HD/wk, 2HD/wk, 3HD/wk* once-weekly, twice-weekly, thrice-weekly hemodialysis, respectively; *RKF* residual renal function

to a dialysis session then becomes important, particularly for patients with less frequent dialysis schedules, as clearance will vary with time from the previous dialysis session and volume status [30]. RKF in the setting of dialysis can be assessed in different ways: Kru slightly underestimates GFR due to tubular reabsorption, whereas creatinine clearance overestimates GFR due to tubular secretion. So the composite clearance is used in clinical practice, with the assumption that tubular function mirrors GFR [28]. Thus, although 24-h urine collections remain the standard method for estimating RKF, the question arises which clearance is most important in patients on dialysis: Kru, the composite urea and creatinine clearance (GFR), or creatinine clearance? As renal function declines, there is a relative change in the balance between tubular creatinine secretion and GFR, and similarly some other tubular functions, such as the clearance of protein-bound azotemic toxins, are relatively preserved at reduced levels of GFR [28]. To overcome such difficulties, other markers of filtration have been advocated such as predialysis plasma levels of cystatin C [31, 32], β_2-microglobulin [32, 33] and β-trace protein [32, 33]. Shafi et al. recently developed and validated equations that estimate Kru in dialysis patients from

serum β_2-microglobulin, β-trace protein, and cystatin C concentrations without requiring urine collection [32]. At the same time, Wong et al. developed and validated equations that predict RKF in HD patients using serum β_2-microglobulin and β-trace protein [33]. However, it is unclear whether any of these markers will prove sufficiently accurate in the range of RKF in dialysis patients. Given the current limitations with using urea clearance, further research is necessary to find alternative inexpensive and easily measured filtration markers that are accurate enough to estimate RKF without the need for urine collections. Until such an alternative is found, the regular monitoring of RKF by periodic urine collections is required to ensure that RKF is being maintained and that dialysis schedules do not require adjustment [29]. RKF is roughly approximated by measuring UO. While RKF and UO do not measure the same physiologic quantities—the former is a clearance while the latter is just a fluid volume—they are closely related, as documented by some unpublished data of our own (Fig. 1). RKF in dialysis patients plays an important role in fluid and salt removal, effective phosphorus excretion, middle molecule clearance, and endogenous vitamin D and erythropoietin production [9, 34, 35]. Loss of RKF is linked to decreased survival [36, 37], likely from poorer uremic solute clearance [36], volume and blood pressure control [17, 38], higher erythropoietin requirements [39], more inflammation [36] and higher left ventricular mass [40].

The available literature suggests greater preservation of RKF with infrequent dialysis [15, 21, 22, 24].

Other potential benefits

Having 2HD sessions per week will also result in less frequent arteriovenous fistula or graft cannulations, which may prolong the longevity of dialysis vascular access [19]. The FHN study has shown that, compared to conventional HD, more frequent HD sessions were associated with a higher risk of vascular complications including repair-, loss-, or vascular access-related hospitalizations [41]. Additionally, by having one less HD treatment a week, patients can spend more time engaging in activities outside of the dialysis center, which may lead to substantially better health-related quality of life [9, 34, 35].

Potential harm of infrequent HD

Incremental HD is certainly not risk-free. It clearly requires close attention to clinical conditions and chemistries of the patient. Deterioration in chemistries or volume status may be unexpectedly abrupt and life threatening [42]. Uremia, a still somewhat mysterious condition, may present in ways that are not being monitored closely such as pericarditis, encephalopathy or neuropathy [43].

Interdialytic weight gain and ultrafiltration

Several studies have identified the long (3 days) interdialytic interval as an independent risk factor for all-cause mortality and cardiovascular hospitalization in patients treated with 3HD/wk [44–46], likely due to fluid overload

