Effect of hemodiafiltration on measured physical activity: primary results of the HDFIT randomized controlled trial

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GRAPHICAL ABSTRACT

In dialysis patients in the HDFIT trial, high-volume hemodiafiltration yielded modestly-sized treatment effect on step counts that was observed at 3 months and not sustained after 6 months of follow-up compared to high-flux hemodialysis.

**RCT**

| Trial characteristics | Trial design | Step count in 24 hours |
|-----------------------|--------------|------------------------|
| **Participants (n=195)** | **Hemodiafiltration (HDF)** | **High-flux hemodialysis (HD)** |
| • Stable HD patients | n=97 | n=98 |
| • Vintage 3–24 months | 52.6 years old | 53.3 years old |
| **Intervention:** High-volume HDF vs. high-flux HD | **Primary outcome:** Accelerometer-captured step count within 24 h after HD | **Primary outcome:** Treatment effect of switching to hemodiafiltration +538 steps (95% CI -330 to 1407) |
| **Baseline** | HDF | HD |
| 5253 | 5045 |
| 3 months | 150 | p=0.027 | 796 |
| 796 | p=0.262 | 1059 |
| 6 months | 709 | 1059 |

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**KEY LEARNING POINTS**

What is already known about this subject?
- Kidney dialysis patients are inactive and generally have decreasing measured activity levels over dialysis time, however kidney transplant patients generally perform higher levels of measured physical activity (PA) than dialysis patients;
- Uremic toxicity has been suggested to be a hypothetical causal factor influencing low activity levels in dialysis patients; and
- Given high-volume online hemodiafiltration (HDF) provides greater removal of high molecular weight uremic retention solutes and is suggested to associate with better outcomes than hemodialysis (HD), studies investigating possible favourable effects of HDF on measured activity are warranted.

What this study adds?
- This trial found that clinically stable HD patients with no limitations in ambulation who were randomized to HDF did not have a statistically significant improvement/preservation in their measured activity levels compared with patients allocated to high-flux HD;
- The observed size of the treatment effect of HDF versus high-flux HD on measured activity levels was modest, was most notable several hours after dialysis and might be clinically meaningful, which deserves further investigation; and
- HDF patients achieved a high convective volume throughout the trial, which was associated with lower urea and phosphorus levels compared with HD patients.

What impact this may have on practice or policy?
- This study adds to the body of evidence that high volume HDF can be effectively and safely implemented with improvements in solute removal; and
- The systematic and standardized collection of accelerometry data will contribute to the understanding of granular levels of PA in dialysis patients in relation to demographic, clinical characteristics and treatment schedules, providing a base for the planning of PA interventions in dialysis patients.

**ABSTRACT**

**Background.** Dialysis patients are typically inactive and their physical activity (PA) decreases over time. Uremic toxicity has been suggested as a potential causal factor of low PA in dialysis patients. Post-dilution high-volume online hemodiafiltration (HDF) provides greater removal of high molecular weight uremic retention solutes and studies suggest better clinical/patient-reported outcomes compared with hemodialysis (HD).

**Methods.** HDFIT was a randomized controlled trial at 13 clinics in Brazil that aimed to investigate the effects of HDF on measured PA (step counts) as a primary outcome. Stable HD patients (vintage 3–24 months) were randomized to receive HDF or high-flux HD. Treatment effect of HDF on the primary outcome from baseline to 3 and 6 months was estimated using a linear mixed-effects model.

**Results.** We randomized 195 patients (HDF 97; HD 98) between August 2016 and October 2017. Despite the achievement of a high convective volume in the majority of sessions and a positive impact on solute removal, the treatment effect HDF on the primary outcome was +538 [95% confidence interval (CI) –330 to 1407] steps/24 h after dialysis compared with HD, and was not statistically significant. Despite a lack of statistical significance, the observed size of the treatment effect was modest and driven by steps taken between 1.5 and 24.0 h after dialysis, in particular between 20 and 24 h (+197 steps; 95% CI –95 to 488).

**Conclusions.** HDF did not have a statistically significant treatment effect on PA 24 h following dialysis, albeit effect sizes may be clinically meaningful and deserve further investigation.

**Keywords:** accelerometry, dialysis recovery time, hemodiafiltration, physical activity, quality of life

**INTRODUCTION**

End-stage kidney disease (ESKD) affects patients’ physical function and vitality, with most being sedentary (taking <5000 steps/day) [1–3]. Inactivity in ESKD is associated with onset/worsening of negative outcomes including poor quality of life (QOL), fatigue, psychiatric diseases, cardiovascular events and mortality [2–6]. Physical activity (PA) is important in maintaining/improving health in all populations [7–9]. ESKD patients with a kidney transplant perform significantly higher levels of objectively measured PA compared with hemodialysis (HD) patients [10]. Given that the attributes of differing dialysis modalities are suggested to associate with distinct outcomes [11–14], it might be possible that dialysis modalities and/or dose may confer an effect on measured free-living PA, but this has not been compared in randomized controlled trials (RCTs).
Compared with HD, high-volume hemodiafiltration (HDF) provides greater solute removal, particularly middle-molecular weight toxins, which are known to associate with poor outcomes, compared with HD [15–18]. Also, HDF may confer hemodynamic stability, which associates with better outcomes [19]. HDF associates with improved patient reported and clinical outcomes versus HD [11–14, 20]. Additionally, HDF may decrease dialysis recovery time (DRT), particularly by reducing hypotensive episodes during dialysis, and improve health-related quality of life (HRQOL) when compared with HD, yet there are inconsistencies in reports [20–22]. Since PA is a surrogate marker of outcomes, it might be possible that the beneficial attributes of HDF could influence PA.

