KI REPORTS
KIReports.org
CLINICAL RESEARCH

Modification of Dialysate Na^+ Concentration but not Ultrafiltration or Dialysis Treatment Time Affects Tissue Na^+ Deposition in Patients on Hemodialysis

Christoph Kopp[1], Lukas Kittler[1], Peter Linz[1,2], Dennis Kannenkeril[1], Stephan Horn[3], Charles Chazot[4], Mario Schiffer[1], Michael Uder[2], Armin M. Nagel[2,5] and Anke Dahlmann[1]

[1]Department of Nephrology and Hypertension, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; [2]Institute of Radiology, Friedrich-Alexander-University Erlangen-Nürnberg, Erlangen, Germany; [3]Kuratorium für Heimdialyse, Erlangen, Germany; [4]Clinique Charcot, Sainte Foy Les Lyon, France; and [5]Division of Medical Physics in Radiology, German Cancer Research Centre (DKFZ), Heidelberg, Germany

Introduction: Tissue Na^+ overload is present in patients receiving hemodialysis (HD) and is associated with cardiovascular mortality. Strategies to actively modify tissue Na^+ amount in these patients by adjusting the HD regimen have not been evaluated.

Methods: In several substudies, including cross-sectional analyses ($n = 75$ patients on HD), a cohort study and a cross-over interventional study ($n = 10$ patients each), we assessed the impact of ultrafiltration (UF) volume, prolongation of dialysis treatment time, and modification of dialysate Na^+ concentration on tissue Na^+ content using ^{23}Na magnetic resonance imaging (^{23}Na-MRI).

Results: In the cross-sectional analysis of our patients on HD, differences in dialysate sodium concentration ([Na^+]) were associated with changes in tissue Na^+ content, whereas neither UF volume nor HD treatment time affected tissue Na^+ amount. Skin Na^+ content was lower in 17 patients on HD, with dialysate [Na^+] of $<$138 mmol/l compared to 58 patients dialyzing at $\geq$138 mmol/l (20.7 $\pm$ 7.3 vs. 26.0 $\pm$ 8.8 arbitrary units [a.u.], $P < 0.05$). In the cohort study, intraindividual prolongation of HD treatment time was not associated with a reduction in tissue Na^+ content. Corresponding to the observational data, intraindividual modification of dialysate [Na^+] from 138 to 142 to 135 mmol/l resulted in concordant changes in skin Na^+ (24.3 $\pm$ 7.6 vs. 26.3 $\pm$ 8.0 vs. 20.8 $\pm$ 5.6 a.u, $P < 0.05$ each), whereas no significant change in muscle Na^+ occurred.

Conclusion: Solely adjustment of dialysate [Na^+] had a reproducible impact on tissue Na^+ content. ^{23}Na-MRI could be utilized to monitor the effectiveness of dialysate [Na^+] modifications in randomized-controlled outcome trials.

Kidney Int Rep (2024) **9,** 1310–1320; https://doi.org/10.1016/j.ekir.2024.02.002
KEYWORDS: ^{23}Na-MRI; dialysate Na^+; hemodialysis prescription; hemodialysis; tissue Na^+

Patients receiving HD are salt-sensitive by virtue of relying on a dialyzer to remove Na^+ from the body. Resulting Na^+ and volume overloads are "prime suspect" for their enhanced end organ damages. Interdialytic salt restriction and/or removal of salt and water during HD evidently lower blood pressure.[1-5] However, normal blood pressure is rare in patients with end-stage renal disease despite counseling about dietary salt reduction and effective body fluid management.[6] Evidence suggests that a high salt intake is associated with greater mortality in patients with end-stage renal disease.[7] Nevertheless, nephrologists were limited in the past to monitor serum Na^+ and dialysate Na^+ concentrations (dialysate [Na^+]), observe interdialytic weight gain, and estimate dietary salt intake to determine a patient's Na^+ balance.[8] However, animal and human studies revealed a capability of several tissues to accumulate Na^+ independent of its water content.[9] ^{23}Na-MRI has been established as a tool to noninvasively detect an overload of Na^+ in skin and muscle tissue of patients on HD.[10,11] Conventional 4-hour HD treatment normalized tissue Na^+ content compared to age-matched controls. However, the observed effects

Correspondence: Anke Dahlmann, Department of Nephrology and Hypertension, Friedrich-Alexander-University Erlangen-Nürnberg, Ulmenweg 18, 91054 Erlangen, Germany. E-mail: anke.dahlmann@uk-erlangen.de

Received 24 November 2023; revised 30 January 2024; accepted 5 February 2024; published online 9 February 2024

were highly variable and independent of Na^+ or water removal from the body by a single HD session.[12] Given that Na^+ deposition is a reversible condition, it might be susceptible to therapeutic interventions, ultimately resulting in a favorable outcome for patients on HD. The intended transfer to daily clinical routine requires feasible applications. Prolonged HD treatment time, a cautious increase in UF volume, and a moderate reduction of dialysate [Na^+] might all have the potential to increase HD-induced tissue Na^+ mobilization rate and thereby reduce tissue Na^+ content. Our intension was to clarify the separate benefits of the above-mentioned modifications in HD regimen. We therefore designed and conducted several substudies to investigate the respective effect on tissue Na^+ content in a cohort of 75 patients on HD with multimodal exploration using ^{23}Na-MRI (before and after HD treatment) and confirmed the results by a cohort study and an interventional trial.

METHODS

The local Ethics Committees of the University of Erlangen-Nuremberg, Germany approved the study (No. 3948 and 271_17B), which was conducted according to the declaration of Helsinki principles. All participants provided written informed consent. The interventional substudy was registered at ClinicalTrials.gov (NCT03525223). Inclusion criterion was age >18 years and HD vintage time of at least 6 months. Exclusion criteria were active malignancy, severe heart failure (NYHA IV), severe liver disease (Child C), acute infection, and recent major surgical procedures (<3 months). In addition, patients with pacemakers, implants or other MRI contraindications were excluded. All scans were conducted at the Institute of Radiology, University Hospital of Erlangen.

General Study Protocol

Prior to ^{23}Na-MRI scans, medical exams determining a subject's height, weight, blood pressure, and body fluids were performed, followed by a venous blood sample. Dialysis regimen, including interdialytic weight gain, residual diuresis, prescribed dialysate composition, and applied UF volume were documented. In all patients, dialysis frequency was 3x/week.

Pilot Study

To initially assess if a longer dialysis treatment time combined with dietary salt restriction—as described for the dialysis center in Tassin, France[13]—might have an impact on tissue Na^+ content, we recruited 11 patients on HD from Tassin and compared them with 11 age-matched and gender-matched local patients on HD from Erlangen, Germany. Patients from Tassin were transferred to Erlangen and all ^{23}Na-MRI scans were performed in Erlangen at the intermediate day between 2 HD sessions.

Cross-Sectional Study

(Part A): Seventy-five patients on HD from Erlangen, Germany were separated retrospectively into 2 groups according to the median of the applied UF. Thirty-seven patients on HD with UF amount <2.4 l were compared with 38 patients on HD who obtained ≥2.4 l UF. (Part B): The same 75 patients on HD were regrouped according to the median of their HD treatment time; 41 patients on HD with a treatment time ≤4.5 hours were compared with 34 patients on HD dialyzing >4.5 hours. (Part C): All patients were finally grouped according to the median of their dialysate [Na^+]. Dialysate [Na^+] 138 mmol/l is the regular dialysate composition in our center; therefore, 17 patients on HD with dialysate [Na^+] <138 mmol/l were compared with 58 patients on HD dialyzing at ≥138 mmol/l. ^{23}Na-MRI scans were performed directly before HD treatment and additionally in 61 patients within 1 to 2 hours after HD treatment.

