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13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31	Correspondence and offprint requests to: Number of Tables: 2. Number of Figures: 3. Word count: 3309.	Francisco Maduell, MD Servicio de Nefrología Hospital Clínic Barcelona C/ Villarroel, 170. 08036 Barcelona Spain Tel.: 93-2275400 Fax: 93-4546033 E-mail: fmaduell@clinic.cat ORCID-ID: 0000-0002-1673-0353 Twitter handle: @FMaduell				
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33	Keywords: Diffusive sodium balance	 Hyponatremia – Interdialytic weight gain – 				
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39 **ABSTRACT**

Introduction. Adherence to a low sodium (Na) diet is crucial in patients under hemodialysis, as it improves cardiovascular outcomes and reduces thirst and interdialytic weight gain. Recommended salt intake is lower than 5 g/day. The new 6008 CareSystem monitors incorporate an Na module that offers the advantage of estimating patients' salt intake. The objective of this study was to evaluate the effect of dietary Na restriction for 1 week, monitored with the Na biosensor.

46 **Methods.** A prospective study was conducted in 48 patients who maintained their 47 usual dialysis parameters and were dialyzed with a 6008 CareSystem monitor with 48 activation of the Na module. Total Na balance, pre/postdialysis weight, serum Na ($_{s}$ Na), 49 changes in pre- to post-dialysis $_{s}$ Na (Δ sNa), diffusive balance, and systolic and 50 diastolic blood pressure were compared twice, once after 1 week of patients' usual Na 51 diet and again after another week with more restricted Na intake.

Results. Restricted Na intake increased the percentage of patients on a low-sodium diet (<85 Na mmol/day) from 8% to 44%. Average daily Na intake decreased from 149 \pm 54 to 95 \pm 49 mmol and interdialytic weight gain was reduced by in 460 \pm 484 g per session. More restricted Na intake also decreased pre-dialysis _sNa and increased both intradialytic diffusive balance and Δ sNa. In hypertensive patients, reducing daily sodium by more than 3 g Na/day lowered their systolic blood pressure.

Conclusions. The new Na module allowed objective monitoring of Na intake, which in
 turn could permit more precise personalized dietary recommendations in patients
 under hemodialysis.

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62 **INTRODUCTION**

Sodium (Na) is the most abundant extracellular ion and is the principal 63 determinant of plasma osmolarity, extracellular volume, and blood pressure [1,2]. 64 Several mechanisms are involved in tightly regulating their homeostasis to maintain 65 66 the internal environment constant [3]. In healthy individuals, the kidney plays a major role in Na regulation. However, in patients under hemodialysis (HD) with minimal or no 67 residual renal function, Na intake must be completely balanced with water intake 68 because Na loads cannot be adequately excreted, and Na removal during dialysis is 69 essential to maintain Na balance [4,5]. 70

71 During HD, Na is removed primarily via convection (ultrafiltration related to interdialytic weight gain) and, to a lesser extent, via diffusion, in relation to the gradient 72 between the patient's pre-dialysis serum sodium (sNa) and the Na prescribed in the 73 dialysis fluid [4]. A positive Na gradient during HD promotes hemodynamic stability and 74 adequate perfusion of vital organs, as well as reducing the risk of intradialytic 75 hypotension [6]. However, it also increases osmolarity, thirst and extracellular volume, 76 -resulting in hypertension-and leads to greater left ventricular hypertrophy and 77 adverse cardiovascular effects [1]. In contrast, a negative Na gradient has been 78 associated with a reduction in interdialytic weight gain and blood pressure control but 79 at the expense of more frequent episodes of intradialytic hypotension and tissue 80 hypoperfusion [6]. 81

Patients under HD are advised to restrict their salt intake to improve cardiovascular outcomes and reduce thirst and interdialytic weight gain [5,7]. Currently, the Kidney Disease Improving Global Outcomes (KDIGO) and the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines recommend a maximum daily salt intake of 5 and 6 g per day, respectively [8,9].

Salt intake can be determined by measuring Na excretion through 24-hour urine collection in patients without renal impairment but not in patients under HD [10]. Previously, monitors with the Diascan biosensor allowed non-invasive determination of ion mass transfer and, therefore, estimation of salt intake in the interdialytic period [11–13]. However, these monitors could not be used with certain dialysis techniques, 92 such as hemodiafiltration. The new 6008 CareSystem monitors can be used with all 93 types of dialysis modalities, including hemodiafiltration, and also incorporate an Na 94 module that quantifies the total Na balance by providing approximate information on 95 salt intake in stable patients on HD without residual renal function, while ignoring other 96 Na losses such as those in stool or sweat [14].

⁹⁷ This study aimed to evaluate the effects of a restrictive Na intake diet versus ⁹⁸ usual Na intake on interdialytic weight gain, sNa, the difference between pre- and post-⁹⁹ dialysis Na, known as delta Na (Δ_s Na), diffusive Na balance, and systolic and diastolic ¹⁰⁰ blood pressure.