The primary objective of the ‘Impact of HemoDiaFilTration (HDFIT) on Physical Activity and Self-Reported Outcomes’ trial was to test the hypothesis that high-volume online HDF will preserve/improve objective PA compared with high-flux HD. In secondary objectives, we also evaluated the effect of HDF on patient-reported outcomes, including DRT and HRQOL.

MATERIALS AND METHODS

Trial design

HDFIT was a prospective, multi-center, unblinded, RCT investigating the impact of dialysis modality on objectively measured PA (ClinicalTrials.gov: NCT02787161). The study design and methodology have been previously published [23]. The trial design was performed by multidisciplinary professionals including clinical research and clinical nephrologists (trial concept, selection of outcomes and implementation of HDF), physical educators (implementation of accelerometry), dietitians, dialysis nurses and study coordinators (implementation of data capture and questionnaire application) and clinical research professionals (protocol, statistical and data management design).

Setting and participants

Fourteen outpatient dialysis centers in south-eastern Brazil were activated for recruitment (Figure 1). Trial was managed by the Center for Epidemiology and Clinical Research (EPICENTER) academic clinical research organization based at Pontificia Universidade Catolica do Paraná (PUCPR).

Informed consent was obtained before any study activities. The trial included adult ESKD patients who started HD ≥3 and ≤24 months before randomization, were using a fistula/graft or permanent catheter with adequate flow, had a Kt/V ≥1.2, and were considered clinically stable. The trial excluded patients who were participating in another trial, had a severe limitation in mobility/ambulation, were nonadherent with HD and/or had a life expectancy of <3 months.

Ethical considerations

The study documents were approved by PUCPR ethics review board (central application # 54926916.7.1001.0020; approval number 1.538.784). The trial was performed in accordance with the Declaration of Helsinki.

Outcomes

Primary outcome was the difference in the change in steps/24 h on dialysis days from baseline to the 6-month follow-up in patients treated with HDF versus HD. The co-secondary outcomes were the differences in the change in self-reported DRT and Kidney Disease Quality of Life (KDQOL) subscores (i.e. physical- and mental-component summary (PCS and MCS) scores) from baseline to the 6-month follow-up in patients treated with HDF versus HD.

FIGURE 1: Map of participant recruitment by study site location in Brazil (map of Brazil obtained from R version 3.4.0 and the packages gmap, maptools, maps and RgoogleMaps) [36].
Table 1. Baseline patient characteristics