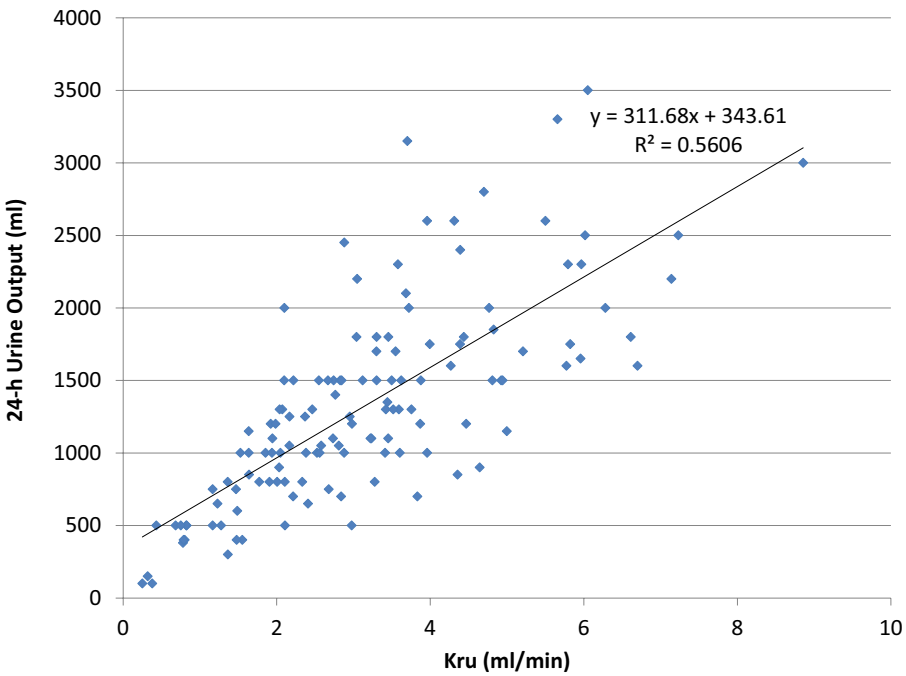

Fig. 1 Relationship between residual renal urea clearance (Kru) and 24-h urine output as measured after about 3 months from the start of HD. Unpublished data of our historical cohort of 130 consecutive incident patients starting HD at the Dialysis Unit of Matera Hospital are reported. They started HD on different treatment schedules: 40 patients on 3HD/wk, 60 on 2HD/wk, and 30 on 1HD/wk regimens, respectively

and/or electrolyte derangements. Although the potential complications of the long interval may seem to counteract the benefits of incremental HD, adverse outcomes associated with the long interdialytic interval were not observed among incident HD patients [44], many of whom likely have a higher RKF than prevalent patients and thus maintained better electrolyte and fluid balance. Moreover, it is possible, although not yet clearly proven, that the higher mortality of the long interdialytic interval relates to excess dialysis and abrupt removal and shifts of fluid and electrolyte (e.g. potassium) [47]. The latter is more likely especially since the high mortality of long HD interval happens on the day of the first dialysis therapy and not during the long interval where mortality is, in fact, the lowest. Interestingly, a recent study from UK showed that patients with RKF do not exhibit the high death rate after long interdialytic interval [47].

There may be misconceptions that larger interdialytic weight gain (IDWG) will be observed with incremental HD schedules compared to 3HD/wk schedules, and that aggressive ultrafiltration may be required. Ironically, indeed, it is far more plausible that more frequent HD would lead to greater IDWGs and cardiac structural abnormalities over time, due to faster loss of RKF [11]. Rapid ultrafiltration rates may also contribute to intradialytic hypotension, subclinical cardiac stunning, and myocardial ischemia [48]. Greater IDWG (≥5% of dry weight) and higher ultrafiltration rate (≥10 ml/h/kg) are associated with a higher risk of mortality [49, 50]. Other potential unfavorable features of incremental HD include persistent azotemia and electrolyte disturbances (e.g. hyperkalemia, hypercalcemia, and hyperphosphatemia), but these complications are less likely to occur in patients with substantial RKF [34].

Application of urea kinetic modelling to incremental HD

It is evident from the published literature [10, 14–26] (Table 1) that there are no well-thought-out standardized methods of applying incremental HD in practice. Infrequent regimens are currently being used arbitrarily, with no systematic process for making the decision as to which patients require less dialysis and then escalating dialysis dose appropriately as RKF declines over time [29].