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102 PATIENTS AND METHODS

We performed a prospective single-center study in 48 patients with end-104 stage kidney disease in a chronic HD program. There were 33 men and 15 women, 105 106 with a mean age of 66 ± 16 (range 25 to 91) years. The inclusion criteria were being adult, prevalent (i.e., > 3 months on hemodialysis), without residual kidney function (< 107 50 ml/day), and continuously assigned to the 6008 monitors. Excluded patients were 108 those who could not understand dietary recommendations (e.g., those with dementia) 109 110 or did not want to participate in the study. The patients were dialyzed through an autologous arteriovenous fistula in 77%, a prosthetic fistula in 2%, and a tunneled 111 112 central catheter in the remaining 21%. The causes of end-stage kidney disease were vascular kidney disease (n = 12), diabetic kidney disease (n = 12), chronic 113 glomerulonephritis (n = 8), interstitial nephritis (n = 3), autosomal dominant polycystic 114 kidney disease (n = 3), urological disease (n = 3), systemic disease (n = 2), and 115 undiagnosed nephropathy (n = 5). Net fluid removal was prescribed according to 116 117 patients' clinical needs. All patients were anuric, i.e. with a urine volume of <50 ml/day. Comorbid conditions were hypertension in 26 (54%), diabetes mellitus in 16 (33%), 118 dyslipidemia in 21 (44%), arrythmia in 7 (15%), heart failure in 12 (25%), ischemic heart 119 disease in 8 (17%), stroke in 4 (8%), peripheral vascular disease in 12 (25%), history 120 of malignancy in 7 (15%), morbid obesity in 5 (10%), respiratory disease in 10 (21%), 121 and depression in 5 (10%). 122

The study protocol was reviewed and approved by the Hospital Clínic of Barcelona ethics committee (approval number HCB/2022/0382) and written informed consent was obtained from all participants. The study was conducted according to the Declaration of Helsinki.

The dialysis parameters were kept constant in each session: mean dialysis time 128 was 349 ± 85 min (range 240-480, 14 patients on 8-hour nocturnal shift); blood flow 129 was 416 \pm 34 (range 350-450) ml/min; and dialysate flow was 338 \pm 91 ml/min. 130 Postdilution hemodiafiltration was used in all patients except one, who received HD 131 with medium cut-off membranes (expanded HD). Fresenius 6008 CareSystem dialysis 132 monitors (Fresenius, Bad Homburg, Germany) were used and all patients received 133 their usual parameters. All patients followed 1 week of their usual Na intake and 1 week 134 of more restrictive Na intake. To facilitate dietary adherence, all patients were given a 135 sheet listing the high-salt foods they should avoid as far as possible and the low-salt 136 foods they were allowed. 137

To compare the results, we calculated the average of the three sessions of each 138 139 weekly period. The dialysis parameters collected in each session consisted of real duration, dialyser, Qb, replacement volume, pre- and post-dialysis systolic and 140 141 diastolic blood pressure, initial and final body weight, and interdialytic weight gain. The new Na biosensor quantifies initial and final sNa, diffusive Na balance, and total Na 142 balance. Intradialysis AsNa was calculated. Total Na balance represents the total 143 amount of Na transferred into or out of the patient per dialysis session and can be split 144 145 into two components: the diffusive component (depending on the dialysate to plasma Na gradient) and the net ultrafiltration component. 146

The total Na balance estimated by the model in a single dialysis session reflects only Na removal during the dialysis session. However, with a longer follow-up in clinically stable patients under HD without residual renal function and ignoring loss of Na in either stool or sweat, intradialytic Na removal must reflect Na intake. To assess daily Na intake, the only consideration needed is a correction in accordance with the previous days without dialysis (i.e. the total Na balance on Mondays and Tuesdays
must be divided by 3 days and the remaining days by 2 days).

Na balance was calculated by 6008 dialysis machines, which rely on the 154 155 dialysate conductivity cells of the online clearance monitor. Since the clearance of other electrolytes, such as potassium and bicarbonate, modifies the composition of 156 spent dialysate and influences the relationship between conductivity and Na 157 concentration, the 6008 machine uses a patient kinetic model. This model 158 approximates changes in plasma electrolyte concentrations during dialysis and allows 159 estimation of Na concentration based on dialysate conductivity. Full details on the 160 model can be found in the appendix "transition from conductivity to concentration 161 balancing" in Ságová et al. [15]. The Na control biosensor continuously monitors the 162 side Na balance of the dialysate, based on measurements of fresh and spent dialysate 163 conductivities and the application of a kinetic model to account for the typical influence 164 165 of other ions on dialysate conductivity. In activated Na control modes, such as the zero diffusive mode, dialysate Na is adjusted continuously to minimize diffusive Na transfer 166 [15–17]. 167

Quantitative variables are expressed as mean ± standard deviation and qualitative 168 variables as absolute and relative frequencies. Differences in qualitative variables were 169 analyzed with the χ^2 test. Quantitative parameters were analyzed with the Student t-test 170 for paired data. P<0.05 was considered statistically significant. A Pearson correlation 171 172 coefficient was computed to assess the linear relationship between dietary Na intake and interdialytic weight gain. Analyses were performed using SPSS software version 23 173 174 (SPSS, Chicago, IL, USA) and graphics were prepared with GraphPad Prism version 8 (GraphPad Software). 175

176

177 **RESULTS**

All dialysis sessions were performed without notable clinical incidents or serious adverse events. Despite constant activation of Na control, patients experienced no cramps or episodes of hypotension.

