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Research Article

Hemodynamic and Laboratory Changes during Incremental Transition from Twice to Thrice-Weekly Hemodialysis

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Keywords

Incremental hemodialysis · Ultrafiltration volume · Twice-weekly hemodialysis

Abstract

Objective: Incremental hemodialysis (HD) is a strategy utilized to gradually intensify dialysis among patients with incident end-stage renal disease. However, there are scarce data about which patients' clinic status changes by increasing treatment frequency. ***Methods:*** We retrospectively examined statistically de-identified data from 569 patients who successfully transitioned from twice- to thrice-weekly HD (2007–2011) and compared the differences in monthly-averaged values of hemodynamic and laboratory indices during the 3 months before and after the transition with the values at 1 month prior to transition serving as the reference. ***Results:*** At 3 months after transitioning from twice- to thrice-weekly HD, ultrafiltration volume decreased by 0.5 (95% CI 0.3–0.6) L/session among 189 patients (33%) with weekly interdialytic weight gain (IDWG) ≥5.4 kg/week, and increased by 0.4 (95% CI 0.3–0.5) L/session among 186 patients (33%) with weekly IDWG <3.3 kg/week. Weekly IDWG consistently increased after the transition irrespective of baseline values (1.7 [95% CI 1.5–1.9] kg/week). Pre-HD systolic blood pressure (SBP) decreased by 12 (95% CI 9–14) mm Hg among 177 patients (31%) with baseline pre-HD SBP ≥160 mm Hg, which coincided with a decreasing trend in

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post-HD body weight (1.3 [95% CI 0.8–1.7] kg). ***Discussion:*** In conclusion, patients who increased HD frequency from twice to thrice weekly treatment experienced increased weekly IDWG and better pre-HD SBP control with lower post-HD body weight.

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Introduction

Incremental hemodialysis (HD) is a strategy to gradually intensify dialysis therapy among incident end-stage renal disease (ESRD) patients with a target weekly urea clearance that takes into account residual kidney function (RKF) [1, 2]. Incremental strategies have already been successfully implemented among peritoneal dialysis patients resulting in better quality of life and equivalent dialysis adequacy when compared to patients with an abrupt introduction of full dose peritoneal dialysis [3]. However, in patients being treated with HD, thrice-weekly HD has been considered the “standard of care” in developed countries [4]. There is mounting evidence that in incident HD patients who have significant RKF, incremental HD therapy is associated with preservation of indices of RKF including urine volume and urea clearance with similar survival [5–7].

It is important to note that the risk-benefit considerations of incremental HD may depend on patient-specific factors such as residual urine output, volume status, and degree of electrolyte abnormality [8]. A recent retrospective cohort study demonstrated that incremental HD regimens were associated with higher mortality among patients without substantial RKF (renal urea clearance ≤3.0 mL/min/1.73 m^2) [6]. Therefore, there are subgroups of incident HD patients who may not benefit and may even experience adverse effects from reduced HD frequency. In light of these observations, a set of criteria have been proposed based on 11 individualized factors including urine volume, interdialytic weight gain (IDWG), and electrolyte abnormalities to determine the suitability of the twice-weekly HD regimen for each patient [9]. By utilizing these criteria, patients who are most likely to benefit from incremental HD may be identified while avoiding those that may be at risk for complications of inadequate dialysis with reduced HD regimens. However, most patients who are initiated on twice-weekly HD regimens will eventually require thrice-weekly treatment due to inevitable decline in RKF and reduction in urine output. Therefore, it is essential that indications for transitioning a patient from twice to thrice-weekly HD be identified to avoid complications of inadequate dialysis therapy. These indications will be especially important for patients who may be vulnerable to the adverse effects of declining RKF including those with congestive heart failure, fluid overload, excessive IDWG, and inadequate solute clearance [10]. Therefore, it is important to assess and validate the clinical and laboratory markers which are routinely used in the conventional care of prevalent HD patients in those being treated with the incremental strategy. While increasing dialysis frequency is expected to improve patients’ hemodynamic and metabolic derangements, there are scarce data on the extent to which clinical parameters would be affected by this incremental transition approach. Therefore, the goal of this study was to assess the changes in ultrafiltration volume (UFV), blood pressure, and metabolic parameters in a cohort of incremental HD patients as they transitioned from twice- to thrice-weekly HD.

Methods

This study was approved by the Institutional Review Committees of the Los Angeles Biomedical Research Institute at Harbor-UCLA and University of California Irvine Medical Center.

