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Title: The Importance of Residual Kidney Function in Haemodialysis Patients

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Abstract:

In contrast to peritoneal dialysis, residual kidney function is commonly disregarded for haemodialysis patients, and not regularly monitored or taken into account in routine clinical care. This is despite evidence that higher levels of residual kidney function in haemodialysis patients associate with better outcomes including survival, total solute clearance, nutrition, inflammation, and fluid balance. This review aims to summarise the clinical effects of residual kidney function specifically in haemodialysis patients. Some level of residual kidney function is present in over 80% of patients at the time of dialysis initiation, and while this declines over time, up to 30% of patients on haemodialysis for 5 years still have a measurable level of native kidney function. There is little evidence on how best to preserve residual kidney function in haemodialysis patients, although it has been observed that intensive haemodialysis regimens in incident haemodialysis patients appear to accelerate residual kidney function decline. Residual kidney function is not commonly factored in to haemodialysis prescription and measures of adequacy, despite the fact that some guidelines such as KDOQI and European Best Practice Guidelines suggest that it is reasonable to do. This likely relates, at least in part, to perceived concerns regarding the inconvenience of timed urine collections, and to the complexity and lack of consensus regarding the methods for integrating the intermittent clearance of haemodialysis with the continuous clearance of native renal function. Further research is required into how best to maintain and maximise the benefits of residual kidney function in haemodialysis patients.

Keywords: residual kidney function, haemodialysis, end stage renal failure, incremental haemodialysis

Introduction

Residual kidney function (RKF) in dialysis patients is defined by the remaining ability of the diseased kidneys to excrete water and uraemic solutes. In contrast to peritoneal dialysis (PD), in haemodialysis (HD) practice RKF is not commonly measured or taken into account in determining clinical care or dialysis prescription. This is despite higher RKF correlating with better outcomes such as improved survival, solute clearance, nutrition[1], anaemia and phosphate control[2], suggesting that efforts for monitoring and preserving RKF in HD patients may be worthwhile (Table 1). Both the Kidney Disease Outcomes Quality Initiative (KDOQI)[3] and European Best Practice Guidelines (EBPG)[4] have suggested that RKF may be incorporated into the HD prescription, so-called incremental HD, but this is not broadly practiced due to uncertainties about how this can be effectively and safely achieved.

This primary purpose of this review is to summarise the current literature about the relationships between RKF and outcomes specifically in the HD population. Furthermore we aim to discuss the methodology for RKF measurement, and to briefly discuss how RKF might be taken into account in the consideration of HD dosing.

Method

Literature was obtained using Ovid MEDLINE, EMBASE search conducted between 15/08/2017- 01/03/2018. The search terms used were “chronic kidney failure”,

"haemodialysis", "residual renal function", "residual kidney function" & "incremental". A total of 650 articles were obtained. Non-English articles, duplicates & articles without an abstract were then excluded. Additional articles were manually sourced from reference lists of relevant retrieved articles. Articles were included if their primary focus pertained to RKF in HD patient population and incremental HD.

Residual Kidney Function and Patient Survival

The importance of RKF has been demonstrated in multiple studies of PD but evidence related to its benefits in HD have only been emerging recently. Regarding PD data, a reanalysis of the CANUSA (Canada-United States Peritoneal Dialysis) study showed a significant contribution of RKF in 601 end stage kidney disease patients who were involved in this multicentre, prospective cohort study[5]. There was a 12% decrease in relative risk of death with each 5L/week per 1.73m^2 increment in glomerular filtration rate (GFR) and 36% decrease in relative risk of death with each 250ml increase in urine volume. In contrast, peritoneal clearance was not shown to be associated with patient survival.

Multiple studies have tried to examine if this association may extend to HD patients. In the NECOSAD (Netherlands Cooperative Study on the Adequacy of Dialysis) study, 740 incident HD patients were followed over a median follow-up time of 1.7 years and patient survival in relation to RKF was investigated[6]. Mortality was 56% lower with each 1.0 unit increase in renal urea standard Kt/V/week (Relative risk (RR) 0.44; 95% CI, 0.30-0.65, $p<0.0001$).

The CHOICE (Choices for Healthy Outcomes in Caring for End-Stage Renal Disease) study followed 734 incident HD patients for a year and found similar results. In this study, RKF was defined as patient-reported urine output (UO) of at least 250ml daily. Preserved RKF at 1-year was independently associated with 30% lower all-cause mortality (HR 0.7, CI 0.52-0.93, p=0.02), even after adjustment for confounders including demographics and clinical characteristics[7].

Furthermore, a prospective observational cohort study by Shemin *et al.* found that presence of RKF, even at a low level, was beneficial. In this study, after adjustment for other factors, RKF was protective against mortality over a 2-year period (Odds ratio (OR) 0.44; 95% CI 0.24-0.81, p=0.008)[8]. The mechanisms through which persistence of RKF may contribute to improved survival are likely to be multifactorial and are outlined below and in Table 1.