181Total Na balance / Na intake

Total Na balance significantly decreased from 324 ± 103 mmol Na/session with 182 usual Na intake to 210 ± 96 mmol Na/session with restrictive Na intake. When 183 calculated as daily Na intake, total Na balance was 149 ± 54 mmol Na/day (8.76 ± 3.2 184 g salt/day) with usual Na intake and 95 ± 49 mmol Na/day (5.59 ± 2.88 g salt/day) with 185 186 restrictive Na intake. With usual Na intake, daily Na intake was < 85 mmol Na/day (<5 g/day) in four patients (8%), 85 to 150 mmol Na/day in 26 (54%), and > 150 mmol/day 187 in 18 patients (38%). With restricted Na intake, these percentages were 44% (<5 g 188 salt/day), 48% (5-9 g salt/day), and 8% (> 9 g salt/day). Individualized values of daily 189 Na intake are shown in Figure 1. 190

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Interdialytic weight gain

Pre-dialysis body weight was significantly higher in the usual Na intake period 192 while post-dialysis body weight was similar in both periods (Table 1). 193

The restricted Na intake diet significantly reduced interdialytic weight gain 194 195 (Table 1). The average reduction was 460 ± 484 g per session.

Total Na balance was significantly correlated with interdialytic weight gain in 196 both periods (Figure 2): 197

Interdialytic weight gain = 0.006 x Total Na balance + 0.341; $R^2 = 0.733$ 198

199

Initial and final plasma Na

The percentage of patients with hyponatremia was 12.5% (n=6) with usual Na 200 intake and 29.2% (n=14) with restricted Na intake. The mean pre-dialysis sNa was 201 138.11 ± 2.33 (range 133 to 142) mmo/L with usual Na intake and was significantly 202 reduced to 136.29 ± 2.87 (range 130 to 144) mmo/L with restricted Na intake. There 203 were no significant differences in postdialysis sNa (Figure 3). 204

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Diffusive Na balance

Diffusive Na balance differed between the two study periods (Table 1), despite 206 activation of the Na biosensor in both periods with a similar Na dialysate margin of 207 variability allowed (133-142 mmol/L). During the restricted Na diet, the percentage of 208 dialysis sessions achieving a zero diffusive balance (0-30 mmol) decreased from 69% 209 to 23%, dialysis sessions with diffusive balance from 31 to 100 mmol increased from 210

21% to 46%, and dialysis sessions with a diffusive balance > 100 mmol increased from
10% to 31%.

213

Difference between initial and final Na or delta Na (Δ_s Na)

Values of Δ_s Na significantly differed between the two study periods (Figure 3). Δ_s Na was negative in the usual Na intake period with activated Na module biosensor and was positive in the restricted Na period. During the second period, the number of patients with Δ_s Na ≥4 mmol/L rose from 1 to 3 patients (2%-6%), and those with Δ_s Na 2 to 4 mmol/L rose from 5 to 9 (10%-19%). The number of patients with Δ_s Na < 2 mmol/L decreased from 42 (88%) to 36 (75%).

Blood pressure

221 Mean pre- and postdialysis systolic and diastolic blood pressures are shown in 222 Table 1. We found no significant differences in either study period. When patients were 223 divided into groups according to normal or high (\geq 130 mmHg) systolic blood pressure 224 and daily Na reduction, systolic blood pressure decreased significantly in those with a 225 daily Na reduction > 3 g/day (Table 2).

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227 **DISCUSSION**

The present study shows that a restrictive Na diet, with a mean of 3.17 g salt/day, was associated with lower interdialytic weight gain and pre-dialysis sNa and higher Δ sNa and diffusive Na balance.

Sodium intake is closely related to fluid volume. Interdialytic weight gain is a 231 crucial predictor of morbidity and mortality in HD patients due to a directly proportional 232 increase in the risk of cardiovascular events, including hypertension, left ventricular 233 234 hypertrophy, and congestive heart failure [18,19]. Previous studies have shown that intradialytic weight gain can be significantly reduced by a hypotonic diet [20,21]. 235 Indeed, a systematic review reported that a hypotonic diet reduced interdialytic weight 236 gain by 1.5 kg compared to a regular diet [22] and these data are supported by our 237 results. 238

Patients on HD need to adhere to a wide range of dietary restrictions that can 239 negatively impact their long-term guality of life and nutritional status [23]. In these 240 patients, international guidelines recommend a diet low in potassium, phosphorus and 241 salt [24,25]. Despite the well-established benefits of salt restriction in these patients, its 242 243 implementation in clinical practice has been challenging mainly due to poor patient adherence to dietary recommendations, and it has been estimated that half of patients 244 under HD cannot adhere to the recommended salt intake [26]. Our study supports these 245 data as only 8% patients on the usual Na diet met these recommendations. However, 246 when the reduction of salt intake was insisted by these dietary recommendations, in a 247 short period of time, compliance was achieved in 44% of the patients, basically by 46% 248 249 of the patients who reduced more than 3 grams of salt/d.