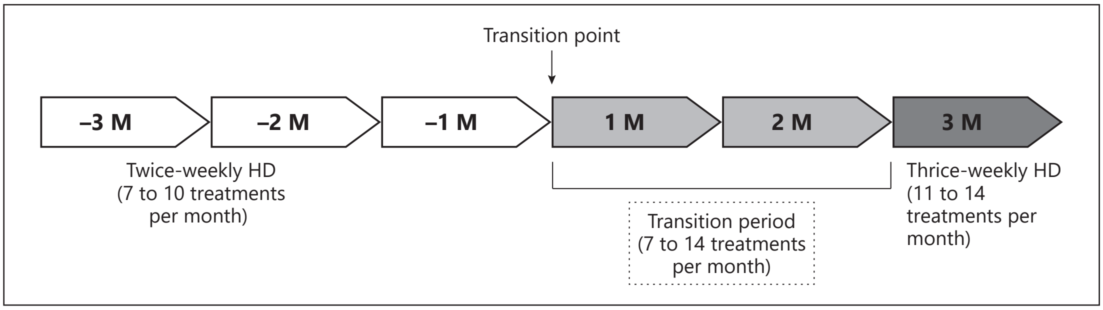

Fig. 1. The treatment frequency of incremental HD. HD, hemodialysis.

Patients and Definition of Incremental HD

We retrospectively extracted, refined, and examined data from a statistically de-identified data set from all incident ESRD patients who were age ≥18 years and received dialysis treatment for ≥60 consecutive days in facilities operated by a large dialysis organization in the United States from January 1, 2007 to December 31, 2011 [11]. We selected 4,576 patients who had ever received twice-weekly HD, which was defined as a consistent treatment schedule (e.g., Monday/Thursday or Monday/Friday) for >6 continuous weeks. Incremental HD is defined by an increase in monthly treatment frequency as follows: 7–10 treatments per month for 3 consecutive months prior to the transition (i.e., –3 to –1 M; twice-weekly period), 7–14 treatments per month for the following 2 months (i.e., 1–2 M; transition period), and 11–14 treatments per months at the third month (i.e., 3 M; thrice-weekly period, Fig. 1). We excluded 333 patients who had switched between twice- and thrice-weekly treatment frequency >3 times. We also excluded 3,674 patients who did not match the definition of incremental HD (Appendix Fig. 1). We examined patient data for 6 months (i.e., 3 months before and after the transition, from –3 to –1 M and from 1 to 3 M, respectively; Appendix Table 1).

Demographic, Clinical, and Laboratory Measures

Information on death, race/ethnicity, primary insurance, cause of ESRD, the presence of comorbidities, vintage, and laboratory variables was obtained from the electronic database of the dialysis provider. Comorbid conditions, defined by International Classification of Diseases-9 codes, included diabetes mellitus, congestive heart failure, atherosclerotic heart disease, other cardiac diseases, and chronic obstructive pulmonary disease. Hemodynamic parameters including pre-HD systolic blood pressure (SBP) and pre- and post-HD body weight were reported at each treatment. We also calculated weekly IDWG averaged within each month. Epoetin-α was exclusively used as the erythropoietin stimulating agent (ESA) in this dialysis organization, and weekly ESA dose were calculated from total dose of epoetin-α in a given month. Blood samples were drawn using uniform techniques in all dialysis clinics and were transported to a central laboratory, typically within 24 h. All laboratory values were measured by automated and standardized methods. Parameters were summarized as arithmetic means for each 30-day period. Most laboratory values were measured monthly, and the frequency of missing data was low (<1%) except for bicarbonate (6%), calcium (4%), phosphorus (4%), potassium (8%), and albumin (6%; Appendix Table 2).

Statistics

Values in variables of interest at –3, –2, 1, 2, and 3 M were compared with those at baseline (i.e., –1 M) by means of paired *t* test. We also categorized patients into tertiles of baseline weekly IDWG (i.e., <3.3, 3.3 to <5.4, and ≥5.4 kg/week) and then compared the differences in UFV per session and weekly IDWG between each month across 3 groups. We also compared the differences in pre-HD blood pressure and post-HD body weight across the 3 groups based on baseline SBP (i.e., <140, 140 to <160, and ≥160 mm Hg).