| Parameter                                      | Overall     | HDF     | HD      | P-value HDF versus HD |
|------------------------------------------------|-------------|---------|---------|-----------------------|
| **Demographics**                               |             |         |         |                       |
| Patient number                                 | 195         | 97      | 98      | NA                    |
| Age, years                                     | 53.0 (15.1) | 52.6 (15.9) | 53.3 (14.3) | 0.748                 |
| Male, %                                        | 139 (71.3)  | 71 (73.2) | 68 (69.4) | 0.668                 |
| Race white, %                                  | 115 (59.0)  | 61 (62.9) | 54 (55.1) | 0.337                 |
| Height, cm                                     | 168.1 (8.4) | 168.3 (8.7) | 167.9 (8.2) | 0.724                 |
| Monthly family income level, %                 |             |         |         |                       |
| >10 minimum wages                              | 17 (9)      | 7 (4)   | 10 (5)  | 0.387                 |
| 4–10 minimum wages                             | 54 (28)     | 26 (13) | 28 (14) |                       |
| 2–4 minimum wages                              | 88 (45)     | 50 (26) | 38 (19) |                       |
| <2 minimum wages                               | 36 (18)     | 14 (7)  | 22 (11) |                       |
| **Transportation type to clinic, %**           |             |         |         |                       |
| Family car                                     | 84 (43)     | 43 (22) | 41 (21) | 0.692                 |
| Public transportation                          | 65 (33)     | 29 (15) | 36 (18) |                       |
| Ambulance                                      | 32 (16)     | 19 (10) | 13 (7)  |                       |
| Taxi                                           | 9 (5)       | 4 (2)   | 5 (3)   |                       |
| Walk                                           | 5 (3)       | 2 (1)   | 3 (2)   |                       |
| Dialysis shift, %                              |             |         |         | 0.866                 |
| First shift                                    | 59 (34)     | 28 (32) | 31 (36) |                       |
| Second shift                                   | 67 (39)     | 35 (40) | 32 (37) |                       |
| Third shift                                    | 48 (28)     | 24 (28) | 24 (28) |                       |
| **Clinical characteristics**                   |             |         |         |                       |
| Estimated dry weight, kg                       | 75.3 (15.9) | 73.8 (15.2) | 76.6 (16.6) | 0.223                 |
| BMI (calculated by post-HD weight), kg/m²      | 26.7 (4.9)  | 26.0 (4.2) | 27.3 (5.4) | 0.056                 |
| BSA (Dubois calculation by post-HD weight)     | 1.85 (0.2)  | 1.83 (0.2) | 1.86 (0.2) | 0.356                 |
| Creactive protein                              |             |         |         |                       |
| Catheter, %                                    | 22 (11.3)   | 11 (11.3) | 11 (11.2) | 1.000                 |
| Pre-dialysis weight, kg                        | 77.8 (16.0) | 76.2 (15.1) | 79.3 (16.7) | 0.171                 |
| Post-dialysis weight, kg                       | 75.5 (15.8) | 73.9 (14.9) | 77.1 (16.6) | 0.167                 |
| Pre-dialysis SBP, mmHg                         | 153 (24)    | 155 (24) | 152 (24) | 0.425                 |
| Pre-dialysis DBP, mmHg                         | 81 (13)     | 81 (13) | 81 (14)  | 0.984                 |
| Pre-dialysis pulse (beats per minute)          | 76 (13)     | 74 (12) | 77 (13)  | 0.122                 |
| Post-dialysis SBP, mmHg                        | 148 (23)    | 151 (25) | 146 (21) | 0.111                 |
| Post-dialysis DBP, mmHg                        | 77 (13)     | 79 (13) | 76 (14)  | 0.213                 |
| Post-dialysis pulse (beats per minute)         | 74 (12)     | 73 (12) | 75 (12)  | 0.235                 |
| **Comorbidities, %**                           |             |         |         |                       |
| Diabetes                                       | 68 (34.9)   | 28 (28.9) | 40 (40.8) | 0.121                 |
| Coronary artery disease                        | 33 (16.9)   | 14 (14.4) | 19 (19.4) | 0.464                 |
| Congestive heart failure                       | 15 (7.7)    | 5 (5.2)  | 10 (10.2) | 0.292                 |
| DRT                                            |             |         |         |                       |
| DRT, median (IQR), min                         | 30 (0–90)   | 30 (0–120) | 30 (0–60) | 0.578                 |
| DRT ≤0.5 h (%)                                 | 110 (57.6)  | 52 (54.2) | 58 (61.1) | 0.872                 |
| DRT >0.5 to ≤1 h (%)                           | 31 (16.2)   | 16 (16.7) | 15 (15.8) |                       |
| DRT >1 to ≤2 h (%)                             | 18 (9.4)    | 10 (10.4) | 8 (8.4)  |                       |
| DRT >2 to ≤4 h (%)                             | 15 (7.9)    | 9 (9.4)  | 6 (6.3)  |                       |
| DRT >4 h (%)                                   | 17 (8.9)    | 9 (9.4)  | 8 (8.4)  |                       |
| **Laboratory values**                          |             |         |         |                       |
| Pre-HD BUN, mg/dL                              | 58.2 (13.1) | 58.8 (12.9) | 57.6 (13.3) | 0.532                 |
| Post-HD BUN, mg/dL                             | 17.1 (7.7)  | 16.4 (6.3) | 17.8 (8.8) | 0.206                 |
| Single pool K/V                                | 1.5 (0.4)   | 1.6 (0.4) | 1.5 (0.4) | 0.121                 |
| Albumin, g/dL                                  | 4.0 (0.4)   | 4.0 (0.3) | 4.0 (0.4) | 0.718                 |
| Potassium, mEq/L                               | 5.2 (0.6)   | 5.2 (0.7) | 5.2 (0.9) | 0.507                 |
| Calcium, mg/dL                                 | 9.0 (0.7)   | 9.0 (0.7) | 8.9 (0.7) | 0.233                 |
| Phosphate, mg/dL                               | 5.3 (1.4)   | 5.2 (1.4) | 5.4 (1.5) | 0.378                 |
| Intact parathyroid hormone, pg/mL              | 351 (290)   | 340 (266) | 361 (313) | 0.624                 |
| Hgb, g/dL                                      | 11.1 (1.6)  | 11.3 (1.6) | 11.0 (1.7) | 0.364                 |

Descriptive statistics are presented as mean ± SD, or as patient number (n) and percent (%) of population with exception of DRT. DRT is presented as the median values (min) and the IQR overall, as well as, by the n and % for defined categories of DRT in blocks of time (h) after dialysis. BMI, body mass index; BSA, body surface area; SBP, systolic blood pressure; DBP, diastolic blood pressure. Minimum wage per individual in Brazil was 880 reais per month in 2016.
in a $2-20$- to $20-24$-h post-dialysis period and an ~4-h slice of data from a $20-24$- to $24$-h post-dialysis period that matches the duration of the prior dialysis session (Figure 2). Moderate-to-vigorous activity (MVPA) level cut points were chosen using the Freedson VM3 Combination (2011) algorithm [23, 30]. The cut points used for calculation of MVPA from acceleration counts per minute (CPM) data considered activity ranging from 2690 to infinity CPM to be MVPA and activity ranging from 0 to 2689 CPM as lower than MVPA. The metabolic rates were estimated by the Freedson Adult 1998 algorithm [31].