Pre-dialysis plasma Na fluctuations in patients are normally small, supporting 250 the hypothesis of an individual Na setpoint [4,27]. However, interindividual variability in 251 252 pre-dialysis sNa is very high, reflecting differences in diet, lifestyle and [28]. In the present study, interindividual variability in pre-dialysis sNa ranged from 130 to 144 253 mmol/L. Hyponatremia has been associated with increased mortality. In 2013, a study 254 of 6127 patients on HD reported that sNa <135 mEq/L was associated with 255 hypercalcemia, elevated alkaline phosphatase, hypoparathyroidism, and a higher risk 256 of 1-year mortality [29]. Three years later, another study of 8883 patients from 257 European countries in the international MONDO initiative found that hyponatremia was 258 259 predictive for all-cause mortality [30]. At the same time, a study of 27180 incident patients reported a U-shaped mortality risk, suggesting that hyponatremia increased 260 261 with both lower (<138 mEq/L) and higher (\geq 144mEq/L) sNa [31]. In 2021, a systematic review and meta-analysis showed that hyponatremia predicted all-cause and 262 cardiovascular mortality in the dialysis population [32]. A subsequent analysis of 184 263 patients reported that pre-dialysis time-averaged hyponatremia was independently 264 265 associated with an increased risk of all-cause mortality and cardiovascular events in patients under HD [33]. In our study, reduced Na intake was associated with an 266 increase in the percentage of patients with hyponatraemia from 12% to 29%, indicating 267 that the risk of mortality could increase in this subgroup. It is therefore important to 268 individualize dietary recommendations. Hyponatremia has been associated with 269

functional and cognitive decline [34], risk of bone fractures [35], risk of infection-related
hospital admissions [36], and malnutrition.

272 A 2018 analysis of data from the Japanese dialysis registry, which included 273 88115 patients under HD, showed that low Na intake was associated with all-cause mortality [37]. Unfortunately, it is known that efforts to intensify Na restriction may 274 increase the risk of compromising energy intake [38]. A retrospective cohort study 275 demonstrated that low salt intake was related to high all-cause mortality in HD patients, 276 possibly due to malnutrition in the context of excessive salt restriction [39]. Along the 277 same line, another study reported that hyponatremia was associated with malnutrition, 278 inflammation, and fluid overload [30], while a review of recommended dietary regimens 279 in patients under HD showed that, since Na is used in a wide variety of foods, Na 280 restriction could increase the risk of malnutrition and energy-protein loss. More 281 recently, a study of 127 patients demonstrated the association between a low daily Na 282 intake and inadequate intake of calories, proteins, minerals, trace elements and, 283 vitamin B₁ [40]. These studies suggest that the benefit of a low-Na diet 284 recommendation should be balanced against the risk of malnutrition. 285

Another advantage of the Na module is that it allows dialysate Na prescription 286 to be customized automatically according to patients' needs. Several authors have 287 proposed a goal of zero diffusive balance as a starting point, as it provides an adequate 288 289 option for most patients under HD [15–17]. In our study, the low Na diet was associated with increased diffusive balance. As previously reported by our group[14] the 290 291 determining factor in achieving a neutral diffusive balance was the pre-dialysis sNa value. As in the present study, the pre-dialysis _sNa decreased by almost 2 mmol/L, 292 293 which would explain this change.

294 Changes in ${}_{s}Na$ concentration from pre- to postdialysis may lead to organ 295 damage and have been associated with independent risk factors for all-cause, 296 cardiovascular, and infectious disease-related mortality. A study based on data from 297 the Japanese dialysis and transplant registry reported that pre-dialysis concentrations 298 of ${}_{s}Na < 136$ mEq/L and $\Delta {}_{s}Na > 4$ mEq/L were related to higher mortality in patients 299 under HD, particularly when both were present [41]. The results of the International MONitoring Dialysis Outcome Initiative showed that increased mortality was associated with higher pre-dialysis $_{s}Na$ variability [42]. In our study, reducing Na intake doubled the number of patients with a $\Delta_{s}Na > 2$ mEq/L (12% to 25%), which again emphasizes the importance of individualizing dietary Na recommendations.