Table 1. Characteristics of 569 patients who transitioned from twice-weekly HD to thrice-weekly HD

Age, years	67±14
Female	264 (46)
Vintage to transition, month	13 (8–22)
Race	
Asian	39 (7)
Black	96 (17)
Caucasian	333 (59)
Hispanic	82 (14)
Other	19 (3)
Primary insurance	
Medicare	337 (59)
Medicaid	31 (5)
Other	201 (36)
ESRD reason	
Diabetes	254 (45)
Hypertension	180 (32)
Glomerulonephritis	47 (8)
Cystic kidney disease	14 (3)
Other	74 (12)
Comorbidities	
Diabetes	379 (67)
Congestive heart failure	267 (47)
ASHD	109 (19)
Other cardiovascular disease	103 (18)
COPD	32 (6)

Values are expressed as mean ± SD, median (IQR) or *n* (%) as appropriate. ASHD, atherosclerotic heart disease; COPD, chronic obstructive pulmonary disease; HD, hemodialysis; ESRD, end-stage renal disease; IQR, interquartile range.

Results

Baseline Demographic, Clinical, and Laboratory Characteristics

The baseline characteristics of the 569 included patients are described in Table 1. Mean age of the patients was 67 (SD 14) years; 46% were female; 59%, 17%, 14%, and 7% were non-Hispanic White, African American, Hispanic, and Asian respectively. The most common cause of ESRD was diabetic nephropathy (45%), followed by hypertension (32%). The prevalence of congestive heart failure, atherosclerotic heart disease, and chronic obstructive pulmonary disease were 47%, 19%, and 6%, respectively. The median vintage at the incremental transition was 13 (interquartile range [IQR] 8–22) months. Median treatment frequencies in the twice weekly, transition, and thrice-weekly period were 9 (IQR 8–9), 12 (IQR 9–13), and 13 (IQR 12–13) per month respectively.

Hemodynamic Changes after Incremental Transition

UFV per session decreased by 0.1 (95% CI 0.0–0.1; p = 0.02) L after incremental transition overall (Table 2). However, changes in UFV per session showed different patterns across baseline weekly IDWG tertiles (Fig. 2a). Patients with the highest baseline weekly IDWG (≥5.4 kg/week, n = 189) showed a decreasing trend in UFV per session after the transition; compared to baseline (–1 M), UFV decreased by 0.3 (95% CI –0.2 to –0.4) L/session, 0.5 (95% CI –0.3 to –0.6) L/session, and 0.5 (95% CI –0.3 to –0.6) L/session at 1, 2, and 3 M, respectively (p < 0.001) in this group. In contrast, patients with the lowest baseline weekly IDWG (<3.3 kg/week, n = 186) were found to have an increasing trend despite the increased

Table 2. Changes in UFV per session and weekly IDWG across the tertiles of weekly IDWG at the incremental transition (i.e., –1 M)

	Period	Total (*n* = 569)	Weekly IDWG, kg/week		
			<3.3 (*n* = 186)	3.3 to <5.4 (*n* = 194)	≥5.4 (*n* = 189)
UFV/session, L	–3 M	2.1±1.1	1.2±0.8	2.0±0.7	3.0±1.0
	–2 M	2.2±1.1	1.1±0.7	2.2±0.6	3.2±0.9
	–1 M (ref.)	**2.2±1.1**	**1.1±0.6**	**2.2±0.4**	**3.4±0.7**
	1 M	2.2±1.1	1.2±0.7	2.2±0.7	3.2±0.8
	2 M	2.2±1.0	1.3±0.7	2.1±0.7	3.0±0.8
	3 M	2.2±1.0	1.4±0.8	2.1±0.7	3.0±0.8
Weekly IDWG, kg/week	–3 M	3.6±2.0	2.0±1.4	3.5±1.3	5.1±1.8
	–2 M	4.3±2.3	2.2±1.5	4.3±1.4	6.4±1.8
	–1 M (ref.)	**4.5±2.3**	**2.0±1.1**	**4.4±0.6**	**7.0±1.3**
	1 M	4.9±2.6	2.7±1.8	4.8±1.9	7.2±2.1
	2 M	5.5±2.8	3.3±1.9	5.5±1.8	7.8±2.5
	3 M	6.2±2.9	4.0±2.2	6.0±2.2	8.5±2.5

Values are expressed as mean ± SD. Values in bold at -1 M represent the baseline values from which change in UFV/session and weekly IDWG before and after transition were calculated. UFV, ultrafiltration volume; IDWG, interdialytic weight gain.

treatment frequency; compared to the baseline (–1 M), UFV increased by 0.1 (95% CI 0.1–0.2) L/session, 0.3 (95% CI 0.2–0.4) L/session, and 0.4 (95% CI 0.3–0.5) L/session at 1, 2, and 3 M respectively ($p < 0.001$).