Cohort Study

Ten male patients on HD from Erlangen, Germany decided to switch from a regular dialysis treatment time (4–5 hours) to prolonged HD treatment times (>6 hours), or vice versa. The decision was not influenced by this study. Patients were recruited between May 2013 and May 2022. ^{23}Na-MRI scans were performed pre-HD treatment before, and at least 3 months after changing their HD-procedure time.

Interventional, Cross-Over Study

In 10 male patients on HD from our local dialysis center, the prescribed dialysate [Na^+] was modified over a period of 14 weeks: an initial stepwise elevation (1–2 mmol/l/wk) from baseline 138 mmol/l to 142 mmol/l was turned in a constant 142 mmol/l plateau phase for 5 weeks, which was then stepwise reduced (1–2 mmol/l/wk) to 135 mmol/l, followed by a 5 week-phase of dialysate [Na^+] 135 mmol/l. During the complete study protocol, each patient was treated with the same dialysis machine to ensure stable dialysate composition.[14] Patients were recruited between April 2018 and December 2020. Drop-out criteria were hospitalization, episodes of severe cramps, symptomatic hypotension or hypertension, and >10 mmol/l difference of Na^+ concentration between blood and dialysate fluid. Two patients dropped out after completing visit 2 because of the following: (i) sepsis leading to intensive care unit treatment ($n = 1$) and (ii) repetitive serum Na^+ concentration of >147 mmol/l during the dialysate

[Na^+] 135 mmol/l phase ($n = 1$). ^{23}Na-MRI scans were performed pre-HD treatment at visit 1 (dialysate [Na^+] 138 mmol/l, $n = 10$), visit 2 (142 mmol/l, $n = 10$) and visit 3 (135 mmol/l, $n = 8$).

Blood Pressure

Blood pressure was measured after 5 minutes of rest in seated position using an automated oscillometric device (Dinamap, Critikon, Carlsbad, CA) before HD. Three consecutive measurements were averaged.

Bioimpedance Spectroscopy

We used multifrequency bioimpedance spectroscopy to noninvasively assess the patient's fluid status (body composition monitor, Fresenius Medical Care, Bad Homburg, Germany). This technique uses bioelectrical impedance to differentiate between extracellular and intracellular water. In addition, the individual excess in extracellular water (overhydration), correcting for gender, age, and body mass was calculated.

^{23}Na-MRI Assessment

Na^+ tissue content of the skin and the triceps surae muscle were measured in a 3 Tesla MRI-scanner (Magnetom Verio/Skyra/Vida, Siemens Healthineers, Erlangen, Germany), using a ^{23}Na volume coil (Stark-Contrast, Erlangen, Germany) positioned around the left calf, centered at the area of the largest circumference. ^{23}Na-MR images were acquired using a 2D gradient-echo sequence (total acquisition time = 13.7 minutes, echo time = 2.07 ms, repetition time = 100 ms, flip angle = 90°, 128 averages, resolution: 3×3×30 mm^3). For anatomical details the leg was scanned by a conventional ^{1}H in-phase-opposed-phase sequence with a resolution of 0.75x0.75x5 mm^3. Acquisition time of both sequences was approximately 20 minutes. Images were analyzed using ImageJ (University of Wisconsin, Madison, WI). Regions of interest for muscle tissue were first outlined in the ^{1}H-images and subsequently projected onto the ^{23}Na image. Skin Na^+ content was evaluated where the lower leg was in contact with the cylindrically shaped surface of the phantom-holder to reduce the influence of partial volume effects. Pixels with an intensity that was 2 times higher than the background noise were included and a layer thickness of 1 pixel evaluated. Four tubes containing NaCl-solutions (10, 20, 30, and 40 mmol/l Na^+) were used to calibrate signal intensities to Na^+ concentrations. The low in-plane resolution of ^{23}Na-MRI and the fast decay of the ^{23}Na-MRI signal can result in an underestimation of tissue Na^+ amount. To account for these limitations, we labeled the tissue Na^+ concentration obtained by the calibration as a.u.

Blood Analysis

Prior to HD treatment, venous blood samples were drawn directly from patient's dialysis access and samples were stored at −80 °C.

Statistics

All data were analyzed by SPSS software (IBM SPSS Statistics, version 28.0, IBM, Armonk, NY). The Kolmogorov-Smirnov test was used to assess the distribution of our data. All normally distributed data were subsequently analyzed using either the paired or independent t test; data with a skewed distribution were analyzed using the Mann-Whitney-U test. In patients who completed all 3 visits of the interventional study, a repeated measures analysis of variance was performed. Results were expressed as mean±SD for normally distributed data and as median and interquartile range for the data lacking a normal distribution. A P-value < 0.05 was considered significant and 2-sided tests of hypotheses were used throughout.

RESULTS

Pilot Study

The dialysis center in Tassin, France is known for its rigorous attention to a low-salt diet and prolonged HD treatment times (overnight session, 7–8 hours).[15] In an observational ^{23}Na-MRI pilot study, we were able to compare 11 patients on HD from Tassin with 11 regional patients on HD, who were treated conventionally (4–5 hours during day time, no dietary advice). Demographic data and HD-related parameter are shown in Table 1. Neither plasma [Na^+] nor dialysate [Na^+] differed between both groups, but a lower interdialytic weight gain resulted in less UF volume in the HD-Tassin group (Figure 1d). The mean skin Na^+ content of HD-Tassin patients was significantly lower than that of local patients on HD (18.1 ± 4.6 vs. 22.6 ± 5.2 a.u., $P < 0.05$; Figure 1b), indicating a lowering effect on skin Na^+ content by the combination of dietary salt restriction, lower interdialytic weight gain, and overnight HD. In contrast, there was no difference in muscle Na^+ content detectable between both groups or in overhydration assessed by body composition monitor (Figure 1b and c). Based on this pilot study, several clinical trials were designed to identify the main parameter of a modified HD regimen that might influence tissue Na^+ content: UF volume, HD treatment time, or dialysate [Na^+].

Effect of UF Volume

Cross-Sectional Study (A)

To determine if the amount of UF volume affects tissue Na^+ content, we divided our local cohort of 75 patients

Table 1. Clinical characteristics of pilot study

Characteristics	HD-local	HD-Tassin	*P*-value
Demographics			
Individuals, *n*	11	11	
Women's quota, (*n*)	2	2	
Age, yr	57.2 ± 12.2	56.4 ± 15.5	0.88
BMI, kg/m^2	28.7 ± 3.9	28.0 ± 4.3	0.70
Diabetes mellitus, *n*	3	3	
SBP, mmHg	139 ± 12	127 ± 13	0.05
DBP, mmHg	76 ± 11	71 ± 10	0.34
HD-related parameter:			
HD vintage, yr	3.5 (IQR 5)	2.5 (IQR 2.5)	0.43
Treatment time, h	4.5 (IQR 0.75)	7.0 (IQR 1.5)	-
Residual diuresis, ml/d	300 (IQR 1000)	0 (IQR 200)	0.22
IDWG, kg	2.7 ± 1.1	1.0 ± 1.5	0.01
Dialysate Na^+, mmol/l	136 (IQR 3)	138 (IQR 0)	0.12
Laboratory data:			
Serum Na^+, mmol/l	137.2 ± 3.6	137.0 ± 2.4	0.88
Serum K^+, mmol/l	5.7 ± 0.9	4.8 ± 0.4	0.01
BIS data:			
Total body water, l	39.6 ± 7.8	38.2 ± 7.3	0.67
Extracellular water, l	18.2 ± 7.3	17.5 ± 3.6	0.70
Intracellular water, l	21.4 ± 4.4	20.6 ± 3.8	0.66
ratio ECW/ICW	0.85 ± 0.08	0.85 ± 0.06	0.93