Overall, reducing Na intake can be an important component of a comprehensive 304 305 approach to managing hypertension in individuals undergoing HD [10,43]. However, a low-Na diet may not be appropriate for all patients under HD, particularly those with 306 malnutrition or hyponatremia. To individualize recommendations and dietary plans for 307 such patients, it is essential to distinguish between dilution hyponatremia, nutritional 308 hyponatremia, depletion hyponatremia, and dilution hyponatremia associated with Na 309 wasting or malnutrition [44]. Moreover, a strict low-Na diet is no longer recommended 310 in ambulatory patients with heart failure, as a result of the publication of the clinical trial 311 SODIUM-HF, which failed to demonstrate a reduction in cardiovascular events, 312 regardless of a modest improvement in quality of life [45]. This result raises new doubts 313 about this general recommendation in other entities such as end-stage kidney disease 314 and emphasizes that one size does not fit all. 315

Overall, reducing Na intake can be an important component of a comprehensive approach to managing hypertension in individuals undergoing HD. Previous research has shown that the patients deriving the greatest benefit from a restricted Na diet are those with hypertension [46]. In our study, we found statistically significant differences only in the subgroup of hypertensive patients who adhered to the low Na dietary recommendations.

A limitation of our study is the absence of long-term clinical follow-up of restricted Na intake (1 week). Another limitation is that not all patients strictly adhered to the dietary recommendations, although we analyzed the data per intention to treat.

In conclusion, the automated dialysate Na control module is a highly useful tool to objectively monitor Na intake, confirming that patients on a more restricted Na diet did indeed reduce their salt intake. Moreover, lower Na intake was accompanied by less interdialytic weight gain, a decrease in pre-dialysis ${}_{s}Na$, and a trend to lower blood pressure. On the other hand, the low Na diet was also associated with a greater

percentage of patients with pre-dialysis hyponatraemia and higher diffusive Na balance 330 and Δ_{s} Na. Therefore, the advantage of this new Na control biosensor is that it allows 331 objective non-invasive monitoring of estimated Na intake and adherence to Na dietary 332 recommendations in each HD session without additional costs. The biosensor thus 333 334 allows dietary recommendations to be individualized with greater precision according to patients' needs. New studies and algorithms are needed to adapt Na dietary 335 prescription with maximum precision in the presence of distinct clinical situations, such 336 as natremia, fluid overhydration, and hypertension. 337

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342

343 **STATEMENT OF ETHICS**

This study protocol was reviewed and approved by the Hospital Clínic of Barcelona
ethics committee (approval number HCB/2022/0382) and written informed consent
was obtained from all participants. The study was conducted according to the
Declaration of Helsinki.

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349 CONFLICTS OF INTEREST STATEMENT

- F.M. has received consultancy fees and lecture fees from Baxter, Fresenius Medical
 Care, Medtronic, Nipro, Toray and Vifor. The other authors declare no conflicts of
 interest.
- 353
- 354 **FUNDING SOURCES**
- 355 The authors declare no financial support for the project.

356

357 AUTHOR CONTRIBUTIONS358

- 559 F.M. conceived the study. L.M., E.Ch., J.B., J.O., V.E., M.M-Ch, LM.R., M.A-G., M.V.,
- and N.F. acquired the data. L.M., E.Ch., J.B, and F.M. analysed the data, created the

³⁶¹ figures, and drafted the paper. All authors have revised the drafts and approved the

362 final manuscript.

363 DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available from the corresponding

author, F.M., upon reasonable request. <u>All data generated or analysed during this study</u>

366 are included in this article. Further enquiries can be directed to the corresponding

- 367 <u>author</u>
- 368

369 **REFERENCES**

- 370
- 3711Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, et al. Long term372effects of dietary sodium reduction on cardiovascular disease outcomes: observational373follow-up of the trials of hypertension prevention (TOHP). BMJ. 2007 Apr;334(7599):885–8.
- Reinhardt HW, Seeliger E. Toward an Integrative Concept of Control of Total Body Sodium.
 News Physiol Sci. 2000 Dec;15:319–25.
- 376 3 Gross CG. Claude Bernard and the Constancy of the Internal Environment. The 377 Neuroscientist. 1998 Sep;4(5):380–5.
- Basile C, Libutti P, Lisi P, Vernaglione L, Casucci F, Losurdo N, et al. Sodium setpoint and
 gradient in bicarbonate hemodialysis. J Nephrol. 2013;26(6):1136–42.
- Mc Causland FR, Waikar SS, Brunelli SM. The relevance of dietary sodium in hemodialysis.
 Nephrology Dialysis Transplantation. 2013 Apr;28(4):797–802.
- MacEwen C, Sutherland S, Daly J, Pugh C, Tarassenko L. Relationship between
 Hypotension and Cerebral Ischemia during Hemodialysis. J Am Soc Nephrol. 2017
 Aug;28(8):2511–20.
- Cole NI, Swift PA, He FJ, MacGregor GA, Suckling RJ. The effect of dietary salt on blood
 pressure in individuals receiving chronic dialysis: a systematic review and meta-analysis of
 randomised controlled trials. J Hum Hypertens. 2019 Apr;33(4):319–26.
- 388 8 KDIGO. Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney
 389 Disease. Kidney Int. 2013;Suppl 3: 1.
- 390
 9 Ikizler TA, Burrowes JD, Byham-Gray LD et al. KDOQI Nutrition in CKD Guideline Work
 391
 392
 Group. KDOQI clinical practice guideline for nutrition in CKD: 2020 update. Am J Kidney Dis.
 2020;76(3)(supp.
- 39310Borrelli S, Provenzano M, Gagliardi I, Michael A, Liberti ME, De Nicola L, et al. Sodium Intake394and Chronic Kidney Disease. Int J Mol Sci. 2020 Jul;21(13). DOI: 10.3390/ijms21134744
- Petitclerc B, Bene B, Goux N, Vantard G, Jacobs C. Non invasive estimation of sodium mass
 transfer (SMT) during hemodialysis sessions. ASAIO. 1993;39: 2930.