Overall, weekly IDWG increased after the transition from 4.5 (SD 2.3) kg/week at –1 M to 6.2 (SD 2.9) kg/week at 3 M, resulting in an averaged increase of 1.7 (95% CI 1.5–1.9) kg/week ($p < 0.001$; Table 2). Those increasing trends were consistently observed across weekly IDWG tertiles but were greater among patients with lower baseline weekly IDWG (Fig. 2b). Patients with lowest baseline weekly IDWG showed increased weekly IDWG by 0.8 (95% CI 0.5–1.0) kg/week at 3 M ($p < 0.001$) and patients with highest baseline weekly IDWG showed increased weekly IDWG by 2.1 (95% CI 1.8–2.4) kg/week at 3 M ($p < 0.001$).

Pre-HD SBP gradually increased before transition, and then showed a decreasing trend across baseline SBP strata (Table 3). Patients with the highest baseline SBP (i.e., ≥160 mm Hg, $n = 177$) showed the greatest decrease in SBP after transition; compared with the baseline (–1 M), pre-HD SBP decreased by –7.6 (95% CI –9.5 to –5.6) mm Hg, –10.4 (95% CI –12.7 to –8.0) mm Hg, and –11.8 (95% CI –14.2 to –9.4) mm Hg, at 1, 2, and 3 M, respectively ($p < 0.001$). Patients with the lowest SBP (i.e., <140 mm Hg, $n = 154$) showed a small increase in pre-HD SBP by 0.9 (95% CI –0.7 to 2.6) mm Hg, 1.4 (95% CI –0.5 to 3.4) mm Hg, and 3.3 (95% CI 1.2–5.4) mm Hg, at 1, 2, and 3 M, respectively ($p = 0.002$; Fig. 2c). A decreasing trend in post-HD body weight after transition was consistently observed across the 2 groups, with the greater change being found in patients with higher baseline pre-HD SBP (Fig. 2d). Patients with the highest baseline SBP showed the greatest decreasing trend in post-HD body weight after the transition; compared with the baseline level (–1 M), post-HD body weight decreased by –0.7 (95% CI –0.4 to –1.0) kg, –1.0 (95% CI –0.6 to –1.4) kg, and –1.3 (95% CI –0.8 to –1.7) kg at 1, 2, and 3 M, respectively ($p < 0.001$).

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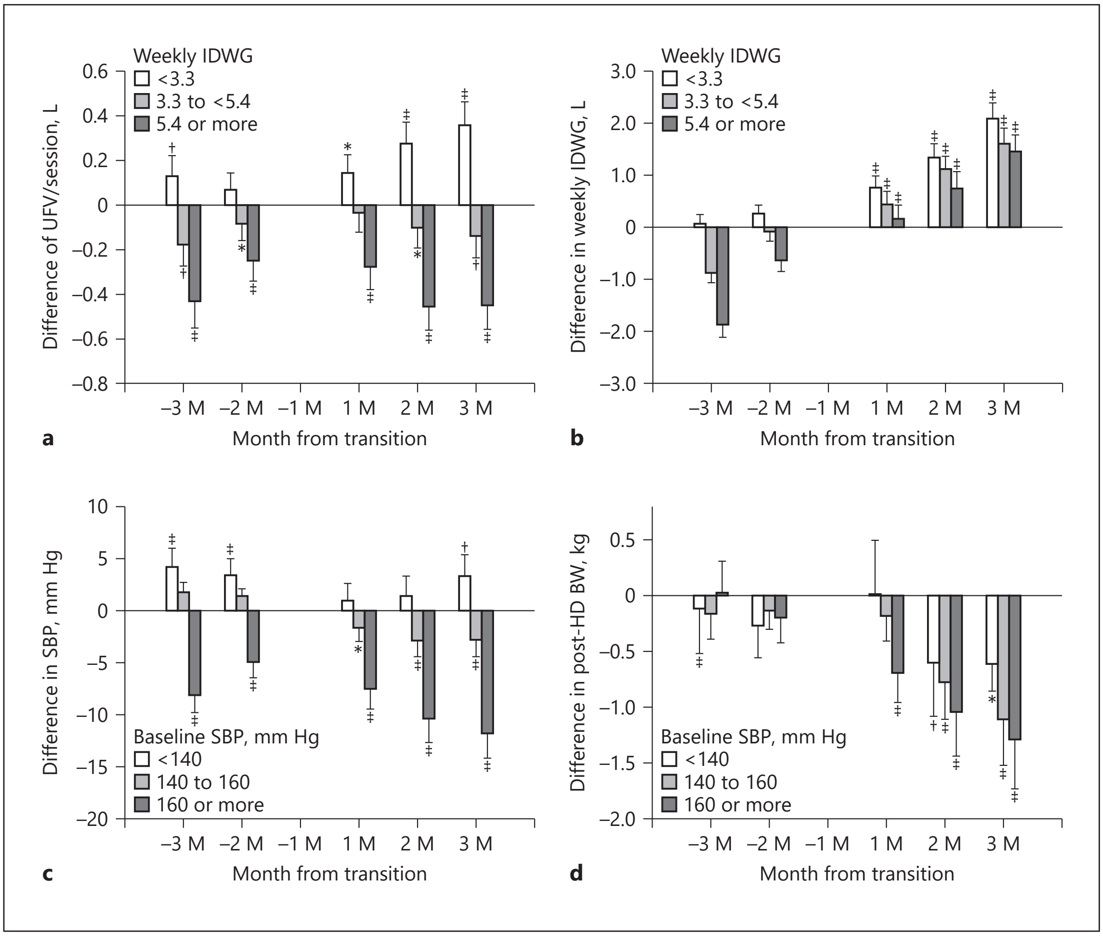