The recently heightened interest in incremental HD [10, 15–26] has been hindered by the current urea kinetic model (UKM)-based prescription that, by overestimating the dialysis needs in the presence of substantial RKF, would require such high values for both the RKF and dialysis dose (Kt/V) [51, 52] that it would be difficult to prescribe less frequent treatments. This could cast doubts on the usefulness of the UKM as a guide to the prescription of incremental HD and drive the search for alternative indices of dialysis adequacy [32, 33]. While agreeing that evaluating the dialysis adequacy should not rely on a single index, we would confirm the need to keep the UKM as the gold standard, not only because it is the only established tool for assessing and prescribing dialysis [53–55], but also because in actual fact it is not responsible for the overestimation of dialysis needs. The problem is not intrinsic to the UKM, but rather is generated by a misconception or rather misunderstanding. The equivalence between Kru and dialysis clearance (Kd), correctly assumed by the UKM, simply means that each ml/min of Kd clears the urea from the blood just as 1 ml/min of Kru does [51, 53, 56]. By no means should such kinetic equivalence imply that 1 ml/min of Kd is clinically equivalent to 1 ml/min of urea clearance provided by the native kidneys. The benefits of retaining RKF appear to be greater than one would expect from simply enhanced small solute clearance: a multivariate survival analysis of patients on incremental HD suggested that 1 ml/min of Kru resulted in a greater survival benefit than 1 ml/min of HD urea clearance, possibly due to greater removal of middle molecules by native kidneys and improved volume control [17]. There is increasing evidence to suggest that clearance of other uremic solutes, particularly middle molecules such as β_2-microglobulin, is highly dependent on RKF. This extends even to very low levels of RKF: patients with Kru of <0.5 ml/min have significantly higher serum β_2-microglobulin levels than those with values between 0.5 and 1 ml/min [57]. Furthermore, RKF is the most significant determinant of β_2-microglobulin levels, even in patients treated with convective modalities such as hemodiafiltration [58, 59]. The same may apply to other middle molecules such as cystatin C [60], and protein-bound solutes such as p-cresol, which are poorly removed by HD and hemodiafiltration [38, 61]. Residual renal tubular function may represent important removal pathways for these and other compounds [62]. There is no universally accepted method of incorporating Kru into dialysis adequacy calculations since different authors have declared their own preferences [51, 63]. However, whatever method is employed, urea clearance targets still need to be met since Kt/V urea is the only marker that has been thoroughly examined in interventional trials [4, 63]. A warning is absolutely mandatory in the context of application of a program of incremental HD to clinical practice: the greatest attention should be paid to other parameters such as nutritional status, volume status, middle molecule removal, anemia, bone mineral metabolism, control of metabolic acidosis and inflammation, all of which contribute to overall well-being in HD patients [64]. It is noteworthy to underline that literature data have shown that RKF is associated with improved anemia control [65], blood pressure [39], nutritional status [66] and bone mineral metabolism [67]. Volume control

is also better due to the significant contribution of RKF to fluid and sodium removal [68]. The general principle for calculating the amount of dialysis required to compensate for RKF reduction is based on the constancy of a given target value for the total (dialytic + renal) equivalent continuous clearance (ECC) over a week period: i.e. at any given point in time, the sum of Kru and the component of the equivalent continuous clearance (ECCd) provided by the intermittent Kd, should achieve the fixed total ECC target [51, 69]. However, fixing the total ECC necessarily implies perfect equivalence of its renal and dialytic components. This assumption is wrong because Kru has much greater clinical weight than Kd; indeed, even though it may sound illogical, it really should not matter if the fixed total target value of 13 ml/min/40 l is obtained by summing Kru = zero and ECCd = 13 ml/min/40 l, or Kru = 13 ml/min/40 l and ECCd = zero. This assumption is no longer tenable, because, in agreement with a basic physiology notion, many studies have shown that the native kidney function is clinically much more important than dialysis clearances [52–56].

Most recently, Casino and Basile suggested that a variable target model (VTM) is more rational that a fixed one (FTM), because it correctly gives more clinical importance to the RKF [70]. In this regard, Casino and Basile proposed that the total ECC target varies as an inverse function of Kru, from a maximum value in anuria to a minimum value at Kru levels not yet requiring dialysis. In other words, they proposed a change in our appoach to dialysis adequacy assessment, which is a paradigm shift, from FTM to VTM in the prescription of incremental HD [70]. The new criteria suggest that, at least in relatively healthy patients, HD can be started at Kru ~5 ml/min/35 l on a 1HD/wk schedule; this can be maintained until Kru falls below 4 ml/min/35 l, at which point the treatment schedule should be changed to a 2HD/wk schedule, which, in turn, could be maintained until Kru falls below 2 ml/min/35 l, when the 3HD/wk schedule becomes really necessary [70].

