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Longitudinal Changes in Kidney Solute Clearance in a Prospective Cohort of Patients Initiating Chronic Hemodialysis

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Introduction: Longitudinal changes in residual kidney function have not been well-examined in patients starting chronic hemodialysis (HD).

Methods: We analyzed urine volume and kidney solute clearances from timed urine collections and corresponding plasma samples from 42 patients randomized to incremental HD ($n = 21$) and conventional HD ($n = 21$) in the TwoPlus pilot study. Samples were collected before HD initiation (baseline); and at 6, 12, 24, and 48 weeks. We assessed temporal trends in urine volume, kidney urea and creatinine clearance, and correlations between urine volume and kidney solute clearance.

Results: Residual kidney function parameters in all patients declined over time; the pattern of decline differed between urine volume and kidney solute clearances. Urine volume declined at a steady rate with median (quartile 1, quartile 3) percentage change relative to baseline of −10% (−36 to 29) at week 6 and −47% (−76 to 5) by week 48. Kidney urea and creatinine clearances exhibited a larger decline than urine volume at week 6, −32% (−61 to 8) and −47% (−57 to −20), respectively. The rate of decline subsequently slowed, reaching about 61% decline for both solutes by week 48. Conventional HD demonstrated larger declines in urine volume and kidney urea clearance than incremental HD at week 6. Urine volume showed moderate correlation with urea (R = 0.47) and weaker correlation with creatinine (R = 0.34).

Conclusion: Despite gradual decrement in urine volume and kidney solute clearances, residual kidney function persists nearly 1 year after HD initiation. This knowledge could motivate increased practice of individualizing HD prescriptions by incorporating residual kidney function.

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Ongoing kidney function is often present when chronic dialysis is added to the treatment of kidney dysfunction requiring dialysis.[1–3] It has long been noted that endogenous residual kidney function contributes importantly to solute clearance and clinical outcomes in patients treated with peritoneal dialysis[4] as well as those treated with HD.[5–7] Accordingly, measurement of residual kidney function as kidney urea clearance and/or kidney creatinine clearance based on timed urine collections is performed routinely in patients treated with peritoneal dialysis. Furthermore, residual kidney function is incorporated into peritoneal dialysis prescriptions to achieve a targeted, per week, total solute clearance as a sum of kidney and peritoneal dialysis clearances.[8] However, residual kidney function is not given the same attention for patients treated with HD. There is so far no biologic rationale to justify the discrepancy of residual kidney function contribution between peritoneal dialysis and HD. Moreover, abundant data has shown that the residual kidney provides valuable solute clearance and volume control in patients treated with HD.[9–13]

Studies have shown a direct correlation between residual kidney function levels and clinical outcomes in patients treated with HD.[4,5,14] Clinical practice

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guidelines have therefore recommended monitoring of residual kidney function in patients treated with HD.[15,16] The HD prescription could then be individualized based on residual kidney function to provide adequate solute and volume control as well as achieve a targeted solute clearance per week—akin to the approach taken in patients treated with peritoneal dialysis.[17] Routine measurement of residual kidney function and its incorporation into HD prescription, however, is infrequently performed. As a result, there is insufficient knowledge of the trajectory and relationship among various residual kidney function parameters over time. To address this knowledge gap, we analyzed the longitudinal changes and relationship of urine volume and kidney solute clearances in patients started on chronic dialysis who participated in the pilot study of twice-weekly HD with adjuvant pharmacologic therapy versus thrice-weekly HD (the TwoPlus pilot study).[2] Specifically, we assessed the change in urine volume and kidney clearances of 2 solutes (urea and creatinine) in individual patients over 48 weeks; and examined associations between urine volume and kidney solute clearances.