Fig. 2. Changes in UFV per session (**a**), weekly IDWG (**b**), pre-HD SBP (**c**), and post-dialysis body weight (**d**). **a**, **b** Were stratified by weekly IDWG at baseline whereas (**c**, **d**) were stratified by the 3 groups of baseline SBP. Data were expressed as mean ± SD. * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$ (vs. values at –1 M). UFV, ultrafiltration volume; IDWG, interdialytic weight gain; SBP, systolic blood pressure; post-HD BW, post-hemodialysis body weight.

Laboratory Differences after Incremental Transition

Hemoglobin levels were slightly lower during the twice-weekly HD period, and then increased during the transition period, reaching a mean of 11.6 (SD 1.2) g/dL at 3M ($p < 0.001$; Fig. 3a) with an increase of 0.3 (95% CI 0.1–0.4) g/dL from –1 M. This increase in hemoglobin level was accompanied by larger doses of ESA. Median ESA doses increased from 8,200 (IQR 4,100–16,900) units/week at –1 M to 10,300 (IQR 4,900–20,800) units/week at 3 M ($p < 0.001$), corresponding to an increase of 3,100 (95% CI 1,900–4,300) units/week (Fig. 3b).

Serum levels of corrected calcium and bicarbonate were significantly higher at 1 M after transition and maintained those levels at the 3 M follow-up. Mean corrected calcium increased by 0.1 (95% CI 0.0–0.1) mg/dL from 9.0 (SD 0.7) mg/dL at –1 M to 9.1 (SD 0.6) mg/dL at 3 M ($p = 0.017$; Fig. 4a). The bicarbonate level also increased by 1.1 (95% CI 0.8–1.3) mEq/L from 22.0 (SD 3.5) mEq/L at –1 M to 23.1 (SD 3.5) mEq/L at 3 M ($p < 0.001$; Fig. 4b). Phosphorus and potassium levels decreased to the lowest values by –0.2 (95% CI –0.1 to –0.3) mg/dL and –0.1 (95% CI –0.0 to –0.2) mEq/L at 2 M, respectively, but these changes were attenuated at 3 M (Fig. 4c, d). Albumin levels very slightly increased by 0.03 (95% CI 0.01–0.06) g/dL from 3.80 (SD 0.02) g/dL at –1 M to 3.83 (SD 0.02) at 3 M ($p < 0.001$; Fig. 4e).

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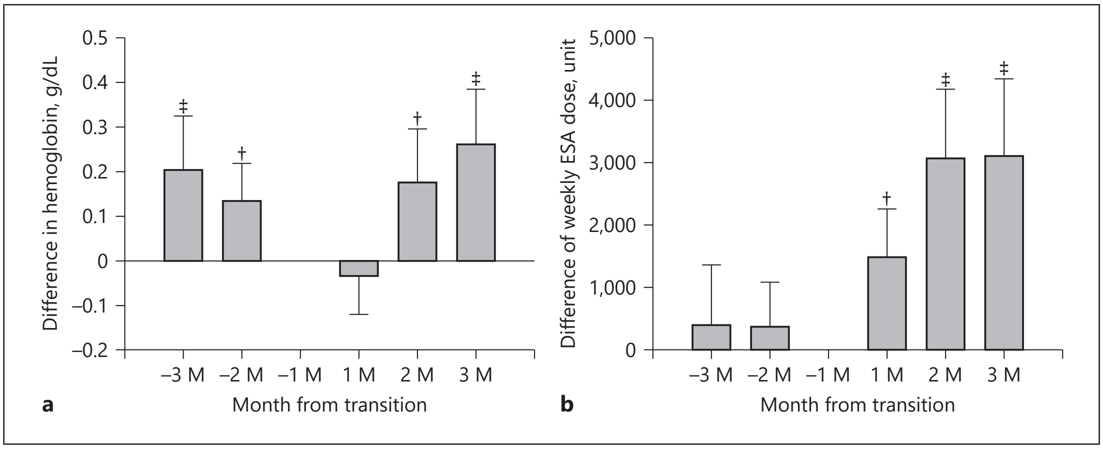