BIS, bioimpedance spectroscopy; BMI, body mass index, DBP, diastolic blood pressure; ECW, extracellular water; HD, hemodialysis; ICW, intracellular water; IDWG, interdialytic weight gain; IQR, interquartile range; SBP, systolic blood pressure.
Variables are presented as mean±SD or as median and IQR.

on HD into a group of 37 patients with UF <2.4 l and compared them with 38 patients who received UF ≥2.4 l. Demographic and bioimpedance spectroscopy data did not differ between both groups (Table 2). Tissue Na^+ content was not different between both groups before HD treatment (Figure 2a and b). To investigate tissue Na^+ mobilization during a HD procedure, we analyzed Na^+ tissue content post-HD treatment and found that patients on HD with less UF presented with higher muscle Na^+ content after their HD session (18.0 ± 5.0 vs. 15.3 ± 3.4 a.u., $P < 0.05$; Figure 2c), whereas skin Na^+ content was not different between both groups post-HD (Figure 2d).

Effect of HD Treatment Time

Cross-Sectional Study (B)

To determine if a prolongation of HD treatment time has an impact on tissue Na^+ content, we separated our local cohort into a group of 41 patients with ≤4.5 hours and compared them with 34 patients who dialyzed >4.5 hours. Demographic data were not different between both groups, whereas prolonged HD time was accompanied by fluid overload (Table 2). Tissue Na^+ content did not differ between both groups, neither pre-HD nor post-HD treatment (Figure 3a–d), indicating no effect of HD treatment time on tissue Na^+ amount.

Cohort Study

To confirm the above-mentioned results, we studied the effect of intraindividual changes in HD treatment time in 10 male patients on HD on tissue Na^+. Demographic data and HD-related parameters of this study are shown in Table 3. A prolongation of HD

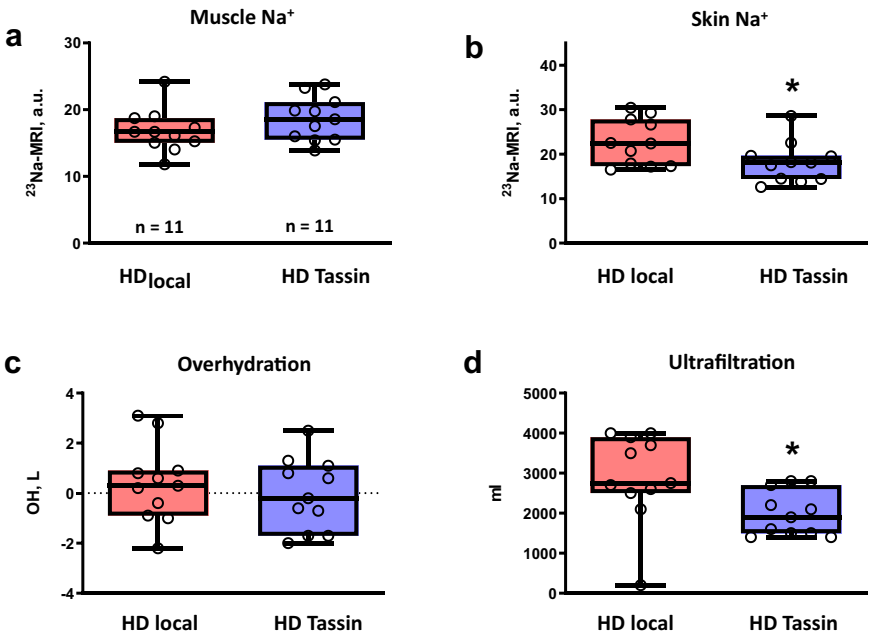

Figure 1. Pilot study: Lower skin Na^+ content in HD-patients from Tassin, France. Tassin patients on HD (blue box) presented with similar muscle (a) but significantly lower skin Na^+ content (b) if compared with matched local patients on HD (red box) as determined by ^{23}Na-MRI. No significant difference of excess extracellular volume (overhydration) was observed between both groups (c), whereas a significantly lower ultrafiltration volume was observed in Tassin-HD patients (d). ^{23}Na-MRI, ^{23}Na magnetic resonance imaging; a.u., arbitrary unit; HD, hemodialysis; OH, overhydration. *$P < 0.05$.

Table 2. Clinical characteristics on substudies of local HD patient cohort

Characteristics	UF <2.4 l	UF ≥2.4 l	*P*-value	HD time <4.5 h	HD time ≥ 4.5 h	*P*-value	Dialysate Na^+ <138 mmol/l	Dialysate Na^+ ≥138 mmol/l	*P*-value
Demographics									
Individuals, *n*	37	38		41	34		17	58	
Age, yr	55.4 ± 14.9	57.1 ± 14.6	0.62	58.4 ± 13.3	53.7 ± 16.0	0.17	56.5 ± 16.1	56.2 ± 14.4	0.93
BMI, kg/m^2	26.7 ± 4.7	28.5 ± 5.0	0.12	27.3 ± 4.2	27.9 ± 5.7	0.62	28.9 ± 5.3	27.2 ± 4.8	0.22
SBP, mmHg	132 ± 17	140 ± 20	0.05	136 ± 19	137 ± 18	0.85	135 ± 22	136 ± 18	0.75
DBP, mmHg	72 ± 10	75 ± 12	0.39	72 ± 10	75 ± 12	0.35	70 ± 13	74 ± 11	0.16
HD-related parameters									
HD vintage, yr	2 (3.1)	4 (5.7)	<0.05	1.75 (3.5)	3 (5.5)	0.15	4 (6.4)	2.1 (4.5)	0.20
Treatment time, h	4.5 (1.25)	4.75 (1.0)	0.1	4.25 (0.5)	5.5 (2.5)	-	4.5 (0.75)	4.5 (1.3)	0.81
Residual diuresis, ml/d	500 (1500)	100 (500)	<0.01	500 (1000)	0 (500)	<0.05	200 (1000)	300 (1000)	0.86
IDWG, kg	0.8 ± 0.9	2.7±1.1	<0.01	1.4 ± 1.2	2.1 ± 1.4	<0.05	1.8 ± 1.5	1.7 ± 1.3	0.84
Ultrafiltration, l	1.3 ± 0.7	3.2±0.7	-	2.0 ± 1.0	2.7 ± 1.3	0.01	2.5 ± 1.5	2.2 ± 1.1	0.45
Dialysate Na^+, mmol/L	138 (0)	138 (2)	0.95	138 (2)	138 (0)	0.55	135 (0)	138 (0)	-
Laboratory data									
Plasma Na^+, mmol/l	138.6 ± 2.5	137.4 ± 2.6	<0.05	138.4 ± 2.5	137.5 ± 2.6	0.16	136.4 ± 3.0	138.4 ± 2.3	<0.01
Plasma K^+, mmol/l	5.2 ± 0.7	5.7 ± 0.8	<0.05	5.4 ± 0.8	5.5 ± 0.7	0.54	5.5 ± 0.9	5.4 ± 0.7	0.85
BIS data	32	35		35	32		13	54	
Total body water, l	40.8 ± 7.9	39.3 ± 6.8	0.40	38.7 ± 7.6	41.5 ± 6.9	0.11	37.7 ± 6.7	40.6 ± 7.5	0.20
Extracellular water, l	19.4 ± 3.9	19.2 ± 3.3	0.83	18.7 ± 3.7	20.0 ± 3.0	0.15	18.7 ± 3.3	19.5 ± 3.6	0.46
Intracellular water, l	21.4 ± 4.5	20.1 ± 4.0	0.21	19.9 ± 4.3	21.5 ± 4.2	0.13	19.0 ± 3.9	21.1 ± 4.3	0.11
ratio ECW/ICW	0.92 ± 0.12	0.97 ± 0.14	0.08	0.95 ± 0.13	0.94 ± 0.14	0.51	0.99 ± 0.13	0.94 ± 0.13	0.15
Overhydration, l	2.1 ± 2.1	1.9 ± 1.5	0.73	1.8 ± 1.9	2.1 ± 1.7	0.76	1.7 ± 1.4	2.0 ± 1.9	0.51