- 397 12 Sadowski R, Allred E, Jabs K. Sodium modeling ameliorates intradialytic and interdialytic
 398 symptoms in young hemodialysis patients. J Am Soc Nephrol. 1993;4: 1192-11.
- 39913Maduell F, Navarro V. [Assessment of salt intake in hemodialysis]. Nefrologia.4002001;21(1):71–7.
- 401 14 Maduell F, Broseta JJ, Rodríguez-Espinosa D, Casals J, Escudero V, Gomez M, et al.
 402 Practical implementation and clinical benefits of the new automated dialysate sodium control
 403 biosensor. Clin Kidney J. 2023 Jan;sfad013.
- Ságová M, Wojke R, Maierhofer A, Gross M, Canaud B, Gauly A. Automated individualization
 of dialysate sodium concentration reduces intradialytic plasma sodium changes in
 hemodialysis. Artif Organs. 2019 Oct;43(10):1002–13.
- Kuhlmann U, Maierhofer A, Canaud B, Hoyer J, Gross M. Zero Diffusive Sodium Balance in
 Hemodialysis Provided by an Algorithm-Based Electrolyte Balancing Controller: A Proof of
 Principle Clinical Study. Artif Organs. 2019 Feb;43(2):150–8.
- 410
 417 Ponce P, Pinto B, Wojke R, Maierhofer AP, Gauly A. Evaluation of intradialytic sodium shifts
 411 during sodium controlled hemodialysis. Int J Artif Organs. 2020 Sep;43(9):620–4.
- 412 18 Flythe JE, Kimmel SE, Brunelli SM. Rapid fluid removal during dialysis is associated with 413 cardiovascular morbidity and mortality. Kidney Int. 2011 Jan;79(2):250–7.
- 414 19 Van Buren PN. Pathophysiology and implications of intradialytic hypertension. Curr Opin
 415 Nephrol Hypertens. 2017 Jul;26(4):303–10.
- Navia B, Aparicio A, Perea JM, Pérez-Farinós N, Villar-Villalba C, Labrado E, et al. Sodium
 intake may promote weight gain; results of the FANPE study in a representative sample of
 the adult Spanish population. Nutr Hosp. 2014;29(6):1283–9.
- Perez LM, Fang HY, Ashrafi SA, Burrows BT, King AC, Larsen RJ, et al. Pilot study to reduce
 interdialytic weight gain by provision of low-sodium, home-delivered meals in hemodialysis
 patients. Hemodial Int. 2021 Apr;25(2):265–74.
- Palmer SC, Hanson CS, Craig JC, Strippoli GFM, Ruospo M, Campbell K, et al. Dietary and
 fluid restrictions in CKD: a thematic synthesis of patient views from qualitative studies. Am J
 Kidney Dis. 2015 Apr;65(4):559–73.
- 425 23 Kalantar-Zadeh K, Tortorici AR, Chen JLT, Kamgar M, Lau W-L, Moradi H, et al. Dietary 426 restrictions in dialysis patients: is there anything left to eat? Semin Dial. 2015;28(2):159–68.
- Levin NW, Kotanko P, Eckardt K-U, Kasiske BL, Chazot C, Cheung AK, et al. Blood pressure
 in chronic kidney disease stage 5D-report from a Kidney Disease: Improving Global
 Outcomes controversies conference. Kidney Int. 2010 Feb;77(4):273–84.
- Sarafidis PA, Persu A, Agarwal R, Burnier M, de Leeuw P, Ferro C, et al. Hypertension in
 dialysis patients: a consensus document by the European Renal and Cardiovascular
 Medicine (EURECA-m) working group of the European Renal Association European
 Dialysis and Transplant Association (ERA-EDTA) and the Hypertension and the Ki. J
 Hypertens. 2017 Apr;35(4):657–76.
- 435 26 Mok E, Tam B. Stressors and coping methods among chronic haemodialysis patients in Hong
 436 Kong. J Clin Nurs. 2001 Jul;10(4):503–11.