Questionnaires administered to capture HRQOL at study visits included the KDQOL-SF version 1.3 and DRT surveys. The KDQOL-SF version 1.3 survey (RAND Healthcare, Santa Monica, CA, USA) has been validated in Brazilian Portuguese [32], while the DRT has only been validated in English [33]. The responses to the first 11 questions of the KDQOL-SF version 1.3 survey, consisting of 36 items (i.e. the SF-36), were captured in the eCRF. PCS and MCS scores were computed from the eight domains in the generic core of the SF-36 items within the KDQOL-SF version 1.3 survey. The self-reported DRT survey used the question ’How long does it take you to recover from a dialysis session?’ and asked patients to answer in minutes after dialysis.

Dialysis treatment characteristics, dialysis access events/ issues and the occurrence of intradialytic hypotension (IDH) events were captured by dedicated research dialysis nurses during routine treatments in the intervention period. Patients were defined to have achieved protocol convective volume (CV) targets (calculated by the sum of the total replacement volume and session ultrafiltration) if the median across all recorded sections was $\geq 22$ L per treatment. Monthly CV data were considered missing for if there was more than one record, and all available data were used to estimate the per-patient medians.

**Statistical methods**

**Sample size.** A power analysis was performed for the primary endpoint and details of sample size calculations have been published [23]. Briefly, it was estimated that 86 patients in each study arm would be needed to complete the 6-month follow-up to provide a 90% power to detect a 20% effect with respect to the primary outcome [23].

**Analysis of outcomes.** Categorical variables were calculated in counts/proportions and continuous variables as mean [standard deviation (SD)] or median and interquartile range (IQR). An intention-to-treat design was used in the analysis of outcomes. Comparisons in absolute values between arms were performed using Student’s t-test methods or Mann–Whitney rank-sum U-test as appropriate. Linear mixed-effects models (LMMs) with random slope and random intercept were constructed for the primary (i.e. steps per 24 h on dialysis days) and sub-outcomes (i.e. DRT, PCS and MCS scores) to determine the treatment effect of the intervention on mean changes from baseline to 3 and 6 months for HDF versus HD.

LMMs included a random intercept and random slope, where random intercept represents the variation for a given
subject from the overall fixed intercept and the random slope represents the variation from one included time point to another. To explain the variability in the model, the dichotomous treatment allocation was included as a fixed effect reflecting the treatment effect of the intervention. In the general rearranged equation of a LMM, our model would present as

$$ Y_{ij} = \beta_{00} + \beta_{01}X_i + \beta_{10}t_{ij} + \beta_{11}X_i t_{ij} + r_{0i} + r_{1i}t_{ij} + \epsilon_{ij} $$

where \( r_{0i} \) and \( r_{1i}t_{ij} \) represents the random effects on slope (\( t \) included as a month into the study) and intercept (subject identifier) and \( \beta_{01} \) the treatment effect of the intervention (1 for HDF and 0 for HD). For the computation of our models, we used R software with the ‘nlme’ package [34]. The function ‘lme’ was employed with the setting to (i) exclude missing values, (ii) model fit by restricted log-likelihood, (iii) maximum iteration of 50 (with uncomplicated convergence of the models) and (iv) employing general-purpose optimization based on Nelder–Mead, quasi-Newton and conjugate-gradient algorithms.

A survival analysis with a log-rank test was performed to compare the rate of time to events for AEs and serious adverse events (SAEs). A chi-squared test was used to compare the number of dialysis treatments with IDH episodes between groups. Normalized protein catabolic rate (nPCR) and the creatinine index were calculated based on previous validated formulas [35]. Since data on residual renal function were not collected, it was assumed to be null for all patients.

RESULTS

Recruitment and retention

Among 14 centers activated for recruitment, 195 eligible patients from 13 centers were randomized to receive post-dilution high-volume online HDF, or to continue high-flux HD, between August 2016 and October 2017 (Figures 1 and 3) [36]. Overall, 44 patients were switched from low-flux HD to high-flux HD during the 4-week run-in period; among these patients, randomized allocation to HDF (\( n = 22 \)) or high-flux HD (\( n = 22 \)) was balanced. Participant attrition was 8% (\( n = 15 \)) and 11% (\( n = 21 \)) at 3 and 6 months, respectively (Figure 3).

AEs

During the 6-month follow-up, there were five SAEs that included hospitalization or mortality (HDF: \( n = 3 \); HD: \( n = 2 \)) and 10 non-serious AEs reported (HDF: \( n = 2 \); HD: \( n = 8 \)). There were no differences in SAE (log-rank test; \( P = 0.63 \)) or AE (log-rank test; \( P = 0.20 \)) rates between HDF and HD. All
SAEs/AEs were determined by the investigator and steering committee to be not related to the HDF intervention.

**Patient characteristics**

Enrolled patients had a mean age of 53 ± 15 years, 71% were male, 11% used a catheter dialysis access and 35% had diabetes (Table 1). There were no differences in demographics and clinical characteristics between patients randomized to HDF versus HD.

**Treatment characteristics**

The median (IQR) dialysis treatment time was 235 min in HDF (233–240) and 235 min in HD (232–240) patients over follow-up. Among 97 patients treated with HDF, 95 had CV data available. There was a median (IQR) of 70 (63–73) sessions with recorded CVs per patient during the follow-up. Monthly mean CV was 27.6 ± 3.0, 27.4 ± 2.8, 27.1 ± 2.9, 27.2 ± 3.0, 27.3 ± 2.9 and 27.5 ± 2.9 L at 1–6 month, respectively. Overall, 99% of HDF patients achieved a mean target CV of 22 L/treatment or greater throughout the follow-up (94 of 95 patients).