BIS, bioimpedance spectroscopy; DBP, diastolic blood pressure; ECW, extracellular water; HD, hemodialysis; ICW, intracellular water; IDWG, interdialytic weight gain; IQR, interquartile range; SBP, systolic blood pressure; UF, ultrafiltration.
Variables are presented as mean±SD or as median and IQR.

treatment time from 4.6 ± 0.5 to 7.2 ± 0.8 hours did not affect tissue Na^+ content in these patients, neither before HD treatment (skin: 23.8 ± 5.9 vs. 25.7 ± 9.2 a.u., $P = 0.46$; muscle: 22.2 ± 5.8 vs. 21.1 ± 3.5 a.u., $P = 0.63$; Figure 4a and b), nor after dialysis procedure (Figure 4c and d).

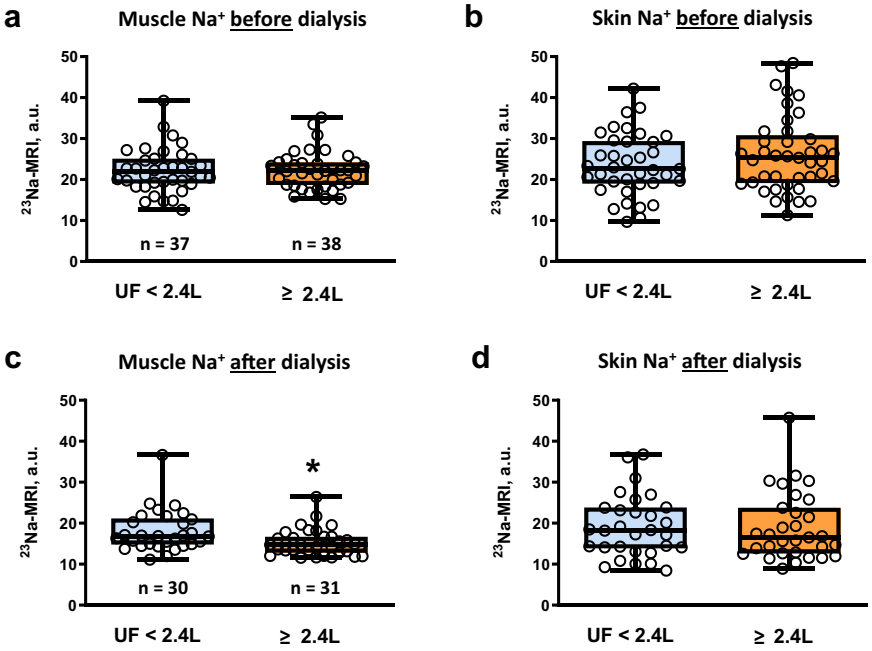

Figure 2. Ultrafiltration volume without an effect on tissue Na^+ content. No significant difference between muscle (a) or skin (b) tissue Na^+ content of patients on HD with high UF volume (blue box) if compared to patients on HD with low UF volume (red box) determined by ^{23}Na-MRI before HD treatment. Significantly lower muscle Na^+ content in high UF-HD patients after HD treatment (c), whereas post-HD skin Na^+ content did not differ between both groups (d). ^{23}Na-MRI, ^{23}Na magnetic resonance imaging; a.u., arbitrary unit; HD, hemodialysis; UF, ultrafiltration. *$P < 0.05$.

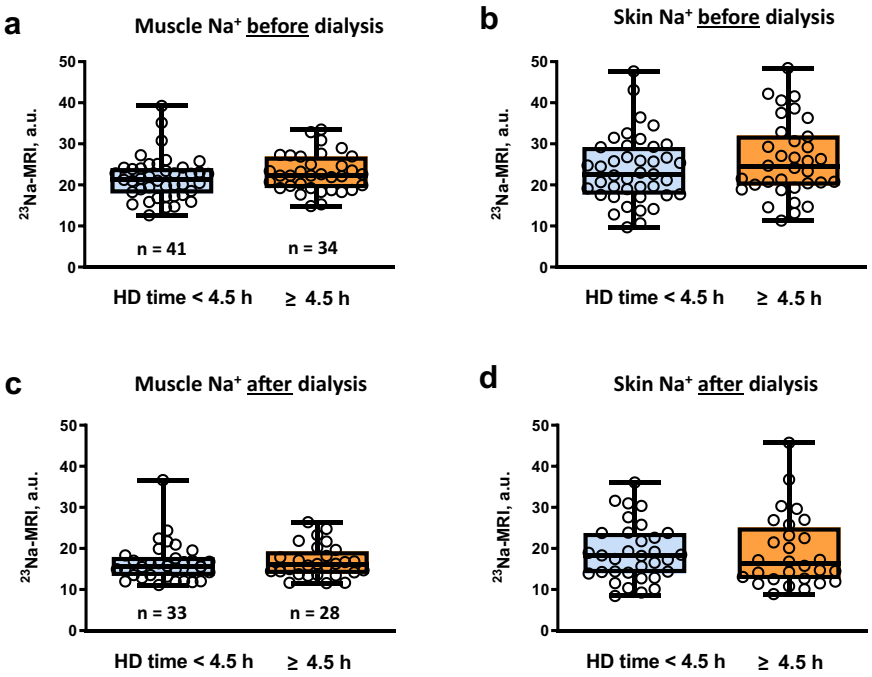

Figure 3. HD treatment time without effect on tissue Na^+ content. No significant difference between tissue Na^+ content of patients on HD with prolonged HD treatment time (red box, $n = 34$) compared to patients on HD with regular HD treatment time (blue box, $n = 41$). Na^+ content of muscle (a/c) and skin (b/d) before and after HD treatment, determined by ^{23}Na-MRI. ^{23}Na-MRI, ^{23}Na magnetic resonance imaging; a.u., arbitrary unit; HD, hemodialysis. *$P < 0.05$.

Effect of Dialysate Na^+ Concentration

Cross-Sectional Study (C)

To determine if a lower dialysate [Na^+] may be associated with reduced tissue Na^+ deposition, we regrouped our local cohort of 75 patients on HD into a group of 17 patients with dialysate [Na^+] <138 mmol/l and compared them with 58 patients who dialyzed at ≥138 mmol/l. Demographic data, HD-related parameters, and bioimpedance spectroscopy data did not differ between both groups (Table 2). Skin Na^+ content before HD treatment was significantly lower in the group with low dialysate [Na^+] (20.7 ± 7.3 vs. 26.0 ± 8.8 a.u., $P < 0.05$; Figure 5b). No difference in muscle Na^+ content was detectable between both groups pre-HD (20.8 ± 3.3 vs. 22.6 ± 5.3 a.u, $P = 0.18$; Figure 5a). Post-HD measurements revealed lower Na^+ content in skin and muscle tissue if patients were dialyzed with lower dialysate [Na^+] (skin: 15.5 ± 4.4 vs. 20.1 ± 8.3 a.u., $P = 0.01$; muscle: 14.8 ± 1.8 vs. 17.2 ± 4.9 a.u., $P < 0.01$; Figure 5c and d).