Effect of RKF on Solute clearance

In contrast to the intermittent clearance of solutes provided by HD, native renal function is continuous, and this may explain benefits conferred by RKF in end stage kidney disease patients. Kt/V_{urea} – dialyzer urea clearance adjusted for volume of distribution, is often used as a marker of dialysis adequacy. A native residual renal urea clearance (KRU) of 3ml/min in an average patient is equivalent to a weekly standard Kt/V_{urea} of approximately 1.0[3].

Fry et al. proposed that the benefits associated with RKF are not only due to the enhanced clearance of small molecular weight solutes, such as urea and creatinine, but also due to that of larger uraemic toxins such as middle molecular weight molecules, which are poorly cleared by HD[9]. In a cross-sectional, retrospective observational study involving 297 patients,

beta-2 microglobulin (β2M) was used as a representative middle molecule. This study found that RKF is associated with better clearance of β2M. Patients with KRU<0.5ml/min had significantly higher β2M levels than those with KRU of 0.5-1ml/min (28.2±6.2 vs 23.1±4.6 mg/l, p<0.001), suggesting that even low levels of RKF may be beneficial. Similar results were reported in another study where patients with RKF were found to have significantly lower levels of β2M[10].

RKF and Fluid Balance

Cardiovascular disease is known to be a leading cause of mortality in HD patients. Important determinants include accelerated atherosclerosis and left ventricular hypertrophy (LVH). Both volume overload and increase of total peripheral vascular resistance in HD patients contribute to LVH. The presence of RKF may improve fluid balance and thus provide cardiovascular benefits.

Previous cross-sectional studies done in PD patients have shown that decline in RKF was independently associated with increased left ventricular mass index[11] as well as poor blood pressure control[12]. In HD patients, RKF contributes to enhanced capacity for sodium removal and volume control, indicated by reduced interdialytic weight gain[13]. Significantly lower ultrafiltration requirement was also noted in patients with KRU e 1ml/min/1.73m^2 [14]. A cross-sectional observational study of 59 maintenance HD patients evaluated the cardiac effects of RKF, defined by having 24-hour urine output >200ml[15]. This study found that LVH and left ventricular systolic dysfunction were less severe in patients with RKF compared to those

without RKF, hypothesised to be related to better fluid balance and blood pressure control conferred by RKF.

This contrasts with results from a prospective study, which suggested that persistence of RKF was e largely dependent on volume overload[16]. Volume status was assessed by cardiothoracic index and left ventricular chamber size on echocardiographic examination. Strict volume control was applied to 19 incident HD patients for 3 months. It was found that left ventricular mass index decreased by 36% during this period, indicating regression of LVH, while a dramatic decrease in RKF was also noted, suggesting that preservation of RKF might contribute to volume overload and LVH. The power of the study is, however, limited by its small sample size and short duration of the study. Nonetheless, this study highlights that chronic hypervolaemia as a method of preserving RKF should be avoided. Of note, studies in patients on PD have found that extracellular volume expansion does not help preserve RKF[17, 18], whereas volume depletion can, as would be expected, negatively impact RKF[19].

RKF and Inflammation

Chronic, low-grade inflammation is common in chronic dialysis patients although the exact underlying mechanisms are not fully understood. Part of the increased inflammatory response may be related to platelet contact activation and complement cascade activation from blood flowing through the extracorporeal circuit, resulting in the release of a range of different proinflammatory cytokines.

A cross-sectional observational study by de Sequera *et al.* found that higher RKF was associated with lower levels of inflammatory parameters[10]. A lower percentage of

CD14+/CD16++ inflammatory monocytes (14.6% vs 28.3%, p=0.02) and lower concentrations of C-reactive protein (CRP) (6.2 vs 21.4mg/L, p=0.038) were found in patients with KRU >1ml/min and diuresis >100ml/day. Activated CD16+ monocytes induce endothelial damage which may contribute to development of atherosclerosis. Shafi *et al.* also observed a similar association between RKF and lower levels of inflammatory markers CRP and interleukin (IL)-6[7]. Similarly, Yang *et al.* observed higher urine output in HD patients correlated with lower levels of high sensitivity C-reactive protein[20].

RKF and Nutritional Status

In a retrospective study of 650 incident HD patients, RKF was shown to be associated with better nutritional status[14]. Compared with patients with KRU <1ml/min/1.73m2, those with KRUe 1ml/min/1.73m2 had higher serum albumin and normalised protein catabolic rate (nPCR) for up to 36 months. A cross-sectional multicentre study conducted in Taipei with 704 maintenance HD patients also found that suggest RKF contributes to improved nutritional status in HD patients, with a one-litre increase in residual 24-hour urine volume associated with a 1.4g/L increase in serum albumin[20].

RKF and Renal Anaemia

Observational studies have found reduced erythropoietin (EPO)-stimulating agent requirement in patients with significant RKF. Vilar *et al.*, found reduced weekly EPO dose and reduced EPO resistance index, for up to 48 months after HD initiation in patients with KRU e 1 ml/min/1.73m2, although no significant difference in serum haemoglobin was noted[14].