METHODS

Study Design and Patients Studied

The TwoPlus pilot study was a prospective, parallel-group, open label, randomized controlled trial that tested 2 modalities of HD initiation in incident patients (NCT03740048). The study was performed at 14 outpatient dialysis units affiliated with a large academic tertiary center in North Carolina, USA. The methods were previously described.[18] Briefly, the objective of the TwoPlus pilot study was to identify design and feasibility components required to conduct a larger clinical trial of incremental, twice-weekly HD versus conventional, thrice-weekly HD in incident patients. Key inclusion criteria included receipt of ≤6 HD sessions before enrollment and urine output ≥500 ml/d. Key exclusion criteria included severe systolic cardiac dysfunction with left ventricular ejection fraction <30% and a medical condition or history of noncompliance that, in the opinion of the investigator or treating nephrologist, would jeopardize the safety of the subject. Patients were randomized in a 1:1 ratio to incremental HD (twice-weekly HD with adjunctive pharmacologic therapy loop diuretic, patiromer, and sodium bicarbonate for 6 weeks followed by transition to thrice-weekly HD) or conventional HD (thrice-weekly HD). Patients were followed-up with for a total of 48 weeks. Feasibility and clinical outcomes in this pilot study have been reported previously.[2]

Data Collection

Measurements of residual kidney function were performed at enrollment (baseline) and at weeks 6, 12, 24, and 48 (± 7days). Timed urine collection at baseline consisted of a 24-hour urine collection obtained within 1 week before HD initiation. At follow-up, timed urine collection consisted of interdialytic urine collection starting at the end of an HD session and ending at the beginning of the next HD session. In the incremental HD group, interdialytic urine collection at week 6 was performed during the week that the patient switched to thrice-weekly HD. A specific time period of the week, relative to HD days, was not imposed on patients for interdialytic urine collection. Duration of urine collections could therefore be performed during the 2-day or 3-day interdialytic interval. Measurements performed on urine collections included volume and urea nitrogen and creatinine concentrations. At each period of interdialytic urine collection, a blood sample was collected at the end of the HD session, which represented the start point of urine collection; and at the beginning of the next HD session, which represented the end point of urine collection. The patients brought in the urine collections to the dialysis unit and the dialysis personnel sourced the samples to the local laboratory affiliated with the respective dialysis unit.

Kidney Solute Clearance

Solute clearance afforded by residual kidney function was assessed by measurement of 2 solutes (urea and creatinine) at 5 different time points for each patient (baseline and weeks 6, 12, 24, and 48). At each time point, clearances were measured using the simultaneously collected blood and urine samples.[19] We calculated kidney solute clearance in ml/min for urea and creatinine using the formula:

$$\text{Clearance (ml/min)} = \frac{\text{urine solute concentration} \times \text{urine volume} / \text{urine collection duration}}{\text{average of post}-\text{HD plasma solute concentration and pre}-\text{HD plasma solute concentration}}$$

Where urine solute concentration is urea nitrogen (mg/dl) or creatinine (mg/dl); urine volume is the volume (ml) collected over an entire interdialytic period; urine collection duration is expressed in minutes and

Table 1. The time course of residual kidney function parameters

Parameter	Baseline		Week 6			Week 12			Week 24			Week 48		
	n	Value	*n*	Value	Delta	*n*	Value	Delta	*n*	Value	Delta	*n*	Value	Delta
All patients														
Urine volume (ml/24 h)	42	1219 (840)	43	1168 (880)	−10% (−36, 29)	41	977 (874)	−22% (−61, 57)	34	827 (509)	−31% (−61, 39)	32	649 (457)	−47% (−76, 5)
Kidney urea clearance, ml/min per 1.73 m^2	38	3.71 (2.79)	37	2.24 (1.42)	−32% (−61, 8)	40	1.95 (1.25)	−50% (−61, 3)	33	1.77 (1.07)	−53% (−78, −5)	30	1.32 (0.97)	−61% (−91, −35)
Kidney creatinine clearance, ml/min per 1.73 m^2	39	9.63 (5.88)	41	5.74 (4.70)	−47% (−57, −20)	41	5.36 (3.54)	−45% (−66, −11)	30	5.04 (3.05)	−46% (−71, −19)	30	3.98 (3.44)	−61% (−84, −31)
Incremental HD group														
Urine volume (ml/24 h)	21	1062 (735)	21	1129 (762)	−6% (−36, 33)	21	931 (637)	−20% (−36, 76)	17	751 (416)	−29% (−61, 53)	17	565 (312)	−29% (−75, 18)
Kidney urea clearance, ml/min per 1.73 m^2	21	3.51 (2.85)	19	2.41 (1.84)	−32% (−61, 11)	20	1.90 (1.32)	−50% (−58, 4)	16	1.53 (1.01)	−64% (−79, −1)	16	1.06 (0.83)	−76% (−91, −37)
Kidney creatinine clearance, ml/min per 1.73 m^2	21	9.17 (5.54)	21	6.43 (5.57)	−46% (−55, −8)	20	5.10 (3.42)	−57% (−66, −7)	14	5.08 (3.41)	−50% (−69, −19)	15	3.52 (3.23)	−64% (−90, −40)
Conventional HD group														
Urine volume (ml/24 h)	21	1369 (970)	20	1091 (970)	−16% (−45, 9)	19	995 (1105)	−47% (−64, 48)	17	902 (591)	−44% (−64, 4)	15	745 (576)	−50% (−84, −26)
Kidney urea clearance, ml/min per 1.73 m^2	16	4.12 (2.79)	19	2.07 (0.90)	−44% (−65, −21)	19	1.99 (1.24)	−54% (−70, −14)	16	2.04 (1.13)	−45% (−76, −2)	13	1.55 (1.08)	−60% (−91, −40)
Kidney creatinine clearance, ml/min per 1.73 m^2	17	10.35 (6.53)	19	4.55 (2.98)	−50% (−63, −39)	20	5.44 (3.72)	−34% (−70, −15)	15	4.69 (2.61)	−49% (−77, −23)	14	3.70 (2.41)	−50% (−77, −17)