- 437 27 Keen ML, Gotch FA. The association of the sodium "setpoint" to interdialytic weight gain and 438 blood pressure in hemodialysis patients. Int J Artif Organs. 2007 Nov;30(11):971–9.
- 439 28 Odudu A, Lambie S, Taal MW, Fluck RJ, McIntyre CW. Use of online conductivity monitoring
 440 to study sodium mass balance in chronic haemodialysis patients: prospects for treatment
 441 individualisation. Kidney Blood Press Res. 2011;34(6):439–46.
- Nigwekar SU, Wenger J, Thadhani R, Bhan I. Hyponatremia, mineral metabolism, and mortality in incident maintenance hemodialysis patients: a cohort study. Am J Kidney Dis. 2013 Oct;62(4):755–62.
- 44530Dekker MJE, Marcelli D, Canaud B, Konings CJAM, Leunissen KM, Levin NW, et al.446Unraveling the relationship between mortality, hyponatremia, inflammation and malnutrition447in hemodialysis patients: results from the international MONDO initiative. Eur J Clin Nutr.4482016;70(7):779–84.
- Rhee CM, Ravel VA, Ayus JC, Sim JJ, Streja E, Mehrotra R, et al. Pre-dialysis serum sodium
 and mortality in a national incident hemodialysis cohort. Nephrol Dial Transplant. 2016
 Jun;31(6):992–1001.
- 452 32 Li J, Song P, Yang D, Liu Y. A Systematic Review and Meta-Analysis: Hyponatremia
 453 Predicted All-Cause and Cardiovascular Mortality in Dialysis Population. Blood Purif.
 454 2022;51(4):345–54.
- 33 Zhang Z, Zheng L, Pan Y, Wang M. The impact of chronic pre-dialysis hyponatremia on clinical outcomes in maintenance hemodialysis patients. Int Urol Nephrol. 2022
 457 Dec;54(12):3221–32.
- 458 34 Shavit L, Mikeladze I, Torem C, Slotki I. Mild hyponatremia is associated with functional and 459 cognitive decline in chronic hemodialysis patients. Clin Nephrol. 2014 Nov;82(5):313–9.
- 460 35 Ayus JC, Fuentes NA, Negri AL, Moritz ML, Giunta DH, Kalantar-Zadeh K, et al. Mild 461 prolonged chronic hyponatremia and risk of hip fracture in the elderly. Nephrol Dial 462 Transplant. 2016 Oct;31(10):1662–9.
- 463 36 Mandai S, Kuwahara M, Kasagi Y, Kusaka K, Tanaka T, Shikuma S, et al. Lower serum
 464 sodium level predicts higher risk of infection-related hospitalization in maintenance
 465 hemodialysis patients: an observational cohort study. BMC Nephrol. 2013 Dec;14:276.
- 466 37 Ikenoue T, Koike K, Fukuma S, Ogata S, Iseki K, Fukuhara S. Salt Intake and All-Cause
 467 Mortality in Hemodialysis Patients. Am J Nephrol. 2018;48(2):87–95.
- 38 Xie Z, McLean R, Marshall M. Dietary Sodium and Other Nutrient Intakes among Patients
 469 Undergoing Hemodialysis in New Zealand. Nutrients. 2018 Apr;10(4). DOI:
 470 10.3390/nu10040502
- 471 39 Suzuki N, Hitomi Y, Takata H, Ushiya S, Yamada M, Sakai Y, et al. Association between salt 472 intake and long-term mortality in hemodialysis patients: A retrospective cohort study. PLoS 473 One. 2021;16(12):e0260671.
- 474 40 Bossola M, Di Stasio E, Viola A, Cenerelli S, Leo A, Santarelli S, et al. Dietary Daily Sodium
 475 Intake Lower than 1500 mg Is Associated with Inadequately Low Intake of Calorie, Protein,
 476 Iron, Zinc and Vitamin B1 in Patients on Chronic Hemodialysis. Nutrients. 2020 Jan;12(1).
 477 DOI: 10.3390/nu12010260

- 478 41 Fujisaki K, Joki N, Tanaka S, Kanda E, Hamano T, Masakane I, et al. Pre-dialysis
 479 Hyponatremia and Change in Serum Sodium Concentration During a Dialysis Session Are
 480 Significant Predictors of Mortality in Patients Undergoing Hemodialysis. Kidney Int Rep. 2021
 481 Feb;6(2):342–50.
- 482 42 Ye X, Kooman JP, van der Sande FM, Canaud B, Stuard S, Etter M, et al. Increased Mortality
 483 Associated with Higher Pre-Dialysis Serum Sodium Variability: Results of the International
 484 MONitoring Dialysis Outcome Initiative. Am J Nephrol. 2019;49(1):1–10.
- 485
 43 Mcmahon EJ, Campbell KL, Bauer JD, Mudge DW. Altered dietary salt intake for people with chronic kidney disease. Cochrane Database Syst Rev. 2015 Feb;2015(2). DOI: 10.1002/14651858.CD010070.PUB2
- 488
 44 Vitova L, Tothova M, Schuck O, Horackova M. Novel Algorithm for the Differential Diagnosis
 489 of Hyponatraemia in Anuric Patients Undergoing Maintenance Haemodialysis. Kidney Blood
 490 Press Res. 2021;46(3):387–92.
- 49145Ezekowitz JA, Colin-Ramirez E, Ross H, Escobedo J, Macdonald P, Troughton R, et al.492Reduction of dietary sodium to less than 100 mmol in heart failure (SODIUM-HF): an493international, open-label, randomised, controlled trial. Lancet. 2022 Apr;399(10333):1391–494400.
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508	Figure 1: Comparison of individualized values of daily Na intake between usual Na
509	intake and restricted Na intake.
510	
511	Figure 2: Correlation between total Na balance and interdialytic weight gain (IWG) in
512	both two periods.
513	
514	Figure 3: A: Comparison of pre- and postdialysis ${}_{s}Na$ with usual Na intake and
515	restricted Na intake. B: Comparison of the difference between the initial and final ${}_{\mbox{\scriptsize s}}$ Na
516	(Δ₅Na) in the two study periods.
517 518	
519 520	