Of note, comparing the results associated with FTM and VTM for three different ECCs, namely, the equivalent renal clearance (EKRc) [51], the original version of the standard Kt/V (stdKt/V) with Kru "compressed" at 70% [56], and the current version of stdKt/V with Kru at 100% [53], the equilibrated Kt/V (eKt/V) values required to attain VT with the original stdKt/V version were found to be similar to those required to attain FT with the current stdKt/V version [70]. Since the latter were also similar to the eKt/V values required to attain VT with EKRc [70], one can realize that either adding Kru at 100% instead of 70% in the calculation of stdKt/V, or reducing the target of EKRc as a function of Kru, both result in an increase in the relative weight of Kru. Hence, the two independent hypotheses, namely (a) adding Kru at 100% to stdKt/V, (b) reducing the total EKRc target as a function of Kru, reinforce each other [70]. Stated differently, the current version of stdKt/V including an increase in the relative weight of Kru should keep on using the current fixed target of 2.3 v/wk, which, on the other hand, could already allow a wider use of the 2HD/wk schedule.

Clearly, Kru and UO, as well as the metabolic and clinical conditions, should be assessed more frequently. In particular, the daily UO should be at least 500 ml/day [24]. Furthermore, since the targets are about 10–15% higher than the minimum required values, there is no need to aim at ECC values higher than the target [70].

This approach is likely to be safe, being in agreement with many observational data in the literature [10, 14–17, 71]. Vilar et al. reported in 650 incident dialysis patients treated with an incremental high-flux HD program that patients with significant RKF, despite receiving a lower dialysis dose, had a survival advantage and lower erythropoietin requirements [17]. Mortality outcomes from the United States Renal Data System population in 15,067 patients undertaking twice-weekly HD showed that prevalent patients had a lower mortality risk (RR = 0.76; p = 0.02) compared to thrice-weekly patients, although in incident patients there was no significant difference in mortality risk when adjusted for the equilibrated GFR at HD initiation (RR = 0.85; p = 0.31) [14]. Similarly, data from the Shanghai Renal Registry also showed similar survival rates between twice-weekly and thrice-weekly HD patients [10]. In addition to preservation of RKF, Lin et al. [15] also reported fewer episodes of hospitalization in twice-weekly HD patients. Nutritional and bone mineral biochemistry status appear to be no worse in infrequent or incremental dialysis regimens [15, 16, 71]. However, the crucial point still remains unsolved, and an RCT comparing incremental HD with the 3HD/wk schedule and focused on hard outcomes, such as survival and health-related quality of life, is urgently needed. It is also clearly evident that the group of patients that would hypothetically benefit most from incremental HD would be elderly patients, whose incidence and prevalence in the dialysis population is constantly growing worldwide. As said, the recent paper by Casino and Basile [70] suggested that VTM, which gives more clinical weight to the RKF, allows less frequent HD treatments at lower RKF as opposed to the FTM, based on the wrong concept of the clinical equivalence between renal and dialysis clearance. To test the VTM hypothesis, an RCT in incident HD patients should be planned: one arm should enroll patients starting either on standard 3HD/wk or on incremental HD with the FTM; the other arm should enroll patients starting on incremental HD with the VTM.

Conclusions

In maintenance dialysis patients, the RKF provides effective and continuous clearance of both small and middle molecules; it plays a role in metabolic homeostasis, nutritional status, and cardiovascular health; and it 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 comorbidities. Preservation of RKF in HD patients requires a careful approach, including regular monitoring, avoidance of nephrotoxins, gentle control of blood pressure, and a personalized initiation of dialysis prescription including consideration of incremental HD with a treatment frequency less than thrice-weekly [72]. In the context of incremental HD, the paradigm shift from the FTM to the VTM, whereby the VTM would allow less frequent treatments at lower Kru, with important clinical and financial implications in the prescription of incremental HD, as suggested by Casino and Basile [70], appears to be very promising. However, this needs to be confirmed by RCTs.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Informed consent For this type of study formal consent is not required.

Research involving human participants and/or animals This article does not contain any studies with human participants or animals performed by any of the authors.

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