HD, hemodialysis.
Value data are presented as mean (standard deviation). Delta denotes median (quartile 1, quartile 3) % change in residual kidney function parameters, relative to baseline values, per patient observation during follow-up.

calculated from the end time of the HD session when collection began to the start time of the following HD session when collection ended; and post-HD plasma solute and pre-HD plasma solute concentrations are the plasma concentrations for urea nitrogen (mg/dl) or creatinine (mg/dl) at the end and beginning of HD sessions (which represent the beginning and the end of the urine collection period, respectively). We expressed each solute clearance per 1.73 m^2 of body surface area calculated by the Dubois formula.[20]

Pre-HD blood samples were drawn from the arterial needle immediately before HD. Post-HD blood samples were taken at the end of HD treatment with the blood pump slowed to 50 ml/min for 30 seconds before sampling to reduce the effects of vascular access recirculation. Urea nitrogen and creatinine were measured by the clinical laboratory.

Data Analysis

Longitudinal changes in residual kidney function parameters were calculated in the entire cohort and in each treatment group (incremental HD and conventional HD); the results were averaged at each assessment time point. Continuous variables were summarized with mean (standard deviation), median (interquartile range), or mean (95% confidence interval), and categorical variables are given as proportion per participant or per visit, as appropriate.

We grouped changes in urine volume at each set of successive time point as follows: (i) decline in urine volume (when the decrease in urine volume exceeded 200 ml/24 h), (ii) no change in urine volume (when the increase or decrease in urine volume was <200 ml/24 h), or (iii) increase in urine volume (when the increase in urine volume exceeded 200 ml/24 h). We grouped changes in kidney solute clearance at each set of successive time point as follows: (i) decline in solute clearance (when the decrease in solute clearance exceeded 1 ml/min per 1.73 m^2), (ii) no change in solute clearance (when the increase or decrease in solute clearance was ≤1 ml/min per 1.73 m^2), or 3) increase in solute clearance (when the increase in solute clearance exceeded 1 ml/min per 1.73 m^2). We calculated the distribution of kidney solute clearance at urine volume cut points of >1000 ml/d, 500 to 1000 ml/d, and <500 ml/d.

The relationship between urine volume and kidney solute clearance was analyzed using scatter plots, Pearson correlation coefficients, and linear regression. The results of all longitudinal measurements of urine volume and kidney solute clearances were combined to analyze the relationship between urine volume and kidney solute clearance. *P*-values are presented without correction for multiple comparisons. A

Table 2. Categories of changes in urine volume observed during follow-up

Change in urine volume	Baseline to week 6, *n* (%)	Week 6 to week 12, *n* (%)	Week 12 to week 24, *n* (%)	Week 24 to week 48, *n* (%)
All patients				
Decrease by >200 ml/24 h	14 (33)	17 (41)	7 (21)	12 (40)
No change, urine volume difference less than +/- 200 ml/24 h	17 (41)	16 (39)	19 (55)	15 (50)
Increase by >200 ml/24 h	11 (26)	8 (20)	8 (24)	3 (10)
Incremental HD group				
Decrease by >200 ml/24 h	5 (24)	9 (45)	1 (6)	6 (40)
No change, urine volume difference less than +/- 200 ml/24 h	10 (48)	9 (45)	12 (75)	8 (53)
Increase by >200 ml/24 h	6 (29)	2 (10)	3 (19)	1 (7)
Conventional HD group				
Decrease by >200 ml/24 h	9 (45)	7 (35)	6 (35)	6 (43)
No change, urine volume difference less than +/- 200 ml/24 h	4 (35)	7 (35)	6 (35)	6 (43)
Increase by >200 ml/24 h	4 (20)	6 (30)	5 (29)	2 (14)

HD, hemodialysis.