Incidence of IDH, as defined by European Best Practice Guidelines criteria [37], occurred in 15 and 12 treatments per 100 patient months for HD and HDF, respectively (P = 0.186).

**Profiles of PA**

Accelerometry yielded valid activity data on 176 (HDF = 89; HD = 87) patients at baseline, 173 (HDF = 88; HD = 85) patients at 3 months and 162 (HDF = 83; HD = 79) patients at 6 months. At baseline, we found no differences in distribution by seasons stratified by region across treatment arms (Supplementary data, Table S1). PA/24-h after dialysis did not differ at baseline between HDF versus HD groups (Table 2).

At 3 months, the HDF group performed consistent PA levels with baseline, while the HD group had a decrease in steps/24 h (HDF 5303 ± 3442 versus HD 4249 ± 2734, P = 0.03). Distinctions were not sustained at 6 months (Figure 4 and Table 2). Granular PA did not differ between arms at baseline, yet there were differences in some select predefined periods >2.0 h after dialysis (Table 3; Supplementary data, Tables S2 and S3).

**Effect of HDF on PA levels**

Assessment of the difference in the change of PA/24 h during the 3 and 6 months showed no statistically significant distinctions between HDF versus HD (Figure 5; Supplementary data, Table S4). The LMM estimation of the primary outcome for the overall treatment effect of HDF found no significant differences, although HDF patients took 538 more steps/24 h (95% confidence interval (CI) –300 to 1407) compared with HD (Figure 5B). We found no interaction between center region on the treatment effect of HDF (P = 0.73) (Supplementary data, Table S1).

A prespecified sub-analysis of the differences in the change of granular PA levels from baseline to 3 and 6 months identified consistent signals (Figure 5C; Supplementary data, Tables S5–S7). At 6 months, the difference in the change from baseline showed HDF patients had 544 more steps (95% CI 37–1051) preserved versus HD during the >11.0- to ≤15.5-h post-dialysis period. LMM estimation of the overall treatment effect of HDF on granular PA levels was not significantly different between treatment groups (Figure 5C). Albeit not significant, the largest qualitative difference among predefined periods was seen between 20 and 24 h after dialysis (197 steps; 95% CI –95 to 488).

### Table 2. Average absolute PA levels per 24 h after dialysis

| PA metric          | Baseline (SD) | 3 months (SD) | P-value | 6 months (SD) | P-value |
|--------------------|---------------|---------------|---------|---------------|---------|
| Step counts (SD)   | 5253 (3062)   | 5045 (3936)   | 0.696   | 4249 (2734)   | 0.027   |
| MVPA (SD) (min)    | 27.6 (29.1)   | 26.6 (38.8)   | 0.851   | 20.0 (20.6)   | 0.091   |
| MET (SD) (kcal/kg/h)| 1.09 (0.09)   | 1.11 (0.12)   | 0.468   | 1.08 (0.10)   | 0.497   |

Absolute PA levels per 24 h after dialysis presented as mean ± SD.
Overall, data for DRT were available for 92% of the population during the follow-up period. Median DRT at baseline was not different between HDF and HD (P = 0.578) (Supplementary data, Table S8). DRT for individual patients is shown in Supplementary data, Figure S1. The difference in the change in DRT from baseline showed no significant distinctions between groups, although HDF patients reported a −38.1 min (95% CI −78.5 to 2.3) shorter DRT at 3 months and −33.7 min (95% CI −79.8 to 12.4) shorter DRT at 6 months (Figure 6, Supplementary data, Table S8). The overall treatment effect of HDF on DRT was confirmed to be not statistically different by construction of an LMM (−30.6 min; 95% CI −74.3 to 13.1) (Figure 6B).

### Components of QOL and effect of HDF

Overall, 88 and 92% of patients had complete data for estimation of PCS and MCS during the follow-up period, respectively. The median PCS and MCS scores were not significantly different in HDF and HD patients at baseline, 3 and 6 months (Supplementary data, Table S9). The difference in the change in PCS scores from baseline was 5.1 points (95% CI −9.9 to −0.3) lower in HDF at 3 months, yet not significantly different at 0.5 points (95% CI −5.1 to 6.1) higher in HDF at 6 months. The difference in the change in MCS scores from baseline did not favour either modality at both 3 and 6 months. The LMM estimation of the overall treatment effect of HDF on PCS and MCS found no differences between the groups.
Laboratory data

Baseline laboratory values did not differ between groups (Table 4). At 3 and 6 months HDF patients had a 0.2 and 0.1 higher Kt/V, as well as a 5 and 2.5% higher urea reduction ratio (URR), respectively, compared with HD patients (Figure 7). Albmin was 0.1 g/dL lower in HDF patients at both 3 and 6 months versus HD (P < 0.01). Phosphate was 0.4 mg/dL lower in HDF versus HD at 3 months (P = 0.022), yet there were no differences at 6 months. Hgb was 0.6 g/dL lower in HDF patients at 6 months compared with HD patients (P = 0.012).