The CHOICE study also showed that patients with daily UO>250ml at 1-year after commencing HD, required a lower dose of EPO compared to those without (p=0.001)[7]. Similar trends were noted with EPO resistance index.

RKF and Phosphate Balance

Hyperphosphataemia is associated with vascular calcification and cardiovascular mortality among dialysis patients. Iwasawa *et al.* investigated if RKF contributes significantly to phosphate elimination, performing a retrospective, cross-sectional study with 79 chronic HD patients being categorised into two groups: 35 patients with GFR e 3ml/min and 44 patients with GFR <3ml/min[21]. Phosphate removed by dialysis was assessed in 9 anuric patients. A linear association was observed between residual GFR and urinary phosphate excretion. Patients with GFR e 3ml/min had approximately double mean weekly phosphate removal (2000.3 ± 804.1mg) compared with amount of phosphate removed in a single HD session (1019.9 ± 300mg) (p<0.001). In contrast, patients with GFR <3ml/min (952.9 ± 418.8mg) had a similar mean weekly phosphate removal compared with that removed by a single HD session.

Another cross-sectional study conducted in China found similar results[22]. RKF was found to be associated with significant capacity to excrete phosphate. Weekly phosphate excretion by urine in patients with RKF (daily urine output >200ml) was found to be ranged from 300 to 1500 mg which was equivalent to the total removal of by a single 4-hour HD session. This was also significantly higher than patients with daily urine output d 200ml (769±318 vs 122±106 mg/week, p<0.001). This corresponded to lower requirements for phosphate binding

medication ($CaCO_3$) in these patients. Interestingly, anuric patients with higher pre-dialysis serum phosphate concentration had lower phosphate removed by one HD session compared to those with RKF. The underlying mechanisms and the kinetics of phosphate during HD, however, are not fully understood yet. This study is similarly limited by the inability to accurately record patients' dietary phosphate intake as well as its small sample size.

RKF and Vascular Disease

Vascular disease is another common complication which contributes to significant cardiovascular morbidity in HD patients, but few studies have examined the relationship between RKF and vascular calcification and atherosclerosis. Most recently, a cross-sectional observational study set out to examine the relationship between RKF and atherosclerosis[23], in a study of 39 PD patients and 53 HD patients who were on maintenance dialysis therapy for at least 3 months to up to 3 years. In this study, atherosclerosis was defined as >10mm carotid artery intima media thickness and/or presence of plaque detected by B-mode ultrasonography. RKF was measured as GFR derived from interdialytic urine collection. In both univariate and multivariate analysis higher RKF predicted a lower risk of atherosclerosis (OR 0.95; 95% CI 0.54-0.99, p=0.041). However, this analysis was not specific to HD patients.

Another cross-sectional study conducted in China reported an association between loss of RKF and abdominal aortic calcification (ACC)[24]. In this study, loss of RKF was defined as daily UO <200ml, and abdominal aortic calcification score was measured based on lateral lumbar radiographs. Loss of RKF was associated with higher calcification score with a beta of 0.22 (95% CI 0.08-0.53, p=0.01) as analysed by multivariable linear regression. This

association was independent of identified confounders of vascular calcification such as age, HD vintage, diabetes, CRP and calcium-phosphorus product.

RKF and Quality of life

RKF has been associated with a better quality of life (QoL) in PD patients[25]. The mechanisms are uncertain, but could be related to improved nutrition, fluid balance, anaemia and phosphate control. In the CHOICE study, HD patients with urine output at baseline have also reported overall better QoL (p=0.05), as assessed by a validated patient self-reporting questionnaire[7]. However, data related to specific symptom burden in relation to RFK is generally lacking in the HD patient population.

RKF Measurement

There is debate regarding the best way of measuring RKF. Renal function is most commonly measured as glomerular filtration rate (GFR). The ideal method for measuring RKF is one that is accurate, reproducible, cost effective, and simple to perform. At present none of the available options perfectly fulfil these criteria, such that choice of methodology involves some compromises between accuracy, convenience and cost. Direct methods such as inulin, [51]chromium ethylenediaminetetra-acetic acid (EDTA), and iothalamate radiocontrast clearance are considered the most accurate way of determining GFR, but have limited place in the routine monitoring of RKF, and have not been adequately studied for this purpose.

Currently, RKF is most commonly measured by a timed urine collection for urea and creatinine clearance[3]. This is ideally done over the whole interdialytic period, typically 44

hours for a thrice-weekly regimen, to reduce the effect of variation in GFR across the interdialytic period. An alternative approach, is a 24-hour urine collection, which may be more convenient for patients. A complicating factor when measuring RKF by timed urine collection in HD patients, compared to PD patients, is the fluctuating urea and creatinine levels across the interdialytic time period. To deal with this the recommended method is to use the mean values of plasma measurements taken at the beginning and end of the timed urine collection[4].