P-value < 0.05 was considered to be statistically significant; all analyses were conducted using SAS (version 9.4, Cary, NC).

Ethical Approval

The study was approved by the Institutional Review Board of Wake Forest University Health Sciences. All patients provided written informed consent before enrollment in the study. All procedures performed in the study involving patients were in accordance with the Declaration of Helsinki.

RESULTS

Baseline characteristics of the 42 patients enrolled in the TwoPlus pilot study, previously published,[2] included patients of mean (standard deviation) age 60.7 (14.2) years, 43% female sex, 45% Black race, 50% with diabetes as the etiology of kidney disease, 64% with presence of diabetes mellitus among comorbid conditions, and 79% using a catheter. At the time of enrollment, patients had been on HD for less than 5 days and none of the patients had a diagnosis of acute kidney injury as a cause of chronic HD initiation. Pre-HD and post-HD plasma concentrations of urea nitrogen and creatinine as well as Kt/V_{urea} are summarized in Supplementary Table S1.

Repeated measurements of urine volume and kidney solute clearance showed a general trend of decline in all residual kidney function parameters over time, as summarized in Table 1. There were differences, however, in the pattern of decline between the urine volume and the kidney solute clearances. Urine volume steadily declined over 48 weeks relative to baseline with median (quartile 1, quartile 3) percentage change of −10% (−36 to 29) at week 6, −22% (−61 to 57) at week 12, −31% (−61 to 39) at week 24, and −47% (−76 to 5) at week 48. In contrast, kidney urea and creatinine clearances showed a larger decline than urine volume in the first 6 weeks at −32% (−61 to 8) and −47% (−57 to −20), respectively. The kidney urea and creatinine clearances continued to decline relative to baseline after 6 weeks; however, the decline was less pronounced with median % change of −50% (−61 to 3) and −45% (−66 to −11) at week 12, −53% (−78 to −5) and −46% (−71 to −19) at week 24, and −61% (−91 to −35) and −61% (−84 to −31) at week 48, respectively. At all time points and relative to baseline, the decline in the kidney solute clearances was greater than the decline in urine volume. Examination of the pattern of the residual kidney function parameters in the 2 randomized groups (incremental HD and conventional HD) are also summarized in Table 1. In the first 6 weeks, the incremental HD group demonstrated slower declines in urine volume (−6% [−33 to 33) vs. −16% [−45 to 9]) and kidney urea clearance (−32% [−61 to 11] vs. −44% [−65 to −21]) than the conventional HD group; whereas the decline in kidney creatinine clearance was similar (−46% [−55 to −8] vs. −50% [−63 to −39]. At week 48, the decline in urine volume remained less pronounced in the incremental HD group (−29% [−75 to 18] vs. −50% [−84 to −26]) whereas the kidney urea and creatinine clearances appeared to worsen in the incremental HD group after the week-6 transition to thrice-weekly HD treatments (urea: −76% [−91 to −37] vs. −60% [−91 to −40]; creatinine: −64% [−90 to −40] vs. −50% [−77 to −17]).

In Table 2 and Supplementary Figure S1, we summarize categories of urine volume changes during follow-up (decrease by >200 ml/24 h, no change +/- 200 ml/24 h, or increase by >200 ml/24 h). Between consecutive assessment time points during the entire study, urine volume decreased in 21% to 41% of patients, was unchanged in 39% to 55% of patients, or increased in 10% to 26% of patients, with the lowest likelihood of identifying an increase in urine volume at

Table 3. Categories of changes in kidney solute clearance observed during follow-up