Table 1: Comparison of pre/postdialysis body weight, interdialytic body weight gain, HDF replacement volume, pre/postdialysis serum Na, diffusive Na balance, and pre/postdialysis blood pressure in the two study periods

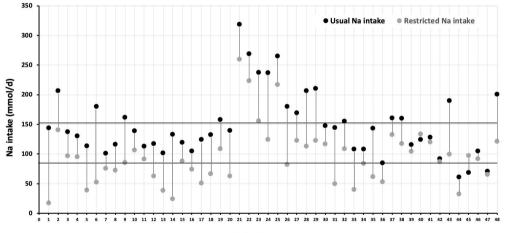
	Usual Na intake	Restricted Na intake	P value	
Pre-dialysis body weight (kg)	70.112 ± 16.77	69.525 ± 16.66	<0.001	
Postdialysis body weight (kg)	67.896 ± 16.60	67.779 ± 16.58	N.S.	
Interdialytic weight gain (g)	2210 ± 816	1750 ± 776	<0.001	
HDF replacement volume (L)	32.6 ± 10.9	32.4 ± 10.6	N.S.	
Pre-dialysis serum Na (mmol/L)	138.11 ± 2.33	136.29 ± 2.87	<0.001	
Postdialysis serum Na (mmol/L)	137.61 ± 1.64	137.08 ± 1.73	0.018	
Diffusive Na balance (mmol/L)	31.85 ± 41.0	73.67 ± 53.1	<0.001	
Pre-dialysis SBP (mmHg)	134.4 ± 23.1	132.2 ± 22.4	N.S.	
Pre-dialysis DBP (mmHg)	68.4 ± 12.6	68.0 ± 12.7	N.S.	
Postdialysis SBP (mmHg)	128.1 ± 20.4	131.1 ± 21.1	N.S.	
Postdialysis DBP (mmHg)	65.7 ± 12.9	66.7 ± 13.5	N.S.	

HDF: hemodiafiltration; Na: sodium; SBP: systolic blood pressure; DBP: diastolic blood pressure;

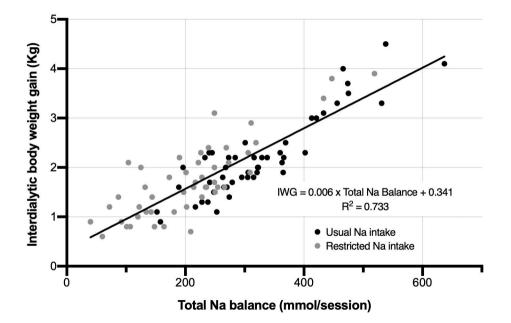
Table 2. Systolic and diastolic blood pressure grouped by normal or high (\geq 130 mmHg) systolic blood pressure and daily sodium reduction in the two study periods.

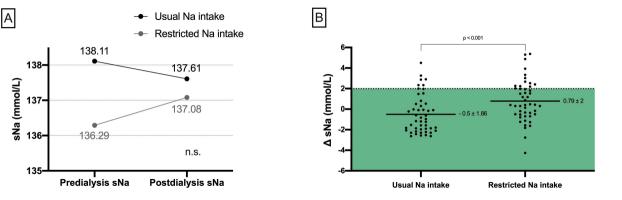
	SBP		DBP			
	Na intake			Na i		
Patient groups	Usual	Restricted	р	Usual	Restricted	р
Normal BP with daily Na reduction > 3 g (n = 8)	114.1 ± 19.6	111.7 ± 22.6	N.S.	58.1 ± 10.4	58.5 ± 13.3	N.S.
Normal BP with daily Na reduction \leq 3 g (n = 14	116.7 ± 9.30	116.6 ± 10.8	N.S.	62.9 ± 9.30	61.4 ± 10.7	N.S.
High BP with daily Na reduction $> 3 \text{ g} (n = 14)$	148.2 ± 14.1	141.4 ± 9.60	0.029	76.4 ± 12.5	75.5 ± 10.5	N.S.
High BP with daily Na reduction ≤ 3 g (n = 12)	152.5 ± 20.1	153.4 ± 18.8	N.S.	72.2 ± 10.4	73.3 ± 9.20	N.S.

SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure; Na: sodium.



Patients





American Journal of Nephrology



Salt intake restriction monitored with automated Na control