Renal urea clearance underestimates GFR due to tubular reabsorption while creatinine clearance overestimates GFR due to tubular secretion. The mean of the urea and creatinine clearances has been shown to correlate well with inulin clearance[26]. For this reason, EBPG guidelines recommend measuring RKF in HD patients as the residual GFR determined as the mean of urea and creatinine clearances[4]. This composite clearance, however, does not accurately account for tubular function or clearance of protein-bound solutes and middle molecular weight molecules. In contrast, the KDOQI guidelines advise measuring RKF by urea clearance (KRU)[3], which has the potential disadvantage of underestimating GFR, but reduces the risk of overestimating GFR and helps facilitate the integration of RKF with dialysis clearance, which by convention is based on urea kinetics.

Recent studies have also considered other methods of measuring RKF on a regular basis including measurement of novel serum biomarkers such as cystatin C, beta 2 microglobulin (β2M) and beta-trace protein. The primary advantage of this approach is avoidance of the need for timed urine collections. Wong et al. demonstrated that serum β2M is independently associated with only RKF and diabetic status, but not with dialysis parameters including Kt/V,

and could potentially be used as a marker for RKF[27]. In this study equations were derived from serum ² 2M and beta-trace protein to predict GFR and KRU, and these equations were then tested in a validation cohort, comparing the calculated values with measured KRU and GFR (calculated from mean of urinary urea and creatinine clearances). Patients with KRU >2ml/min were correctly identified in 90% cases. A prediction equation for GFR that includes both beta-trace protein and ² 2M provided a better estimate than either alone. Hypothetically, if this method was used to identify patients with sufficient RKF to allow adjustment of HD dose, more than 95% of patients would receive a dialysis dose at or above target set by KDOQI guidelines but 5% of patients would be under-dialysed. A limitation of the study was that biomarkers were also only measured at a single time point and hence the rate of change of these markers relative to the progressive decline of RKF was not studied. In addition, β2M levels may also be affected by co-morbidities and other clinical factors which are not fully understood. Estimation of RKF using plasma beta-trace protein also might be less accurate in patients doing haemodiafiltration, which has been reported to reduce beta-trace protein levels by 61%[28].

Trend and Prevalence of RKF

RKF has been reported to be better maintained in PD patients than in HD patients[19]. Jansen *et al.* found that after adjustment for baseline variables and dropout, PD patients were shown to have 30% higher GFR than HD patients ($p<0.0001$) at 1 year after start of treatment. The most pronounced rate of decline in GFR occurred in the first three months after the start of treatment. In contrast, however, Mckane et al. found no difference in rate of decline of KRU between patients receiving high-flux biocompatible HD and those receiving continuous

ambulatory PD[29]. The more rapid decline of KRU was noted in the first 12 months after dialysis initiation. Whilst RKF declines following dialysis initiation, it is maintained in some patients. A UK study of 650 incident HD patients found that 58.1% and 31% of patients had a KRU e 1ml/min/1.73m2 at 2 years and 5 years after HD initiation respectively[14]. Little is known about incident and prevalent RKF in most HD populations, with registries such as ANZDATA not collecting data on this.

Clinical Strategies for the Preservation of RKF

In general, factors influencing the rate of RKF loss are less well studied and understood in HD, as compared to PD. Relevant variables potentially affecting the rate of decline of RKF in HD patients are summarised in Table 2, and include demographic factors and co-morbidities. Evidence regarding clinical strategies for the preservation of RKF in HD is limited, although there is some evidence that RKF loss can be influenced by the aspects of the HD prescription including the intensity and frequency of the haemodialysis regimen (Table 2)[30, 31]. Avoidance of intradialytic hypotension may also help preserve RKF[19, 31]. In failed renal transplant patients, maintenance of immunosuppression is associated with better preservation of RKF in peritoneal dialysis patients[32], however, data is not available on this in HD patients. The use of ultrapure dialysis fluid has been reported to the slow the loss of RKF in HD patients[33]. Avoidance of nephrotoxins such as radiocontrast dye, nonsteroidal anti-inflammatory drugs, and aminoglycosides is advised[34], although direct data on this is lacking.

Blockade of the renin-angiotensin system with angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers has been shown in several randomised controlled trials

to help preserve RKF in PD patients[35]. However, while there is some observational evidence that use of these agents is associated with preservation of RKF in HD patients, the only prospective randomised controlled trial performed in HD patients found that irbesartan treatment for 1 year did not affect the decline in GFR or urine volume[36].

Incremental Haemodialysis

It remains uncommon in current practice to take RKF into account when determining HD prescription and adequacy. This contrasts with PD, where RKF is routinely measured and systematically contributes to measures of treatment adequacy. Incorporation of RKF into HD prescription has been promoted by some investigators, so-called incremental HD, whereby patients with more RKF do less HD, whereas patients lacking RKF do more HD. Notably, both K-DOQI and EBPG guidelines support the use of Incremental HD prescription, provided careful monitoring of RKF is performed. In contrast, there are no current KHA-CARI guidelines for HD adequacy, and previous versions of those guidelines did not address a role for RKF. Specifically, the KDOQI guideline suggested that for haemodialysis patients with KRU e 2 ml/min/1.73m2, the dose of haemodialysis may be reduced provided RKF is measured periodically to avoid inadequate dialysis[3]. Similarly, the EBPG recommend measuring RKF in HD patients using the mean of urea and creatinine clearances to estimate residual GFR and offer suggestions to incorporate this into the HD prescription to allow individual adjustment of dialysis prescription to meet minimum dialysis adequacy target[4].