	Urea, *n* (%)				Creatinine, *n* (%)			
Change in Solute Clearance	Baseline to week 6	Week 6 to week 12	Week 12 to week 24	Week 24 to week 48	Baseline to week 6	Week 6 to week 12	Week 12 to week 24	Week 24 to week 48
All patients								
Decrease by >1 ml/min per 1.73 m^2	20 (54)	7 (17)	4 (12)	8 (28)	28 (78)	12 (31)	9 (30)	11 (44)
No change, +/- 1 ml/min per 1.73 m^2	13 (35)	26 (63)	24 (73)	17 (59)	4 (11)	13 (33)	15 (50)	9 (36)
Increase by >1 ml/min per 1.73 m^2	4 (11)	8 (20)	5 (15)	4 (14)	4 (11)	14 (36)	6 (20)	5 (20)
Incremental HD group								
Decrease by >1 ml/min per 1.73 m^2	9 (41)	3 (14)	1 (6)	3 (19)	15 (68)	7 (33)	4 (27)	5 (42)
No change, +/- 1 ml/min per 1.73 m^2	10 (45)	16 (78)	14 (82)	11 (69)	3 (14)	8 (38)	9 (60)	5 (42)
Increase by >1 ml/min per 1.73 m^2	3 (14)	2 (10)	2 (12)	2 (13)	4 (18)	6 (29)	2 (13)	2 (17)
Conventional HD group								
Decrease by >1 ml/min per 1.73 m^2	11 (73)	4 (20)	3 (19)	5 (38)	13 (93)	5 (28)	5 (33)	6 (50)
No change, +/- 1 ml/min per 1.73 m^2	3 (20)	10 (50)	10 (62)	6 (46)	1 (7)	5 (28)	6 (40)	4 (33)
Increase by >1 ml/min per 1.73 m^2	1 (7)	6 (30)	3 (19)	2 (15)	0	8 (44)	4 (27)	2 (17)

HD, hemodialysis.

week 48. Similar trends were seen when examining the incremental and conventional HD groups separately.

In Table 3 and Supplementary Figure S2, we summarize categories of kidney solute clearance changes during follow-up (decrease by >1 ml/min per 1.73 m^2, no change +/- 1 ml/min per 1.73 m^2, or increase by >1 ml/min per 1.73 m^2). For all patients, the proportion with a decline in kidney solute clearance was largest in the first 6 weeks (54% of patients for urea and 78% of patients for creatinine), whereas the proportion of patients with stabilized kidney solute clearance was largest between weeks 12 and 24 (73% of patients for urea and 50% of patients for creatinine). During the last time period of the study between week 24 and 48, kidney urea clearance decreased in 28%, remained unchanged in 59%, and increased in 14% of patients; kidney creatinine clearance decreased in 44%, remained unchanged in 36%, and increased in 20% of patients. Separate examination of the randomized groups revealed even higher proportions of patients in the conventional HD group with a decline in kidney solute clearance in the first 6 weeks (73% for urea and 93% for creatinine), as further summarized in Table 3. The proportion of kidney solute clearance changes during the last time period between weeks 24 and 48 in each group followed a similar pattern as the entire patient cohort.

The distribution of kidney solute clearance at urine volume cut points of >1000 ml/24 h, 500 to 1000 ml/24 h, and <500 ml/24 h, per each assessment time point, is shown in Supplementary Table S2 and Supplementary Figure S3. A series of linear regressions was performed using urine volume (ml/24 h) as the independent variable and kidney solute clearance as the dependent variable. Each regression included measurements obtained at all time points (Supplementary Table S3). Urine volume had a modest correlation with urea clearance ($R = 0.47$, $P < 0.0001$) and a weak correlation with creatinine clearance ($R = 0.34$, $P < 0.0001$) (Figure 1). A direct relationship was also noted between kidney urea clearance and kidney creatinine clearance at all time points (Supplementary Figure S4). There were no associations between dialysis std Kt/V and urine volume (Supplementary Figure S5), kidney urea clearance (Supplementary Figure S6), or kidney creatinine clearance (Supplementary Figure S7).

Over the entire 48-week period, the mean (percent of baseline) per-month slope of decline in residual kidney function was −50.5 ml/24 h (−4.2%) for urine volume, −0.16 ml/min per 1.73 m^2 (−5.6%) for kidney urea clearance, and −0.35 ml/min per 1.73 m^2 (−4.6%) for kidney creatinine clearance (Table 4). There were no significant differences in the monthly slope of residual kidney function decline among the 3 parameters studied ($P = 0.68$ comparing urine volume, $P = 0.45$ comparing kidney urea clearance, and $P = 0.92$ comparing kidney creatinine clearance).