Table 3. Clinical characteristics of patients with intraindividual changes of HD treatment time

Characteristics	Regular HD time	Prolonged HD time	*P*-value
Demographics			
Age, yr		47.1 ± 13.6	
Time between visit 1 and 2, months		8.8 ± 6.0	
Body weight, kg	87.3 ± 16.7	88.7 ± 17.9	0.24
SBP, mmHg	146 ± 18	140 ± 28	0.41
DBP, mmHg	82 ± 9	80 ± 11	0.52
HD-related parameters			
HD vintage, yr		1.75 (IQR 5.75)	
Treatment time, h	4.5 (IQR 1.0)	7.5 (IQR 2.0)	-
Remaining diuresis, ml/d	500 (IQR 1500)	0 (IQR 1500)	0.45
IDWG, kg	2.0 ± 1.3	2.4 ± 1.7	0.45
Dialysate Na^+, mmol/l	138 (IQR 2)	138 (IQR 0)	0.34
Laboratory data			
Plasma Na^+, mmol/l	137.6 ± 2.7	138.2 ± 2.3	0.38
Plasma K^+, mmol/l	5.7 ± 0.7	5.1 ± 0.2	0.06
BIS data			
Total body water, l	45.4 ± 6.2	46.3 ± 8.1	0.54
Extracellular water, l	21.7 ± 3.5	22.0 ± 4.2	0.66
Intracellular water, l	23.8 ± 3.4	24.2 ± 4.3	0.46
ratio ECW/ICW	0.92 ± 0.14	0.91 ± 0.09	0.68

BIS, bioimpedance spectroscopy; DBP, diastolic blood pressure; HD, hemodialysis; IDWG, interdialytic weight gain; IQR, interquartile range; SBP, systolic blood pressure. Variables are presented as mean±SD or as median and IQR.

Interventional Cross-Over Study

To confirm the results of the latter observational study, we intraindividually modulated dialysate [Na^+] in 10 male patients on HD within physiological limits. Following a baseline dialysate [Na^+] of 138 mmol/l, a stepwise elevation to 142 mmol/l was turned into a stepwise reduction to 135 mmol/l (see Methods section and Figure 6). No other HD-related parameters were changed and serum Na^+ concentrations were not affected by dialysate [Na^+] variation (Table 4). Patients tolerated the dialysate [Na^+] changes well. Especially, the reduction of dialysate [Na^+] from 142 to 135 mmol/l did not result in severe side effects: 1

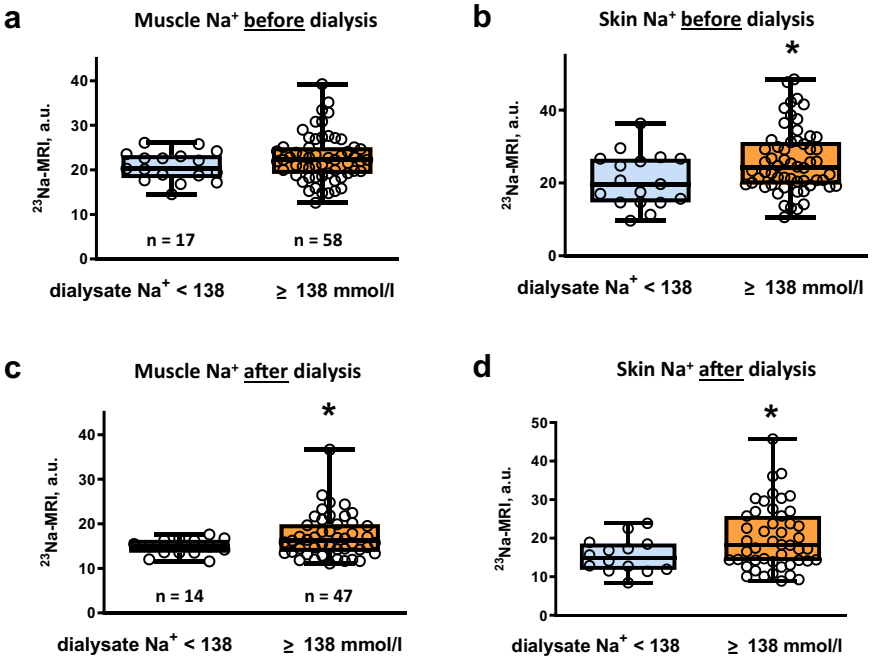

Figure 4. Dialysate [Na^+] is associated with differences in tissue Na^+ content. Before HD treatment, patients who dialyzed at dialysate [Na^+] <138 mmol/l (blue box) presented with similar muscle (a) but significantly lower skin Na^+ content (b) if compared with patients on HD dialyzing at ≥138 mmol/l (red box). Significantly lower tissue Na^+ content in patients on HD with low dialysate [Na^+] after HD treatment in muscle (c) and skin (d). ^{23}Na-MRI, ^{23}Na magnetic resonance imaging; a.u., arbitrary unit; HD, hemodialysis. *$P < 0.05$.

patient developed recurrent mild muscle cramps at the 135 mmol/l level; and in 1 patient who was known for his prevalent hypotension, low intradialytic blood pressure (as defined by Kidney Disease: Improving Global Outcomes)[5] without clinical symptoms was more often observed in the 135 mmol/l dialysate [Na^+] phase (Supplementary Table S1). As shown in Figure 7a, the adjustments of dialysate [Na^+] were accompanied by corresponding changes in skin Na^+ content. Skin Na^+ significantly increased from 24.3 ± 7.6 a.u. on the 138 mmol/l level to 26.3 ± 8.0 a.u. at 142 mmol/l level ($P < 0.05$), whereas no change in

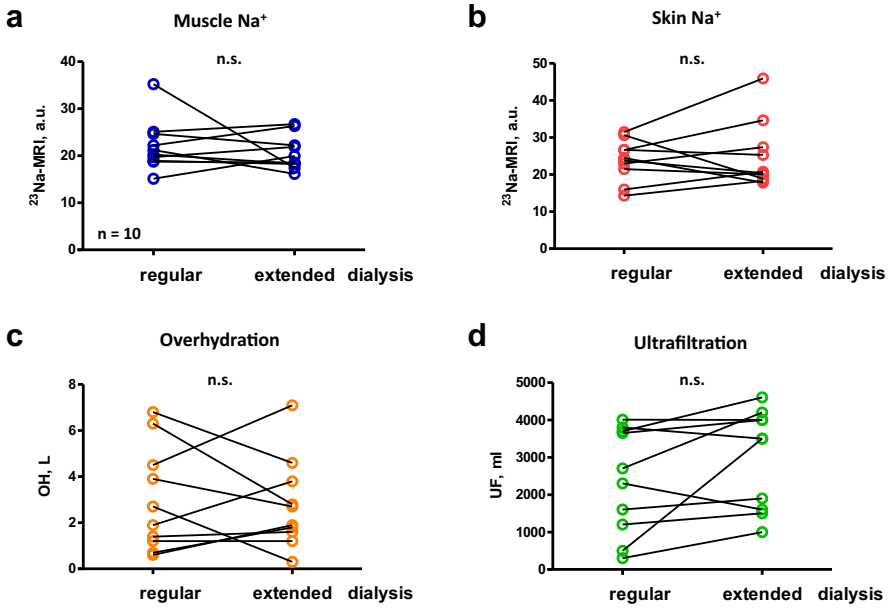

Figure 5. Individual changes in HD treatment time without an effect on tissue Na^+ content. No significant difference in muscle (a) or skin (b) tissue Na^+ content of 10 patients on HD due to intraindividual change of HD treatment time. No significant difference of excess extracellular volume (overhydration) (c), nor of ultrafiltration volume (d) was observed between treatment times. ^{23}Na-MRI, ^{23}Na magnetic resonance imaging; a.u., arbitrary unit; HD, hemodialysis; n.s.: not significant; OH, overhydration; UF, ultrafiltration.