Fig. 3. Changes in hemoglobin (**a**) and weekly ESA dose (**b**). Data was expressed as mean ± SD. † $p < 0.01$, ‡ $p < 0.001$ (vs. values at –1 M). ESA, erythropoietin-stimulating agent.

Table 3. Changes in pre-HD SBP and post-dialysis body weight across three groups stratified by baseline SBP

	Period	Total (*n* = 569)	Baseline SBP, mm Hg		
			<140 (*n* = 154)	140 to <160 (*n* = 238)	≥160 (*n* = 177)
Pre-HD SBP, mm Hg	–3 M	151±20	131±15	151±14	166±15
	–2 M	151±20	131±13	150±12	169±13
	–1 M (ref.)	**152±20**	**128±9**	**150±6**	**175±11**
	1 M	149±19	129±13	148±12	167±14
	2 M	148±19	129±14	147±14	164±16
	3 M	148±19	131±16	147±14	162±16
Post-dialysis bodyweight, kg	–3 M	76±20	75±18	78±21	75±20
	–2 M	76±20	75±18	78±21	75±20
	–1 M (ref.)	**76±20**	**75±18**	**78±21**	**75±20**
	1 M	76±20	75±18	78±21	75±20
	2 M	75±20	74±18	77±21	74±19
	3 M	75±20	74±18	77±21	74±19

Values are expressed as mean ± SD. Values in bold at -1 M represent the baseline values from which change in Pre-HD SBP and Post-dialysis bodyweight before and after transition were calculated. SBP, systolic blood pressure; HD, Hemodialysis

Discussion

In this retrospective cohort study of incremental HD patients, we reported the hemodynamic and laboratory changes after increasing HD frequency from twice- to thrice-weekly treatment. UFV per session decreased except in the lowest weekly IDWG group, while weekly IDWG increased in all strata. Pre-HD systolic BP decreased with reductions in post-HD body weight. Hemoglobin and serum bicarbonate levels increased, while serum potassium and phosphorus did not show significant changes.

In the middle to high weekly IDWG groups, UFV per session decreased after increasing the HD frequency. However, UFV per session increased in the lowest weekly IDWG group