DISCUSSION

This is the first study to describe the longitudinal evolution of urine volume and kidney solute clearances in patients started on chronic HD. Our study has 3 novel findings.

First, during the initial year of treatment with intermittent HD, urine volume steadily declines. However, variability in periodic declines in urine volume was noted, with some patients experiencing no change (+/- 200 ml/24 h) in urine volume between subsequent assessment time points. Our results further showed unexpected improvements in urine volume in about 24% of patients during the first 6 months of starting HD, and in only 10% of the patients in the remaining 6 months of the first year on HD. The

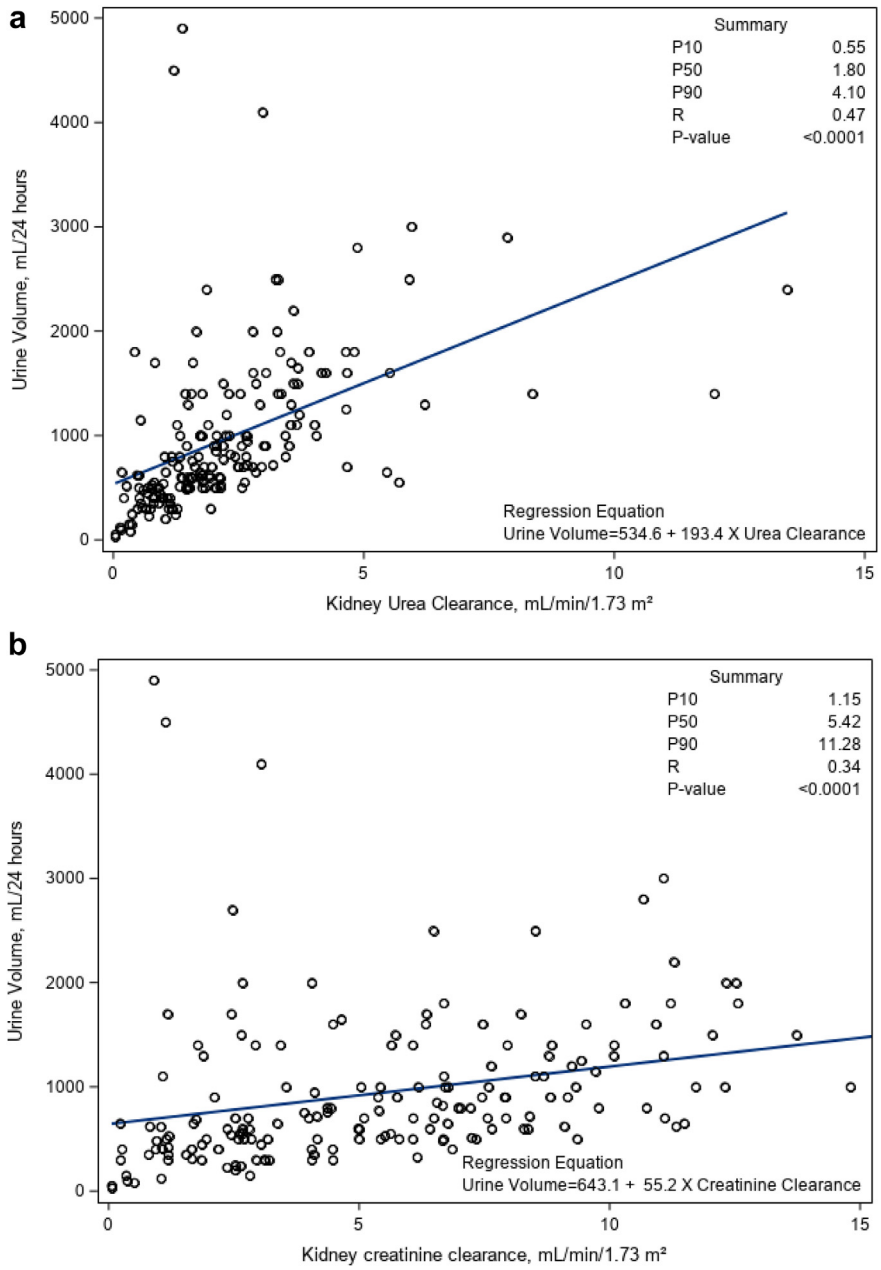

Figure 1. Relationship between urine volume and (a) kidney urea clearance and (b) kidney creatinine clearance.

variability of urine volume in individual patients over time may be attributed to changes in the ability of the residual kidneys to maintain fluid balance, dietary fluid and sodium intake of the patients, and volume removal with HD.