DISCUSSION

In this unique RCT using objectively measured PA as the primary outcome, we failed to demonstrate a significant treatment effect of high-volume HDF in comparison with high-flux HD on steps taken 24 h after dialysis, nor the co-secondary outcomes of DRT, PCS and MCS between HDF and HD. Despite this, the size of the treatment effect indicates that the impact of HDF on PA may be clinically meaningful, which should be addressed in future investigations. A high CV was achieved in HDF patients and was associated with lower urea and phosphorus levels compared with HD with the same treatment time. The overall treatment effect of HDF on steps/24 h after dialysis did not statistically differ from HD. However, HDF patients took >1000 steps/24 h post-dialysis after 3 months, which was not sustained by 6 months. This lack of a sustained significant effect in the HDF group is intriguing and possibly related to an inadvertent spontaneous reaction, given there was no education or program to stimulate PA in both arms. We did not include strategies to motivate patients to increase their PA nor a standardized physical performance test, which may yield different results and can be tested in future design strategies using our baseline laboratory values presented as mean ± SD. TSAT, transferrin saturation.

| Table 4. Average laboratory profiles |
|-------------------------------------|
| Parameter                          | Baseline HDF (±SD) | Baseline HD (±SD) | P-value | 3 months HDF (±SD) | P-value | 6 months HDF (±SD) | P-value |
| Pre-HD BUN, mg/dL                  | 58.8 (12.9)        | 57.6 (13.3)       | 0.532   | 52.1 (13.9)        | 0.001   | 55.5 (14.9)        | 0.185   |
| Post-HD BUN, mg/dL                 | 16.4 (6.3)         | 17.8 (8.8)        | 0.206   | 11.8 (4.9)         | 0.000   | 12.9 (6.6)         | 0.021   |
| Kt/V                               | 1.6 (0.4)          | 1.5 (0.4)         | 0.121   | 1.8 (0.4)          | 0.000   | 1.8 (0.5)          | 0.174   |
| URR, %                             | 72.4 (9.1)         | 70.7 (9.7)        | 0.205   | 77.9 (6.4)         | 0.000   | 77.1 (8.7)         | 0.057   |
| Albumin, g/dL                      | 4.0 (0.3)          | 4.0 (0.4)         | 0.718   | 3.9 (0.4)          | 0.002   | 3.9 (0.3)          | 0.003   |
| Potassium, mEq/L                   | 5.2 (0.7)          | 5.2 (0.9)         | 0.507   | 5.1 (0.8)          | 0.215   | 5.0 (0.8)          | 0.243   |
| Calcium, mg/dL                     | 9.0 (0.7)          | 8.9 (0.7)         | 0.233   | 8.9 (0.8)          | 0.731   | 9.1 (0.7)          | 0.584   |
| Phosphate, mg/dL                   | 5.2 (1.4)          | 5.4 (1.5)         | 0.378   | 4.8 (1.3)          | 0.022   | 4.9 (1.5)          | 0.278   |
| Intact parathyroid hormone, pg/mL  | 340 (266)          | 361 (313)         | 0.624   | 371 (321)          | 0.266   | 340 (326)          | 0.611   |
| Hgb, g/dL                          | 11.3 (1.6)         | 11.0 (1.7)        | 0.364   | 11.6 (1.4)         | 0.441   | 10.9 (1.7)         | 0.012   |
| Ferritin, ng/mL                    | 387.7 (388.0)      | 309.9 (270.2)     | 0.108   | 363.6 (340.2)      | 0.491   | 331.0 (286.7)      | 0.693   |
| TSAT, %                            | 30.7 (15.2)        | 29.1 (17.9)       | 0.500   | 32.4 (21.7)        | 0.604   | 31.6 (12.6)        | 0.519   |
| nPCR                               | 1.13 (0.31)        | 1.06 (0.27)       | 0.129   | 1.11 (0.29)        | 1.11 (0.25) | 0.854   | 1.17 (0.34)        | 1.16 (0.33) | 0.682   |

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results as background information. Previous RCTs in distinct populations showed that motivational interviews and structured rehabilitation programs can improve measured PA, as well as potentially improve QOL, particularly fatigue [38, 39]. Our finding provides insights for the design of future studies using measured PA as endpoints.

We found both groups performed relatively low PA levels, consistent with previous studies in ESKD [6, 10, 28, 40–43]. Temporal observations found PA decreased over time in both arms, which is consistent with previous longitudinal studies in prevalent HD patients (vintage 7 years) that found annual decreases of ~130–428 steps/calendar day (i.e. 00:00–23:59 h) [6, 43]. We observed significant intra-group decreases of >900 steps/24 h from baseline to 6 months in HD patients, while HDF patients had nonsignificant decreases of ~500 steps/24 h. Measured PA has not been shown to decrease with more advanced chronic kidney disease (CKD) stages before progression to ESKD [44]. Given that PA decreases with dialysis time, it might be possible that the changes associate with the dialysis treatment itself, which assumes only some functions of the diseased kidney, as well as a worsening comorbidity burden in advanced CKD and other parameters.

Our approach to defining granular slices from accelerometry data, which is the gold standard for characterizing PA, contributes to the novelty of this study. Changes in granular PA levels identified periods that may be driving distinctions 24 h after dialysis (Figure 5C). The lack of impact from HDF in the initial period post-dialysis (which defined our hypothesis and served as a basis for the study design) was unexpected, and patients presented relatively high PA immediately post-dialysis as compared with later periods. Although transportation from the clinic may impact findings, there were no differences in treatment allocation by transportation type. An analysis of PA with a standardized physical performance test particularly in this post-dialysis period would be interesting to include in future trials.