Effect of HD on RKF

One concern that has been raised is that more intensive HD regimens might better accelerate loss of RKF. Data from the Frequent Hemodialysis Network (FHN) Trials showed that more frequent nocturnal HD of 6 times per week accelerates loss of RKF, compared with standard 3 times per week HD[30]. In the FHN nocturnal study, 52% and 67% of patients receiving frequent nocturnal HD have zero urine volume at months 4 and 12, compared with 18% and 36% respectively in conventional HD group. This association was not found in the FHN frequent daily HD study, where patients had a lower baseline RKF.

Obi *et al*. also compared the changes in renal urea clearance and urine volume between patients initiated on conventional thrice-weekly HD regimen and those initiated on incremental twice-weekly HD regimen for >6 continuous weeks[37]. Three hundred and fifty-one incremental HD patients were matched to 8068 conventional HD patients. From month 3 onwards up to month 15, patients who were initiated on a twice-weekly regimen had 16% higher renal urea clearance (95% CI, 5-28%) than those who received a thrice-weekly dialysis regimen. In this study, increased mortality was observed in patients doing twice a week HD with a KRU d 3.0 ml/min/1.73m^2, but was not different for those with KRU > 3.0 ml/min/1.73m^2.

Similar results have been found in a retrospective Chinese study involving 85 incident HD patients with urine output e 500ml/day at baseline[38]. 30 patients were initiated with twice-weekly HD for 6 months or longer and 55 patients were started and maintained on thrice-weekly HD treatment. Selection of patients for twice-weekly HD was not random and was determined based on clinical condition, patient choice, compliance and economic conditions.

Compared with the thrice-weekly group, twice-weekly HD group was shown to have a lower RKF loss (10% vs 40%, p=0.03) especially in the first year of HD initiation.

Intradialytic hypotension has been hypothesised to be a possible cause of accelerated loss of RKF, with transient drops in blood pressure during dialysis causing ischaemic injury to kidneys. In a prospective observational study conducted in Taiwan, twice-weekly HD was associated with a slower decline in RKF, as indicated by urine volume and creatinine clearance, which was consistent with results from other studies. In addition, significantly fewer intradialytic hypotensive episodes were observed in the twice-weekly HD group compared to the thrice-weekly HD group. (0.26 ± 0.49 times/month vs 1.10±1.21 times/month; P<0.001)[39].

Methodology and Safety of Incorporating RKF into the HD Prescription

To include RKF into the HD prescription for an incremental HD approach, RKF clearance needs to be added to dialyzer clearance to calculate the total clearance. However, because HD is intermittent while RKF is continuous, either RKF needs to be converted to an equivalent intermittent clearance or dialysis clearance needs to be converted to an equivalent continuous clearance. Multiple approaches have been proposed but there is yet to be a universally accepted consensus as to the best method. Options include converting the weekly dialysis clearance into the equivalent renal urea clearance (EKRc)[40], use of the (weekly) standard Kt/V[41], and converting RKF to the equivalent intermittent clearance (Kt/V)[14]. Details of these methods are beyond the scope of this review and readers are referred to the primary references and other reviews.

A potential concern with Incremental HD is a higher risk of poor outcomes related to inadequate HD. This concern relates to real world questions about the reliability of methods for monitoring RKF, need for patients to comply with timed urine collections, and need for physicians to proactively increase the HD dose when RKF declines. There are no large randomised trials comparing incremental HD to a standard HD prescription.

Vilar *et al* reported the outcomes of 650 incident patients managed in an incremental high-flux HD programme over a 15-year period[14]. A key finding was that better outcomes were seen in patients with KRU e 1 ml/min/1.73m^2, despite these patients being treated with a lower dose of HD. While this provides some reassurance for the safety of incremental HD, the lack of a control group for the study limits its generalisability.

Zhang *et al.* also found no difference in clinical outcome in terms of HD adequacy, biochemical measures, cardiovascular morbidity or hospitalization rates between twice-weekly and thrice-weekly HD groups[31]. However, the power of this study is limited by its small sample size of 85 incident HD patients.

Obi *et al*. examined the relationship between incremental dialysis regimen and mortality risk[37]. In survival analyses after 1 year, there was no difference in all-cause mortality risk associated with incremental HD compared with conventional HD. Subgroup analyses, however, revealed 61% higher mortality risk in patients with lower baseline KRU of <3ml/min/1.73m2 (HR 1.61, 95% CI 1.07-2.44) but not in those with KRU>3ml/min/1.73m2 (HR 0.99, 95% CI 0.76-1.28). Limitations of this study include selection bias, as patients who have lower KRU and higher comorbidity burden were less likely to be prescribed an

incremental regimen. In addition, the sample size of patients receiving the incremental regimen was relatively small resulting in a wide confidence interval for the estimate. Nonetheless, this study underscores the potential risks of twice weekly dialysis in patients with minimal RKF. This is consistent with other studies showing increased mortality with twice weekly dialysis when RKF is not incorporated into the prescription[42].