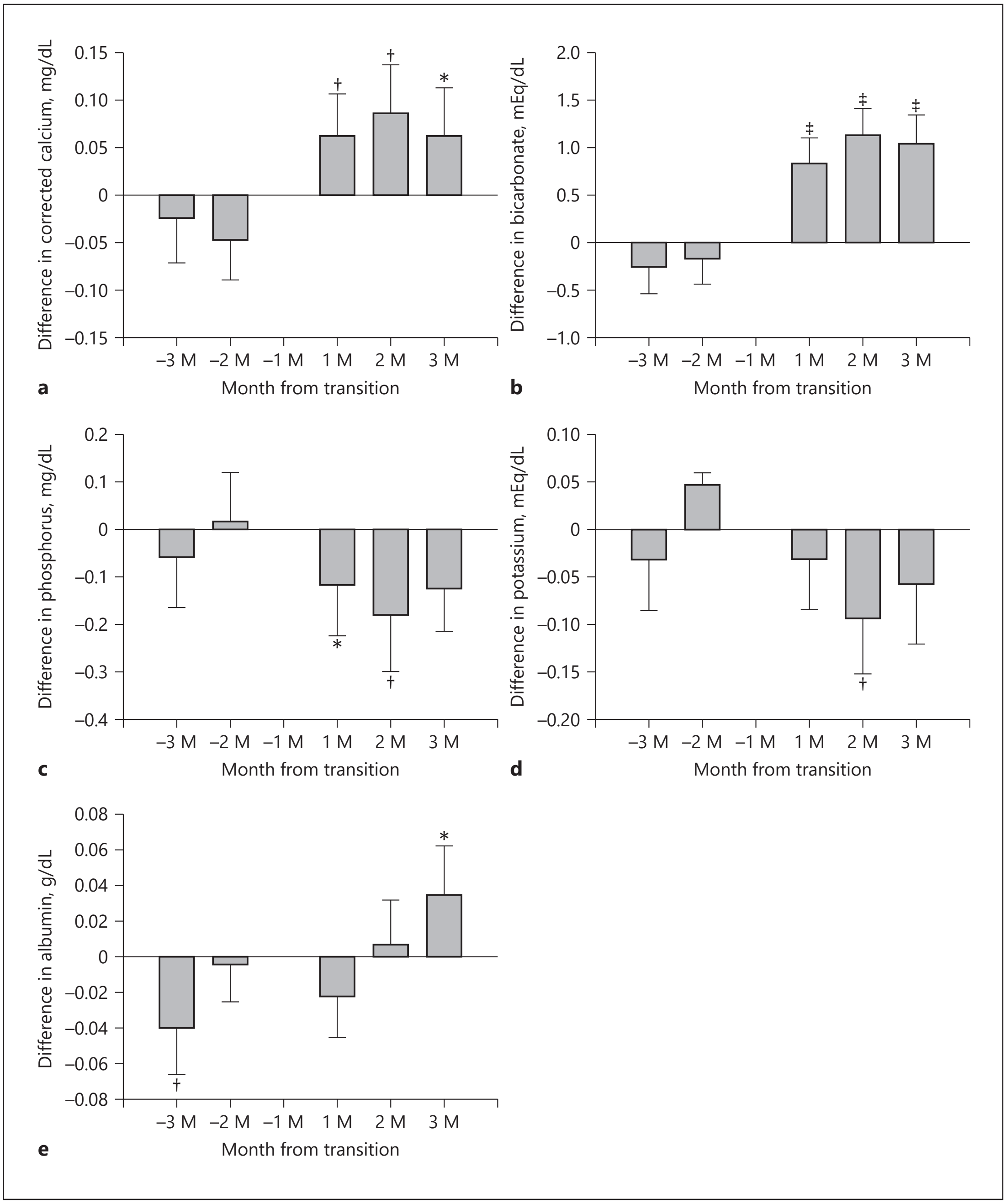

Fig. 4. Changes in serum levels of corrected calcium (**a**), bicarbonate (**b**), phosphorus (**c**), potassium (**d**), and albumin (**e**). Data was expressed as mean ± SD. * $p < 0.05$, † $p < 0.01$, ‡ $p < 0.001$ (vs. values at –1 M).

after transition. While the decrease in UFV in the upper IDWG group can be explained by the fact that increased frequency can mitigate the need for excess UF per session, the increase in UFV in the lowest weekly IDWG group may seem somewhat unexpected. Moreover, the latter finding can be interpreted with several differing views. First, given that weekly IDWG may be representative of the amount of food intake among HD patients, increased HD frequency may have improved appetite among undernourished patients in the lowest IDWG group due to enhanced clearance of uremic toxins, particularly if they had little or no RKF. This increase in food intake may have been accounted for in each session's UFV. In contrast, it is also possible that decreased urine output resulted in increased IDWG requiring greater UFV per session. Those explanations, increased dietary intake and loss of RKF, may also explain the lack of significant changes in serum potassium and phosphorus levels despite the incremental transition to more frequent HD. Conversely, serum albumin level indicative of both nutrition and inflammation status only increased slightly in 3 M after transition. In addition, we are unable to discriminate the cause-effect relationship between decrease in urine output and the incremental transition. Some patients may have transitioned to thrice-weekly HD due to decreased urine out, but more frequent HD may also have further diminished residual urine output. Indeed, the Frequent HD Network Nocturnal Trial has shown that residual function declined more rapidly among patients treated with frequent nocturnal HD, compared to those with conventional thrice-weekly HD [12]. Future studies are needed to examine these possible mechanisms by accounting for changes in urine volume and dietary intake after incremental transition.

Pre-HD SBP changed toward the recommended target (i.e., 140 mm Hg) [13] after increasing the dialysis dose, which coincided with changes in post-dialysis body weight. This finding is consistent with the previous report by Inrig et al. [14] showing that every 1% increase in IDWG was associated with a 1.0 mm Hg increase in pre-HD SBP and may suggest that body fluid volume control was not adequate while patients were on twice-weekly HD. Hemoglobin levels increased after transition likely because patients received more frequent ESA therapy without dose adjustment. Normalization of hemoglobin levels by ESA treatment may increase the risk of adverse events including hypertension, vascular access thrombosis, and cerebrovascular and cardiovascular events [15]. Therefore, it is important to monitor the ESA dose at the time of transition to more frequent HD and make adjustments if needed to avoid over correction of hemoglobin. Serum bicarbonate levels also increased after the transition. The K/DOQI guidelines have suggested that the mid-week pre-HD plasma bicarbonate levels be maintained at a value ≥22 mEq/L, but the correction of pre-HD acidosis is more difficult with the less frequent HD regimen due to the longer inter-dialytic interval [16, 17]. Hence, thrice weekly may be warranted for patients with persistent acidosis not amenable to oral bicarbonate therapy.