The qualitative effect of HDF on PA was the most pronounced 20- to 24-h post-dialysis (Figure 5C). This may indicate that the effect of HDF on PA might not be detected

**FIGURE 7:** Average laboratory values in HDF (red line) and HD (blue line) patients. (A) Kt/V, (B) URR, (C) phosphate, (D) pre-dialysis BUN and (E) post-dialysis BUN. *P < 0.05; **P < 0.01; ***P < 0.001.
immediately, but perhaps several hours after the dialytic procedure, particularly when patients have returned to their homes and spontaneous PA behaviors may be identified. We speculate that this late effect may be driven by improvement in uremic toxin clearance. Since our study rationale and estimates were based on the assumption that the impact of HDF on PA levels would be primarily driven by behaviors immediately post-dialysis, our findings may also be attributed to this unexpected finding.

Preservation of PA in dialysis patients can potentially impact more traditional outcomes, serving as a proxy or a surrogate marker. HD patients with ≥30% increase in daily steps/year have been found to exhibit a 3-fold decrease in mortality risk versus those with ≤30% reduction [43]. US adult PA guidelines suggest that any amount of higher PA yields some health benefits [45]. In the general population, cardiovascular event rates decrease by ~10% for every 2000 more steps/day [46]. A study of 16,741 elderly women (age 72 ± 5.7 years; mean 5499 steps/day) found all-cause mortality risk decreased by 15% for every 1000 more steps/day [47], which is consistent with other observations in the elderly [48–50].

HDF patients presented ~30-min improvement in DRT compared with HD patients, although this was not statistically significant. There were distinctions in intra-group changes that decreased significantly in HDF patients at both time points, yet not in HD patients. We cannot exclude a clinically important benefit of HDF considering the magnitude of the effect sizes. Frequent HD trials estimated benefits up to 80 min for daily compared with conventional HD [51]. The CIs we provided for the between-groups difference would be compatible with a benefit close to daily HD trials, considering a shorter follow-up period and a conventional treatment frequency. It is noteworthy that DRT patterns are likely multifactorial and more complex measurement methods of DRT (e.g. interviews) and analytical approaches are warranted in future studies to understand the interactions between DRT, PA levels and KDQOL subscores.

Dialysis laboratory targets were achieved in both modalities in our trial. HDF patients achieved a monthly CV of ≥27 L and had higher $K_t/V$ and urea reduction rates. Higher removal of uremic toxins may reduce muscle wasting, improve muscle function and preserve PA [52]. In fact, although we detected a small decrease in albumin in HDF compared with high-flux HD, the nPCR was similar across groups, which suggests neutral effects of HDF on nutritional parameters. Optimal volume control and hemodynamic stability can also improve exercise capacity and may influence PA. The French Convective versus Hemodialysis in Elderly (FRENCHIE) trial found that HDF associates with a lower incidence of IDH [19]. However, we did not see differences in the incidence of IDH between groups. Further trials are needed to evaluate physiologic drivers of changes in PA and DRT.

The treatment effect of HDF on KDQOL subscores for PCS and MCS showed no meaningful differences [53, 54] versus HD patients. There are inconsistent reports on the effects of HDF on QOL, which may be influenced by patient characteristics [19, 20, 22, 55]. Most studies suggest no difference in PCS and MCS metrics, yet there have been findings suggesting that HDF causes improved self-reported social activity scores versus HD [20, 22].

The HDFIT trial has many strengths, including being a multicenter RCT representative of in-center dialysis patients who are adherent with treatments and have no impairments in mobility/ambulation. Also, an innovative and novel method of analyzing measured PA was developed. We designed the trial in a multidisciplinary framework, with integrative efforts across distinct disciplines of nephrology and physical education and included objective measurements of PA using accelerometers and patient-reported outcomes. We explored the potential impact of dialysis modalities on objective and subjective patient-centric outcomes; however, it will be essential to understand how to treat patients in a person-centric manner that integrates dialysis care in a broader structure that accounts for the individual patients’ social, emotional and practical needs, and experiences with decisions regarding health services and medical therapies [56].

There are some limitations to the trial, including an unblinded intervention. Also, PA was estimated using ActiLife software’s default algorithm and undercounting has been reported versus pedometers in elderly populations [30]. However, the accelerometer has been validated in the elderly to reasonably estimate free-living energy expenditure in steps against doubly labeled water-determined energy expenditure [27]. Also, the accelerometer has internal consistency and PA levels are similar to previous reports in the ESKD population [6, 10, 28, 40, 41, 43]. However, currently there is no validation data for ESKD patients. Although we found patient characteristics were similar between groups at baseline, it is unknown if changes in psychosocial factors and other determinants of health that could potentially affect PA were equal between groups through follow-up.

In conclusion, despite the achievement of a high CV and a positive impact on solute removal, high volume HDF did not improve measured PA compared with high-flux HD. However, the observed size of the treatment effect may be clinically meaningful and deserve further investigation. The innovative approach of using objectively measure PA as a trial endpoint in dialysis patients may help in the design of future studies in this population.

**SUPPLEMENTARY DATA**

Supplementary data are available at ndt online.