Concerning results were shown in a prospective, multicentre observational study by Hwang *et al*.[43]. They found an increased risk of mortality (HR 4.2; 95% CI, 1.02-17.32, p=0.04) in patients with RKF undergoing twice-weekly HD (n= 113) compared with those with RKF undergoing thrice-weekly HD (n=137), despite adequate dialysis dose and fluid control. The authors postulated that this was possibly related to the poorer nutrition (reduced normalised protein catabolic rate) observed in twice-weekly group at 24 and 36 months, and suggested that other risk factors other than RKF should also be taken into account when prescribing twice-weekly HD.

Conclusion

In summary, there is substantial evidence suggesting that there are many benefits conferred by RKF, such as improved fluid balance, nutritional status and better clearance of solutes. Efforts to preserve RKF are justified although how best to do this is unclear. Avoidance of nephrotoxins in HD patients with remaining RKF is advised. Some evidence suggests that more intensive HD regimens accelerate the loss of RKF, so this should be taken into account, particularly around the time of HD initiation. Adjustment of HD prescription taking into account RKF, incremental HD, may have advantages in terms of RKF preservation, quality of

life, and health care costs, which need to be balanced against the risks including the dangers of inadequate dialysis. Further research is required into how to best preserve RKF in HD patients, and to clarify the role for RKF in determining the optimal HD prescription.

Effect	References
Patient survival	5, 7, 8, 14, 44
Solute clearance	3, 4, 10, 13, 44, 45
Nutrition	14, 20
Inflammation	7, 10, 20
Quality of Life	7
Anaemia Control	7, 14
Fluid Balance	13, 14
Phosphate balance	13, 22, 46
Cardiovascular disease	11, 15, 23, 24

Table 1: Reported beneficial associations of residual kidney function in dialysis patients

Factor	Comments and References
Gender	Inconsistent data[31, 47]
Race	Faster RKF decline in non-white race[47]
Co-morbidities	Faster RKF decline with diabetes[47], cardiac failure[47], proteinuria[19], and failed kidney transplant[13]
Dialysis modality	Possibly slower RKF decline with PD than HD[19, 29, 47, 48]
Intensity and Frequency of Haemodialysis Regimen	Accelerated RKF loss seen with frequent nocturnal HD[30] Slower RKF loss with incremental (twice weekly) HD initiation[31]
High flux biocompatible membranes and ultrapure water	Adverse effects of membrane incompatibility and non-ultrapure water might account for differences between PD and HD seen in earlier studies[29, 33]
Intradialytic hypotension	Likely mechanism is renal vasoconstriction and ischaemia[19, 31]
Other nephrotoxins (e.g. aminoglycosides, NSAIDs, radiocontrast)	Likely to be relevant even though direct data is not available

Table 2: Possible factors affecting rate of decline of RKF in haemodialysis Patients

References

1 Suda T, Hiroshige K, Ohta T, Watanabe Y, Iwamoto M, Kanegae K*, et al.* The contribution of residual renal function to overall nutritional status in chronic haemodialysis patients. *Nephrol Dial Transplant*. 2000; **15**: 396-401.

2 Penne EL, van der Weerd NC, Grooteman MP, Mazairac AH, van den Dorpel MA, Nube MJ*, et al.* Role of residual renal function in phosphate control and anemia management in chronic hemodialysis patients. *Clin J Am Soc Nephrol*. 2011; **6**: 281-9.

3 National Kidney F. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. *Am J Kidney Dis*. 2015; **66**: 884-930.

4 European Best Practice Guidelines Expert Group on Hemodialysis ERA. Section II. Haemodialysis adequacy. *Nephrol Dial Transplant*. 2002; **17 Suppl 7**: 16-31.

5 Bargman JM, Thorpe KE, Churchill DN, Group CPDS. Relative contribution of residual renal function and peritoneal clearance to adequacy of dialysis: a reanalysis of the CANUSA study. *J Am Soc Nephrol*. 2001; **12**: 2158-62.

6 Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT*, et al.* Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *J Am Soc Nephrol*. 2004; **15**: 1061-70.

7 Shafi T, Jaar BG, Plantinga LC, Fink NE, Sadler JH, Parekh RS*, et al.* Association of residual urine output with mortality, quality of life, and inflammation in incident hemodialysis patients: the Choices for Healthy Outcomes in Caring for End-Stage Renal Disease (CHOICE) Study. *American Journal of Kidney Diseases*. 2010; **56**: 348-58.

8 Shemin D, Bostom AG, Laliberty P, Dworkin LD. Residual renal function and mortality risk in hemodialysis patients. *American Journal of Kidney Diseases*. 2001; **38**: 85-90.

9 Fry AC, Singh DK, Chandna SM, Farrington K. Relative importance of residual renal function and convection in determining beta-2-microglobulin levels in high-flux haemodialysis and on-line haemodiafiltration. *Blood Purif*. 2007; **25**: 295-302.