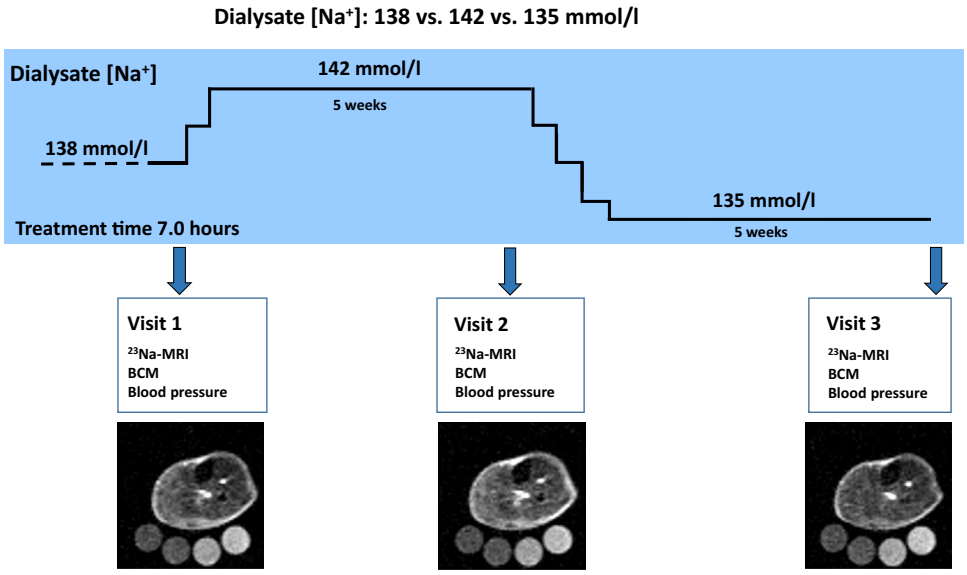

Figure 6. Study synopsis of interventional cross-over adaptation of dialysate [Na^+]. Upper panel: timeline of stepwise changes in dialysate [Na^+] from 138 to 142 to 135 mmol/l with according visits 1 to 3. Lower panel: Representative ^{23}Na-MR images of the left calf during visits 1 to 3. Calibration tubes with 10, 20, 30, and 40 mmol/l NaCl are situated below the leg; the brightness of the resonance signal reflects the Na^+ amount. ^{23}Na-MRI, ^{23}Na magnetic resonance imaging; a.u., arbitrary unit; BCM, body composition monitor.

muscle Na^+ content occurred (21.7 ± 5.6 vs. 21.6 ± 5.4 a.u., $P = 0.91$; Figure 7b). Reduction to dialysate [Na^+] 135 mmol/l was associated with a significant decrease in skin Na^+ to 20.8 ± 5.6 a.u ($P < 0.05$; Figure 7a), without affecting muscle Na^+ content (Figure 7b). Systolic blood pressure decreased from 147 ± 24 to 129 ± 18 mmHg after dialysate [Na^+] reduction from 142 to 135 mmol/l without reaching significance ($P = 0.07$; Figure 7d) and overhydration changed accordingly to dialysate [Na^+] adjustments (2.5 ± 1.2 vs. 3.6 ± 1.6 vs. 1.7 ± 1.0 l, $P < 0.05$ and $P = 0.06$; Figure 7c). In addition, we applied repeated measures analysis of variance in the 8 patients who attended all 3 visits. Dialysate [Na^+] had a significant effect on skin Na^+ content ($P = 0.04$) throughout all 3 visits, whereas muscle Na^+ ($P = 0.20$), overhydration ($P = 0.06$) and systolic blood pressure ($P = 0.08$) were not significantly associated with changes in dialysate [Na^+].

Table 4. Clinical characteristics of patients on HD with intraindividual changes of dialysate [Na^+]

Characteristics	Dialysate Na^+ 138 mmol/l $n = 10$	Dialysate Na^+ 142 mmol/l $n = 10$	Dialysate Na^+ 135 mmol/l $n = 8$	*P* value 138 vs. 142/ 142 vs. 135
Demographics				
Age, yr	50.5 ± 13.2	-	-	-
Body weight, kg	89.8 ± 14.5	89.9 ± 15.3	89.8 ± 14.6	0.80/0.74
HD-related parameter				
HD vintage, yr	5.6 (IQR 7.1)	-	-	-
Treatment time, h	7.0 (IQR 1.6)	7.4 (IQR 1.7)	7.4 (IQR 2.3)	0.34/0.67
Ultrafiltration volume, l	2.1 ± 1.6	1.9 ± 1.3	1.7 ± 0.9	0.62/0.83
Laboratory data				
Serum Na^+, mmol/l	138.6 ± 4.4	138.8 ± 2.2	140.6 ± 3.0	0.78/0.12
Serum K^+, mmol/l	5.5 ± 0.7	5.5 ± 0.7	5.7 ± 0.9	0.60/0.12
BIS data				
Total body water, l	46.7 ± 6.1	47.3 ± 6.1	44.9 ± 4.3	0.16/0.34
Extracellular water, l	22.0 ± 3.1	22.9 ± 3.8	20.9 ± 2.7	<0.05/0.11
Intracellular water, l	24.1 ± 2.9	24.4 ± 2.5	24.0 ± 2.2	0.60/0.09
ratio ECW/ ICW	0.90 ± 0.08	0.94 ± 0.09	0.87 ± 0.10	0.09/0.05

BIS, bioimpedance spectroscopy; HD, hemodialysis; IQR, interquartile range.
Variables are presented as mean±SD or as median and IQR.

DISCUSSION

In this study, we investigated different modifications of HD parameters in their capability to modulate tissue Na^+ content in patients on dialysis. In order to conduct a comprehensive analysis, we explored 3 relevant parameters in our local cohort of patients on dialysis, namely UF volume, HD treatment time and dialysate [Na^+] retrospectively and, if feasible, confirmed the results by prospective intraindividual adaptations. Because fluid removal on dialysis has to be individually tailored to the volume homeostasis of the patient, the latter was not possible for UF volume. The main finding that could be extracted from our substudies was that, solely, dialysate [Na^+] exerted an effect on tissue Na^+ content. An interventional approach, where dialysate [Na^+] was actively increased and reduced over a prolonged period of time, could validate dialysate [Na^+] as a key factor for tissue Na^+ regulation in patients on HD. Intraindividual extension of dialysis treatment time had no sustained effect on tissue Na^+ content. Although Lemoine *et al.*[16] described an association between dialysate [Na^+] and skin Na^+ content in a cohort of patients on dialysis, we are the first to confirm in an interventional cross-over approach that