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We would like to acknowledge and thank the site investigators, participating dialysis centers and staff conducting this trial (Supplementary data, Appendix A); the EPICENTER program for the design, coordination and funding of the trial; the anonymous peer reviewers for their helpful comments; and our Fundación Cardiovascular de la Caixa/CSIC group for their help in completing the trial.

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academic contract research organization (ACRO) staff and affiliates managing the trial (Supplementary data, Appendix B); and the external advisory committee members Bernard Canaud, MD, PhD, Cristina Marelli, MD, Len A. Usvyat, PhD and Rodrigo S. Reis, PhD, MSc.

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Investigators were involved in the design of the protocol and performed medical oversight and the coordination of data collection during the trial. The principal investigator provided medical oversight of the conduct of the trial at all sites under the guidance of the steering committee and coordinated the trial management.

The proponent institution Pontifícia Universidade Católica do Paraná supported the trial with infrastructure for study management through use of the university’s ACRO, hosting of the REDCap eCRF on the university’s server, and use of the university’s central ERB and Research Council.

The outpatient dialysis centers permitted clinical research at the clinics and supported the trial with their clinical staff, who performed data collection and the conduct of study procedures under the oversight of the site investigators and local trial leadership.

Fresenius Medical Care provided the sites with the infrastructure for the conduct of the trial including HDF machines, dialysis supplies for study participants, body composition monitor (BCM) machines in clinics without them. Also, they provided some staff for site monitoring. Fresenius Medical Care provided a monetary award to PUCPR’s academic clinical research organization (EPICENTER), which performed the central management, data acquisition and monitoring. Fresenius Medical Care and the subsidiary company Renal Research Institute provided support from statistical experts to assist in the analysis of trial data under the oversight of the steering committee. Fresenius Medical Care has supported three investigator meetings, as well as three steering committee meetings. The leadership of Fresenius Medical Care reviewed and approved the protocol prior to commencement.

The steering committee members who represent supporting institutions reviewed and approved the research design, protocol, addendums and changes to the protocol, analyses and this publication of study data, as well as provided oversight of the trial conduct and safety.

**AUTHORS’ CONTRIBUTIONS**

Trial procedures were performed under the oversight of the principal investigator (R.P.-F.) and site investigators (Supplementary data, Appendix A). The trial was jointly designed by the steering committee (Supplementary data, Appendix C), the site investigators (Supplementary data, Appendix A) and external advisors listed in the Acknowledgements section. The selection of the primary outcome measure of PA, and the measurement methods, were performed under the guidance of PA surveillance experts (P.B.G. and the external advisor Rodrigo S. Reis, PhD, MSc). The selection of the co-secondary outcome measures of DRT and KDQOL subscores for PCS and MCS were performed under the guidance of patient-reported outcome experts (R.P.-F. and T.P.M.). The conduct of the study was performed by: R.P.-F., P.B.G., V.C.-S., M.C.M.C., C.E.P.-F., A.L.C.N., A.B.L.B, T.P.M., M.E.F.C. and the HDFIT investigators and research staff (Supplementary data, Appendix A) and EPICENTER ACRO and affiliated staff (Supplementary Appendix B). The data collection, analytical design and analysis for this study was performed by: R.P.-F., J.L., P.B.G., S.S., M.G., M.H., V.C.-S., M.C.M.C., C.E.P.-F., A.L.C.N., P.K., T.P.M., J.G.R. and the HDFIT investigators and research staff (Supplementary data, Appendix A). The interpretation, drafting and revision of this manuscript were performed by all authors, and the HDFIT investigators (Supplementary data, Appendix A) and steering committee (Supplementary data, Appendix C). The decision to submit this manuscript for publication was jointly made by all parties; this manuscript was confirmed to be accurate and approved by all authors.

**CONFLICT OF INTEREST STATEMENT**

R.P.-F. and T.P.M. are employed by Pontifícia Universidade Católica do Paraná. R.P.-F. is employed by Arbor Research Collaborative for Health, and receives research grants, consulting fees, and honoraria from Astra Zeneca, Novo Nordisc, Akibia and Fresenius Medical Care. R.P.-F., C.E.P.-F., T.P.M. and M.E.F.C. are recipients of scholarships from the Brazilian Council for Research (CNPq). J.L., M.G. and M.H. are students at Pontifícia Universidade Católica do Paraná. J.L. is an employee of Fresenius Medical Care, and S.S., M.H., P.K. and J.G.R. are employees of Renal Research Institute, a wholly-owned subsidiary of Fresenius Medical Care North America. C.E.P.-F. and A.L.C.N. receive consulting fees and speaker honorarium from Fresenius Medical Care. C.E.P.-F. receives lecture fees and travel support from Fresenius Medical Care, Alexion, Baxter and Astra Zeneca and is employed by Pontifícia Universidade Católica do Rio Grande do Sul. A.B.L.B. is an employee of Fresenius Medical Care Brazil. P.B.G. receives travel support from Fresenius Medical Care. P.K. has share options/ownership in Fresenius Medical Care, receives author honorarium from Up-To-Date, and is on the Editorial Board of Blood Purification and Kidney and Blood Pressure Research. M.E.F.C. is an employee by Federal University of São Paulo, and receives research grants, consulting fees and honoraria from Baxter Healthcare and Fresenius Medical Care.

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