10 de Sequera P, Corchete E, Bohorquez L, Albalate M, Perez-Garcia R, Alique M*, et al.* Residual Renal Function in Hemodialysis and Inflammation. *Therapeutic Apheresis and Dialysis*. 2017; **21**: 592-98.

11 Wang AY-M, Wang M, Woo J, Law M-C, Chow K-M, Li PK-T*, et al.* A novel association between residual renal function and left ventricular hypertrophy in peritoneal dialysis patients. *Kidney International*. 2002; **62**: 639-47.

12 Menon MK, Naimark DM, Bargman JM, Vas SI, Oreopoulos DG. Long-term blood pressure control in a cohort of peritoneal dialysis patients and its association with residual renal function. *Nephrol Dial Transplant*. 2001; **16**: 2207-13.

13 Morduchowicz G, Winkler J, Zabludowski JR, Boner G. Effects of residual renal function in haemodialysis patients. *Int Urol Nephrol*. 1994; **26**: 125-31.

14 Vilar E, Wellsted D, Chandna SM, Greenwood RN, Farrington K. Residual renal function improves outcome in incremental haemodialysis despite reduced dialysis dose. *Nephrology Dialysis Transplantation*. 2009; **24**: 2502-10.

15 Ma T, Ding G. Effects of residual renal function on left ventricle and analysis of related factors in patients with hemodialysis. *Renal Failure*. 2013; **35**: 198-203.

16 Gunal AI, Kirciman E, Guler M, Yavuzkir M, Celiker H. Should the preservation of residual renal function cost volume overload and its consequence left ventricular hypertrophy in new hemodialysis patients? *Renal Failure*. 2004; **26**: 405-9.
17 McCafferty K, Fan S, Davenport A. Extracellular volume expansion, measured by multifrequency bioimpedance, does not help preserve residual renal function in peritoneal dialysis patients. *Kidney International*. 2014; **85**: 151-7.
18 Rhee H, Baek MJ, Chung HC, Park JM, Jung WJ, Park SM*, et al.* Extracellular volume expansion and the preservation of residual renal function in Korean peritoneal dialysis patients: a long-term follow up study. *Clin Exp Nephrol*. 2016; **20**: 778-86.
19 Jansen MA, Hart AA, Korevaar JC, Dekker FW, Boeschoten EW, Krediet RT*, et al.* Predictors of the rate of decline of residual renal function in incident dialysis patients. *Kidney International*. 2002; **62**: 1046-53.
20 Yang PY, Lin JL, Lin-Tan DT, Hsu CW, Yen TH, Chen KH*, et al.* Residual daily urine volume association with inflammation and nutrition status in maintenance hemodialysis patients. *Renal Failure*. 2009; **31**: 423-30.
21 Iwasawa H, Nakao T, Matsumoto H, Okada T, Nagaoka Y, Wada T. Phosphate handling by end-stage kidneys and benefits of residual renal function on phosphate removal in patients on haemodialysis. *Nephrology (Carlton)*. 2013; **18**: 285-91.
22 Wang M, You L, Li H, Lin Y, Zhang Z, Hao C*, et al.* Association of circulating fibroblast growth factor-23 with renal phosphate excretion among hemodialysis patients with residual renal function. *Clinical Journal of The American Society of Nephrology: CJASN*. 2013; **8**: 116-25.
23 Rroji M, Spahia N, Seferi S, Barbullushi M, Spasovski G. Influence of Residual Renal Function in Carotid Modeling as a Marker of Early Atherosclerosis in Dialysis Patients. *Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy*. 2017; **21**: 451-58.
24 Chen HC, Chou CY, Jheng JS, Chen IR, Liang CC, Wang SM*, et al.* Loss of Residual Renal Function is Associated With Vascular Calcification in Hemodialysis Patients. *Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy*. 2016; **20**: 27-30.
25 Termorshuizen F, Korevaar JC, Dekker FW, van Manen JG, Boeschoten EW, Krediet RT*, et al.* The relative importance of residual renal function compared with peritoneal clearance for patient survival and quality of life: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Am J Kidney Dis*. 2003; **41**: 1293-302.
26 Milutinovic J, Cutler RE, Hoover P, Meijsen B, Scribner BH. Measurement of residual glomerular filtration rate in the patient receiving repetitive hemodialysis. *Kidney Int*. 1975; **8**: 185-90.
27 Wong J, Sridharan S, Berdeprado J, Vilar E, Viljoen A, Wellsted D*, et al.* Predicting residual kidney function in hemodialysis patients using serum beta-trace protein and beta2-microglobulin. *Kidney Int*. 2016; **89**: 1090-98.
28 van Craenenbroeck AH, Bragfors-Helin AC, Qureshi AR, Lindholm B, Sjoberg B, Anderstam B*, et al.* Plasma Beta-Trace Protein as a Marker of Residual Renal Function: The Effect of Different Hemodialysis Modalities and Intra-Individual Variability over Time. *Kidney Blood Press Res*. 2017; **42**: 877-85.
29 McKane W, Chandna SM, Tattersall JE, Greenwood RN, Farrington K. Identical decline of residual renal function in high-flux biocompatible hemodialysis and CAPD. *Kidney International*. 2002; **61**: 256-65.