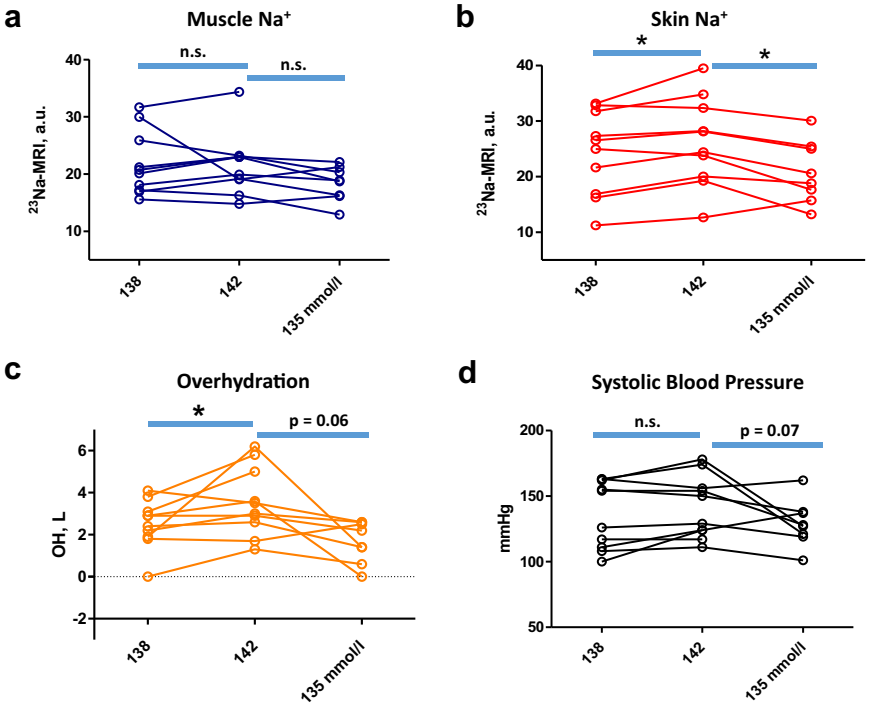

Figure 7. Individual changes in dialysate [Na^+] modify skin Na^+ content. No effect on muscle Na^+ content (a) but significantly corresponding changes in skin Na^+ content (b) of 10 patients on HD during the adaptation of their dialysate [Na^+] from 138 to 142 and to 135 mmol/l. Changes of excess extracellular volume (overhydration) (c), as well as changes in systolic blood pressure (d) did not reach significance. ^{23}Na-MRI, ^{23}Na magnetic resonance imaging; a.u., arbitrary unit; HD, hemodialysis; n.s., not significant; OH, overhydration. *$P < 0.05$.

adjustment of dialysate [Na^+] results in skin Na^+ changes and additionally ruled out other relevant parameters.

Increased UF resulted in only a transient reduction of muscle Na^+ content as found in the ^{23}Na-MRI assessment immediately after dialysis treatment. However, skin Na^+ changes due to adjustment of the dialysate [Na^+] prescription could be still detected directly before the following HD treatment, indicating a persistent effect on tissue Na^+ rather than a short-term modification. Data on dialysate [Na^+] reduction are manifold and conflicting.[17,18] Higher dialysate [Na^+] promotes hemodynamic stability and reduces adverse symptoms such as muscle cramps during HD session, thereby facilitating HD treatment procedure and possibly preventing organ hypoperfusion.[19] Albeit, this might come at the expense of Na^+ overload and might result in interdialytic hypertension and ultimately in increased cardiovascular events. Indeed, several studies were able to demonstrate a blood pressure reduction upon administration of low dialysate [Na^+].[20,21] However, a recent historical retrospective study found a higher mortality rate in patients on HD treated with a dialysate [Na^+] of ≤138 mmol/l.[22] In summary, overall study quality is poor, randomized controlled trials are very limited, and long-term data on cardiovascular outcome of this intervention are still missing.[23]

Recent evidence indicates that high skin Na^+ content is associated with a poorer cardiovascular and overall outcome in patients on dialysis.[24] Furthermore, skin Na^+ amount was found to be the best predictive factor for left ventricular hypertrophy in patients with chronic kidney disease; and patients on dialysis with a history of cardiovascular events were characterized by tissue Na^+ overload.[10,25] In the latter trial, both muscle and skin tissues showed a significant Na^+ accumulation in patients with a history of cardiovascular events; whereas in the first mentioned outcome study, solely skin Na^+ deposition was associated with a higher mortality rate in patients on dialysis. Why in the current trial no significant changes in muscle Na^+ occurred and whether muscle Na^+ is also a relevant and modifiable outcome parameter, remains unclear.

Our observations increase the urgency for interventions that are able to persistently reduce the tissue Na^+ burden in the dialysis patient group. Based on our findings, a long-term moderate reduction in dialysate [Na^+] appears to be a simple and feasible way to modulate tissue Na^+ amount. In addition, its effectiveness for the individual patient could be monitored by ^{23}Na-MRI and patients with tissue Na^+ overload that might benefit from the treatment could be specifically selected.

Although our results rely on various studies and were confirmed by interventional approaches, there are

several limitations that have to be addressed. The interventional studies were performed with a relatively low patient number due to the demanding study protocol. Nevertheless, results were conclusive and congruent with the observational trials. However, because we solely assessed male Caucasian patients, the data are not representative of the whole dialysis population and further studies are necessary to approach, for example, gender specific differences. Furthermore, we cannot rule out a selection bias in the cohort study, because patients who actively opt for a prolonged dialysis treatment regimen are typically younger and might be more therapy-adherent than the general dialysis population. The patients of the interventional study were in a relatively good general state of health and tolerated the dialysate [Na^+] reduction well. Whether elderly or multimorbid patients on HD (e.g., with diabetes mellitus) tolerate a low dialysate [Na^+] and also experience a significant mobilization of tissue Na^+ has to be further investigated. On the one hand, intradialytic hypotension might be more frequent in this patient group;[26] however, on the other hand, previous studies could identify the most pronounced tissue Na^+ deposition in patients on HD with diabetes mellitus, and render them an ideal population for tissue Na^+ lowering interventions.[11] Dietary salt intake was not assessed or controlled in our studies because estimating salt intake by a single 24-hour urine specimen has limited validity and the percentage of anuric or oliguric patients was high (50.6%).[27] Individual salt habits might be a confounder affecting, for example, the dialysate [Na^+] prescription in the observational study. Furthermore, excessive Na^+ intake in patients on dialysis likely contributes to tissue Na^+ accumulation, as seen in animal experiments,[9] thereby counteracting dialysate [Na^+] prescription. Indeed, in the initial pilot study, the retrospectively main difference between both cohorts was adhesion to a consequent low salt diet. Finally, our study was not designed to assess the impact of dialysate [Na^+] on "hard" end points and their association with tissue Na^+. Adequately powered randomized-controlled studies focusing on dialysate [Na^+] and cardiovascular events, ideally also involving ^{23}Na-MRI, are urgently needed to resolve this issue.

In conclusion, our study highlights dialysate [Na^+] among other dialysate prescription parameters as a main target to modulate tissue Na^+ amount. ^{23}Na-MRI might evolve as a tool to assess the efficacy and relevance of dialysate Na^+ reduction in future outcome studies.

DISCLOSURE

All the authors declared no conflicting interests.

ACKNOWLEDGMENTS

We sincerely thank our study participants, the staff of our Dialysis Core Unit and our study nurses Daniela Rosenhauer, Ingrid Weissbrod, and Manuela Linß. We also thank Prof. Jörg Vienken from Fresenius Medical Care, Germany.

This work was supported by grants from the Deutsche Forschungsgemeinschaft (282123235, 445440403 and 509149993) as well as the Else Kröner-Fresenius Foundation (2016_A45). The present work was performed in (partial) fulfillment of the requirements for obtaining the degree "Dr. med.".