Our study has several limitations. First, given the observational nature of our study, we cannot make clinical decision-making recommendations based on our findings. However, our findings reveal clinically relevant trends which should be considered in the care of patients undergoing incremental HD therapy. Second, we had limited data about RKF and urine volume longitudinally and therefore, could not fully account for longitudinal changes in these important variables in this study. Third, potential confounding by prescribed medications cannot be ruled out given the potential use of diuretics, antihypertensive agents, intravenous iron, phosphate-binding agents, dialysis bath change, and in some cases sodium polystyrene sulfonate in HD patients. Fourth, this study did not capture clinical events during this transition period including hospitalization. Finally, we are not able to discriminate the changes associated with incremental transition from spontaneous changes with time on HD.

In conclusion, increasing HD frequency was associated with decreased UFV per session, an increase in weekly IDWG, improved pre-HD systolic BP, higher hemoglobin level, and higher serum bicarbonate. However, serum potassium and phosphorus did not show significant changes. Further prospective studies are needed to examine the indication and effectiveness of incremental transition on clinical parameters and important patient outcomes in HD patients.

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Disclosure Statement

K.K.-Z. has received honoraria and/or support from Abbott, Abbvie, Alexion, Amgen, American Society of Nephrology, Astra-Zeneca, Aveo, Chugai, Fresenius, Genetech, Haymarket Media, Hospira, Kabi, Keryx, National Institutes of Health, National Kidney Foundation, Relypsa, Resverlogix, Sanofi, Shire, Vifor, and ZS-Pharma.

Appendix

Table A1. Numbers of HD Patients According to Treatment Frequency

Treatment frequency	–3 M	–2 M	–1 M	1 M	2 M	3 M
7	41	6	0	39	17	0
8	264	196	294	92	47	0
9	245	359	275	158	49	0
10	19	8	0	67	43	0
11	0	0	0	69	58	85
12	0	0	0	43	118	154
13	0	0	0	94	233	318
14	0	0	0	7	4	12
Total	569	569	569	569	569	569

Table A2. Missing Frequencies and Percentages at Baseline (–1 M) Among the Variables

Variable	Missing frequency	%
Age, years	0	0.0
Gender, male	0	0.0
Race	0	0.0
Cause of ESRD	0	0.0
Comorbid conditions	0	0.0
Ultrafiltration volume per session	0	0.0
IDWG	0	0.0
Pre-HD systolic blood pressure	3	0.0
Post-dialysis body weight	8	0.0
Laboratory variables		
Hemoglobin	4	0.7
Bicarbonate	36	6.3
Calcium	21	3.7
Phosphorus	21	3.7
Potassium	45	7.9
Albumin	33	5.8

ESRD, end-stage renal disease; IDWG, inter-dialytic weight gain; HD, hemodialysis.

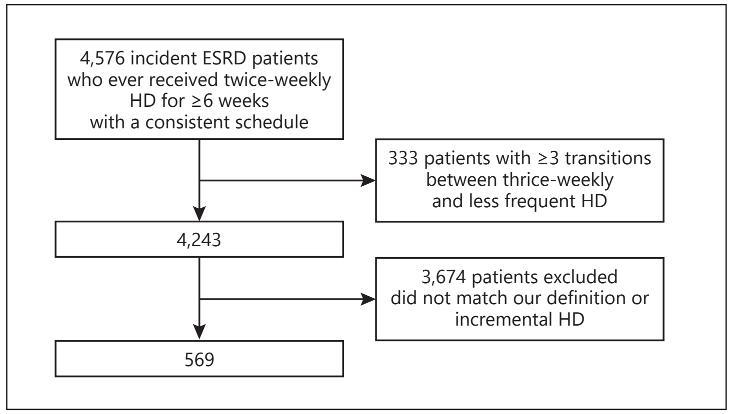

Fig. A1. Study flow diagram. Incremental hemodialysis was strictly defined as the gradual increase in treatment frequency starting from 7 to 10/month for consecutive 3 months (i.e., –3 to –1 M) that were followed by 2 months of the transition period (7–14/month) and the thrice-weekly hemodialysis period (11–14/month) at the third month (3 M). ESRD, end-stage renal disease; HD, hemodialysis.

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