Second, we saw a difference in the trajectories of kidney clearances of the 2 solutes analyzed compared to urine volume and compared to each other. Kidney clearances of both urea and creatinine declined to a greater degree than urine volume the first 6 weeks; however, their decline subsequently slowed down over the remainder of the study. Interestingly, between the 2 solutes, a larger proportion of patients displayed an increase in kidney creatinine clearance, whether the patients were in the incremental or conventional HD group, suggesting that creatinine clearance may be better preserved over time. The varying patterns in urea and creatinine clearances may be explained by how the kidneys process each solute. Both creatinine and urea are cleared by glomerular filtration; however, creatinine is partially secreted whereas urea is partially reabsorbed in the proximal tubule. Previous studies have shown that tubular secretion of creatinine tended to increase with decline in glomerular filtration[21] although other studies have shown that it fluctuates relative to the timing of HD initiation.[22,23] These variable effects on creatinine secretion may be attributed to competitive inhibition of the transporters in the

Table 4. Rate of decline in residual kidney function parameters during the 48-week period of follow-up

Estimated rate of decline, per month, mean (95% CI), % of baseline	All patients	Incremental HD group	Conventional HD group
Urine volume, ml/24 h	−50.5 (−71.6, −29.3), −4.2%	−46.0 (−72.9, −19.2), −4.1%	−56.3 (−90.1, −22.4), −4.6%
Kidney urea clearance, ml/min per 1.73 m^2	−0.16 (−0.22, −0.10), −5.6%	−0.17 (−0.26, −0.09), −6.2%	−0.15 (−0.25, −0.05), −5.1%
Kidney creatinine clearance, ml/min per 1.73 m^2	−0.35 (−0.49, −0.20), −4.6%	−0.36 (−0.56, −0.17), −4.8%	−0.32 (−0.54, −0.11), −4.4%

CI, confidence interval; HD, hemodialysis.

proximal tubule by other uremic solutes and medications.[24] Another potential reason for the discrepant changes in kidney urea and creatinine clearances is hemodynamically-induced increases in tubular urea reabsorption that reduce its overall kidney clearance.

Third, we found a modest-to-weak strength of correlation between the urine volume and kidney solute clearances, with better correlation for urea than for creatinine clearance. This suggests that urine volume alone should not be used as a surrogate for glomerular filtration rate or kidney urea clearance, which is similar to the findings of Lindsey *et al*.[25] Our study further suggests the possibility of a dissociation between glomerular filtration and tubular processing. In other words, low urine volume, generally determined by glomerular filtration rate and tubular handling of sodium and water, is not proportional to the degree of impaired tubular handling of solutes. Indeed, the kidney clearance of creatinine, a solute that is cleared by glomerular filtration and tubular secretion, displayed a wider distribution at urine volumes of <1000 ml/24 h compared to the kidney clearance of urea.

We note that the association between urine volume and kidney solute clearance has previously been evaluated in patients with residual kidney function undergoing peritoneal dialysis. Pinto *et al*. showed that urine volume correlated with the kidney clearances of urea, creatinine, and phosphorus.[26] In our study, that was comprised solely of patients treated with HD, we noted a weaker correlation between the urine volume and residual kidney urea and creatinine clearances. However, comparisons are difficult to undertake given differences in metabolic dynamics and extracorporeal clearances between peritoneal dialysis and HD.

Another intriguing finding from our study pertains to the longitudinal changes in residual kidney function parameters between the incremental and conventional HD groups. During the initial 6 weeks of incremental twice-weekly HD treatment, there was a notably gentler decline in residual kidney function parameters compared to the conventional HD. At subsequent assessments, however, the rate of decline for residual kidney function parameters increased in the incremental HD group, eventually reaching similar rates as the conventional HD group by week 48. Indeed, this change in longitudinal trend of residual kidney function in the incremental HD group coincided with the transition from twice-weekly to thrice-weekly HD. This transition to thrice-weekly HD (so that all patients were receiving thrice-weekly HD after week 6) may explain why the average monthly rate of residual kidney function decline did not differ between the 2 treatment groups by week 48.