30 Daugirdas JT, Greene T, Rocco MV, Kaysen GA, Depner TA, Levin NW*, et al.* Effect of frequent hemodialysis on residual kidney function. *Kidney Int*. 2013; **83**: 949-58.
31 Zhang M, Wang M, Li H, Yu P, Yuan L, Hao C*, et al.* Association of initial twice-weekly hemodialysis treatment with preservation of residual kidney function in ESRD patients. *American Journal of Nephrology*. 2014; **40**: 140-50.
32 Jassal SV, Lok CE, Walele A, Bargman JM. Continued transplant immunosuppression may prolong survival after return to peritoneal dialysis: results of a decision analysis. *Am J Kidney Dis*. 2002; **40**: 178-83.
33 Schiffl H, Lang SM, Fischer R. Ultrapure dialysis fluid slows loss of residual renal function in new dialysis patients. *Nephrology Dialysis Transplantation*. 2002; **17**: 1814-8.
34 Mathew AT, Fishbane S, Obi Y, Kalantar-Zadeh K. Preservation of residual kidney function in hemodialysis patients: reviving an old concept. *Kidney International*. 2016; **90**: 262-71.
35 Liu Y, Ma X, Zheng J, Jia J, Yan T. Effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on cardiovascular events and residual renal function in dialysis patients: a meta-analysis of randomised controlled trials. *BMC Nephrol*. 2017; **18**: 206.
36 Kjaergaard KD, Peters CD, Jespersen B, Tietze IN, Madsen JK, Pedersen BB*, et al.* Angiotensin blockade and progressive loss of kidney function in hemodialysis patients: a randomized controlled trial. *Am J Kidney Dis*. 2014; **64**: 892-901.
37 Obi Y, Streja E, Rhee CM, Ravel V, Amin AN, Cupisti A*, et al.* Incremental Hemodialysis, Residual Kidney Function, and Mortality Risk in Incident Dialysis Patients: A Cohort Study. *American Journal of Kidney Diseases*. 2016; **68**: 256-65.
38 Zhang M, Wang M, Li H, Yu P, Yuan L, Hao C*, et al.* Association of initial twice-weekly hemodialysis treatment with preservation of residual kidney function in ESRD patients. *Am J Nephrol*. 2014; **40**: 140-50.
39 Lin YF, Huang JW, Wu MS, Chu TS, Lin SL, Chen YM*, et al.* Comparison of residual renal function in patients undergoing twice-weekly versus three-times-weekly haemodialysis. *Nephrology*. 2009; **14**: 59-64.
40 Casino FG, Lopez T. The equivalent renal urea clearance: a new parameter to assess dialysis dose. *Nephrol Dial Transplant*. 1996; **11**: 1574-81.
41 Daugirdas JT, Depner TA, Greene T, Levin NW, Chertow GM, Rocco MV*, et al.* Standard Kt/V-urea: a method of calculation that includes effects of fluid removal and residual kidney clearance. *Kidney International*. 2010; **77**: 637-44.
42 Stankuviene A, Ziginskiene E, Kuzminskis V, Bumblyte IA. Impact of hemodialysis dose and frequency on survival of patients on chronic hemodialysis in Lithuania during 1998-2005. *Medicina (Kaunas)*. 2010; **46**: 516-21.
43 Hwang HS, Hong YA, Yoon HE, Chang YK, Kim SY, Kim YO*, et al.* Comparison of Clinical Outcome Between Twice-Weekly and Thrice-Weekly Hemodialysis in Patients With Residual Kidney Function. *Medicine (Baltimore)*. 2016; **95**: e2767.
44 Termorshuizen F, Dekker FW, van Manen JG, Korevaar JC, Boeschoten EW, Krediet RT*, et al.* Relative contribution of residual renal function and different measures of adequacy to survival in hemodialysis patients: an analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2. *Journal of the American Society of Nephrology*. 2004; **15**: 1061-70.
45 Fry AC, Singh DK, Chandna SM, Farrington K. Relative importance of residual renal function and convection in determining beta-2-microglobulin levels in high-flux haemodialysis and on-line haemodiafiltration. *Blood Purification*. 2007; **25**: 295-302.

46 Iwasawa H, Nakao T, Matsumoto H, Okada T, Nagaoka Y, Wada T. Phosphate handling by end-stage kidneys and benefits of residual renal function on phosphate removal in patients on haemodialysis. *Nephrology*. 2013; **18**: 285-91.
47 Moist LM, Port FK, Orzol SM, Young EW, Ostbye T, Wolfe RA*, et al.* Predictors of loss of residual renal function among new dialysis patients. *Journal of the American Society of Nephrology*. 2000; **11**: 556-64.
48 Lang SM, Bergner A, Topfer M, Schiffl H. Preservation of residual renal function in dialysis patients: effects of dialysis-technique-related factors. *Peritoneal Dialysis International*. 2001; **21**: 52-7.