DATA AVAILABILITY STATEMENT

The full data set will be provided on request.

AUTHOR CONTRIBUTIONS

AD and CK conceived and designed the study. PL and AMN implemented, conducted, and analyzed the magnetic resonance imaging measurements. AD, CK, CC and SH enrolled the participants. LK conducted the body composition monitor, conceived and carried out laboratory tests, and collected the data. AD and CK analyzed and interpreted the data and drafted the manuscript. DK, MU, and MS critically revised the manuscript. All authors approved the final version of the manuscript.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Adverse events and STROBE statement.

REFERENCES

1. Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension*. 2009;53:500–507. https://doi.org/10.1161/HYPERTENSIONAHA.108.125674
2. Al-Hilali N, Al-Humoud H, Ninan VT, Nampoory MR, Johny KV. Blood pressure control in haemodialysis patients: an audit. *Nephrol (Carlton)*. 2006;11:100–104. https://doi.org/10.1111/j.1440-1797.2006.00549.x
3. Davenport A. Audit of the effect of dialysate sodium concentration on inter-dialytic weight gains and blood pressure control in chronic haemodialysis patients. *Nephron Clin Pract*. 2006;104:c120–c125. https://doi.org/10.1159/000094544
4. Krautzig S, Janssen U, Koch KM, Granolleras C, Shaldon S. Dietary salt restriction and reduction of dialysate sodium to control hypertension in maintenance haemodialysis patients. *Nephrol Dial Transplant*. 1998;13:552–553. https://doi.org/10.1093/ndt/13.3.552
5. Flythe JE, Chang TI, Gallagher MP, et al. Blood pressure and volume management in dialysis: conclusions from a Kidney Disease: improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2020;97:861–876. https://doi.org/10.1016/j.kint.2020.01.046

6. Kayikcioglu M, Tumuklu M, Ozkahya M, et al. The benefit of salt restriction in the treatment of end-stage renal disease by haemodialysis. *Nephrol Dial Transplant*. 2009;24:956–962. https://doi.org/10.1093/ndt/gfn599
7. Mc Causland FR, Waikar SS, Brunelli SM. Increased dietary sodium is independently associated with greater mortality among prevalent hemodialysis patients. *Kidney Int*. 2012;82:204–211. https://doi.org/10.1038/ki.2012.42
8. Canaud B, Kooman J, Maierhofer A, Raimann J, Titze J, Kotanko P. Sodium first approach, to reset our mind for improving management of sodium, water, volume and pressure in hemodialysis patients, and to reduce cardiovascular burden and improve outcomes. *Front Nephrol*. 2022;2:935388. https://doi.org/10.3389/fneph.2022.935388
9. Machnik A, Neuhofer W, Jantsch J, et al. Macrophages regulate salt-dependent volume and blood pressure by a vascular endothelial growth factor-C-dependent buffering mechanism. *Nat Med*. 2009;15:545–552. https://doi.org/10.1038/nm.1960
10. Friedrich AC, Linz P, Nagel AM, et al. Hemodialysis patients with cardiovascular disease reveal increased tissue Na+ deposition. *Kidney Blood Press Res*. 2022;47:185–193. https://doi.org/10.1159/000520821
11. Kopp C, Linz P, Maier C, et al. Elevated tissue sodium deposition in patients with type 2 diabetes on hemodialysis detected by (23)Na magnetic resonance imaging. *Kidney Int*. 2018;93:1191–1197. https://doi.org/10.1016/j.kint.2017.11.021
12. Dahlmann A, Dorfelt K, Eicher F, et al. Magnetic resonance-determined sodium removal from tissue stores in hemodialysis patients. *Kidney Int*. 2015;87:434–441. https://doi.org/10.1038/ki.2014.269
13. Charra B, Calemard E, Ruffet M, et al. Survival as an index of adequacy of dialysis. *Kidney Int*. 1992;41:1286–1291. https://doi.org/10.1038/ki.1992.191
14. Ng JKC, Smyth B, Marshall MR, et al. Relationship between measured and prescribed dialysate sodium in haemodialysis: a systematic review and meta-analysis. *Nephrol Dial Transpl*. 2021;36:695–703. https://doi.org/10.1093/ndt/gfaa287
15. Charra B, Terrat JC, Vanel T, et al. Long thrice weekly hemodialysis: the Tassin experience. *Int J Artif Organs*. 2004;27:265–283. https://doi.org/10.1177/039139880402700403
16. Lemoine S, Salerno FR, Akbari A, McIntyre CW. Influence of dialysate sodium prescription on skin and muscle sodium concentration. *Am J Kidney Dis*. 2021;78:156–159. https://doi.org/10.1053/j.ajkd.2020.11.025
17. Hecking M, Karaboyas A, Saran R, et al. Predialysis serum sodium level, dialysate sodium, and mortality in maintenance hemodialysis patients: the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis*. 2012;59:238–248. https://doi.org/10.1053/j.ajkd.2011.07.013
18. Mc Causland FR, Brunelli SM, Waikar SS. Dialysate sodium, serum sodium and mortality in maintenance hemodialysis. *Nephrol Dial Transplant*. 2012;27:1613–1618. https://doi.org/10.1093/ndt/gfr497
19. Donati G, Ursino M, Spazzoli A, et al. Sodium prescription in the prevention of intradialytic hypotension: new insights into an old concept? *Blood Purificat*. 2018;45:61–70. https://doi.org/10.1159/000480221
20. Inrig JK, Molina C, D'Silva K, et al. Effect of Low versus High dialysate sodium concentration on blood pressure and endothelial-derived vasoregulators during hemodialysis: a randomized crossover study. *Am J Kidney Dis*. 2015;65:464–473. https://doi.org/10.1053/j.ajkd.2014.10.021
21. Shah A, Davenport A. Does a reduction in dialysate sodium improve blood pressure control in haemodialysis patients? *Nephrology (Carlton)*. 2012;17:358–363. https://doi.org/10.1111/j.1440-1797.2012.01576.x
22. Pinter J, Smyth B, Stuard S, et al. Impact of dialysate and plasma sodium on mortality in a global historical hemodialysis cohort. *J Am Soc Nephrol*. 2024;35:167–176. https://doi.org/10.1681/ASN.0000000000000262
23. Dunlop JL, Vandal AC, Marshall MR. Low dialysate sodium levels for chronic haemodialysis. *Cochrane Database Syst Rev*. 2019;1:CD011204. https://doi.org/10.1002/14651858.CD011204.pub2
24. Salerno FR, Akbari A, Lemoine S, Filler G, Scholl TJ, McIntyre CW. Outcomes and predictors of skin sodium concentration in dialysis patients. *Clin Kidney J*. 2022;15:1129–1136. https://doi.org/10.1093/ckj/sfac021
25. Schneider MP, Raff U, Kopp C, et al. Skin sodium concentration correlates with left ventricular hypertrophy in CKD. *J Am Soc Nephrol*. 2017;28:1867–1876. https://doi.org/10.1681/ASN.2016060662
26. Kuipers J, Verboom LM, Ipema KJR, et al. The prevalence of intradialytic hypotension in patients on conventional hemodialysis: a systematic review with meta-analysis. *Am J Nephrol*. 2019;49:497–506. https://doi.org/10.1159/000500877
27. Lerchl K, Rakova N, Dahlmann A, et al. Agreement between 24-hour salt ingestion and sodium excretion in a controlled environment. *Hypertension*. 2015;66:850–857. https://doi.org/10.1161/HYPERTENSIONAHA.115.05851