Our study is the first to characterize the residual kidney excretion of different solutes with repeated measurements up to nearly 1 year after HD initiation. Importantly, kidney urea and creatinine clearances were still present despite an initial decline at 6 weeks after HD initiation. At 48 weeks, the kidney urea clearance was 1.32 ml/min per 1.73 m^2 and the kidney creatinine clearance was 3.98 ml/min per 1.73 m^2. This degree of residual function could still provide clearance of other uremic solutes that is sufficient to limit their plasma accumulation.[12] However, the contribution of residual kidney function, though embraced in the prescription of peritoneal dialysis, has been unreservedly discounted in patients treated with HD. Described almost 2 decades ago and corroborated in subsequent studies, is the lack of clinical benefits with full-dose HD when patients have residual kidney function that can still provide volume control and solute clearance.[14] The effect on outcomes of ongoing kidney clearance of solutes that cannot be removed as well by dialysis has not been extensively studied. The concept of "total solute clearance" as a component of "total kidney function and dialysis" would be particularly useful to guide HD prescription or to develop ways to improve the clearance of other uremic solutes. Knowledge of which uremic solutes to target, however, would first be required.

Our study has some limitations, which include possible errors in urine collection, absence of measured inulin clearance as a reference for glomerular filtration, and the low number of patient observations accrued at the end of 48 weeks of follow-up. Given that patient recruitment and follow-up took place at dialysis centers affiliated with a single health care system, results may not be generalizable to patients treated at other clinical practices.

In conclusion, our study offers new insights into changes in urine volume and kidney solute clearances over time in patients started on chronic HD. We note a gradual decline in urine volume and a larger initial decrement in creatinine and urea clearances that

became less pronounced over time. Importantly, residual kidney function is still present after nearly 1 year of chronic HD, which could motivate the practice of individualizing HD prescriptions based on residual urea and/or creatinine kidney clearances. There is important heterogeneity in residual kidney function change over time, because a small proportion of patients may temporarily experience an increase in kidney urea and creatinine clearances. We also note a positive correlation, albeit modest-to-weak, between urine volume and kidney solute clearances with different correlation strengths suggesting a possible dissociation in molecular handling across the nephron in patients on HD. Future studies are warranted to identify factors that impact the rate of residual kidney function decline and evaluate whether a broader metric of solute excretion comprised of various molecules could better guide HD prescription to improve patient outcomes.

DISCLOSURE

TLS has served as a consultant for Baxter. All the other authors declared no competing interests.

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AUTHOR CONTRIBUTIONS

MM and TLS conceptualized, wrote, and finalized the manuscript. BRH, ZL and ZT wrote parts of the first draft of the manuscript. GBR conducted the statistical analyses.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Distribution of urine volume changes observed during follow-up in (A) all patients, (B) patients in the incremental HD group, and (C) patients in the conventional HD group.

Figure S2. Distribution of kidney solute clearance changes observed during follow-up in (A) all patients, (B) incremental HD group, and (C) conventional HD group.

Figure S3. Distribution of kidney solute clearance by urine volume category at all assessment time points. (A) urine volume >1000 ml/24 h; (B) urine volume 500 to 1000 ml/24 h; (C) urine volume <500 ml/24 h.

Figure S4. Relationship between kidney urea clearance and kidney creatinine clearance across all patient participants at each assessment time point, (A) baseline, (B) week 6, (C) week 12, (D) week 24, and (E) week 48.

Figure S5. Relationship between dialysis std Kt/V and urine volume across all patient participants at each assessment time point (A) baseline, (B) week 6, (C) week 12, (D) week 24, and (E) week 48.

Figure S6. Relationship between dialysis std Kt/V and kidney urea clearance across all patient participants at each assessment timepoint, (A) baseline, (B) week 6, (C) week 12, (D) week 24, and (E) week 48.

Figure S7. Relationship between dialysis std Kt/V and kidney creatinine clearance across all patient participants at each assessment timepoint, (A) baseline, (B) week 6, (C) week 12, (D) week 24, and (E) week 48.

Table S1. The time course of pre- and post-HD blood tests.

Table S2. Distribution of kidney solute clearance by urine volume subgroups.

Table S3. Correlation between urine volume and kidney solute clearance.

STROBE Statement

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