



Sodium intake and urinary losses in children on dialysis: a European multicenter prospective study

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Abstract

Background Sodium (Na) balance is unexplored in dialyzed children. We assessed a simplified sodium balance (sNaB) and its correlates in pediatric patients receiving maintenance dialysis.

Methods Patients < 18 years old on hemodialysis (HD) or peritoneal dialysis (PD) in six European Pediatric Dialysis Working Group centers were recruited. sNaB was calculated from enteral Na, obtained by a 3-day diet diary, Na intake from medications, and 24-h urinary Na (uNa). Primary outcomes were systolic blood pressure and diastolic blood pressure standard deviation scores (SBP and DBP SDS), obtained by 24-h ambulatory blood pressure monitoring or office BP according to age, and interdialytic weight gain (IDWG).

Results Forty-one patients (31 HD), with a median age of 13.3 (IQR 5.2) years, were enrolled. Twelve patients (29.3%) received Na-containing drugs, accounting for 0.6 (0.7) mEq/kg/day. Median total Na intake was 1.5 (1.1) mEq/kg/day, corresponding to 60.6% of the maximum recommended daily intake for healthy children. Median uNa and sNaB were 0.6 (1.8) mEq/kg/day and 0.9 (1.7) mEq/kg/day, respectively. The strongest independent predictor of sNaB in the cohort was urine output. In patients receiving HD, sNaB correlated with IDWG, pre-HD DBP, and first-hour refill index, a volume index based on blood volume monitoring. sNaB was the strongest predictor of IDWG in multiple regression analysis ($\beta=0.63$; $p=0.005$). Neither SBP SDS nor DBP SDS correlated with sNaB.

Conclusions Na intake is higher than uNa in children on dialysis, and medications may be an important source of Na. sNaB is best predicted by urine output in the population, and it is a significant independent predictor of IDWG in children on HD.

Keywords Sodium balance · Interdialytic weight gain · Salt intake · Hemodialysis · Children

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Introduction

Fluid overload is a major cause of cardiovascular complications in patients with chronic kidney disease stage 5 (CKD 5) [1–3]. In particular, interdialytic weight gain (IDWG) is significantly correlated with blood pressure (BP) and left ventricular mass index in children on hemodialysis (HD) [4, 5]. High IDWG due to osmotic thirst is largely secondary to salt ingestion, while other osmotic causes of thirst are negligible [6].

Sodium (Na) overload has a negative impact on cardiovascular status through several mechanisms other than fluid expansion, such as increased total peripheral resistance, vascular smooth muscle cell hypertrophy, and reactive oxygen species promotion [7].

A few studies of adults on dialysis showed that a low-Na diet can result in lower IDWG, better BP, reduced left ventricular mass index, and lower mortality [8–10]. Both the KDOQI and KDIGO guidelines recommend restriction of Na intake for children with chronic kidney disease (CKD) with hypertension or pre-hypertension, on the basis of the age-related recommended daily intake (RDI) for healthy children [11–13]. Data from the Chronic Kidney Disease in Children (CKiD) study showed that the median Na intake in children with CKD stages 2–3 exceeded the maximum RDI for all age groups [14].

No studies have, at present, investigated the Na intake of children on dialysis, and their optimal Na requirements remain unknown. While 24-h urinary Na (uNa) excretion is considered the gold standard method to assess Na intake in healthy children [15, 16], this is not the case for those with CKD 5, whose uNa losses mainly depend on primary kidney disease and residual kidney function. In addition, the relation between Na and cardiovascular outcome has never been explored in this population.

We aimed to assess an interdialytic simplified Na balance (sNaB) model in a population of children on maintenance dialysis, based on enteral Na (eNa) intake, medication-related Na intake, and uNa, and explore its correlations with BP and IDWG. To make it feasible in the daily clinical practice, we did not include in the model other losses of Na, such as skin, feces, and dialysis fluid.

Materials and methods

Six centers from the European Pediatric Dialysis Working Group participated in this prospective observational study. All patients less than 18 years old undergoing chronic thrice weekly conventional HD or hemodiafiltration (HDF) or daily automated peritoneal dialysis (PD) in the period April 2020 to March 2021 were eligible.

Exclusion criteria were as follows: intensified HD (home or nocturnal HD/HDF, ≥ 4 sessions/week), incremental HD/HDF (< 3 sessions/week), chronic ambulatory PD, non-renal Na-losing conditions (i.e., cystic fibrosis), intercurrent diseases or clinical instability as judged by the clinician, and any physical or psychosocial condition that could make it difficult to adhere to the study protocol.

Primary endpoints were as follows:

- Daily sNaB
- Association between sNaB and BP
- Association between sNaB and IDWG in patients on HD

The study was performed according to the principles of the Declaration of Helsinki. Approval from local institutional review boards was obtained for each participating site.

The following data were collected: (1) simplified Na balance, (2) blood pressure, (3) biochemical parameters, (4) specific measurements in patients on HD, and (5) specific variables for patients on PD.

Simplified Na balance

sNaB was calculated as the difference between daily total sodium (tNa) intake and daily uNa losses; tNa was calculated as the sum of eNa and medication-related Na intake, expressed in mEq/kg/day, and as percentage of the maximum RDI (%RDI) for healthy children [17]. eNa was assessed by a 3 day prospective diet diary, which included two weekdays and one weekend day. At least one non-HD day was included for patients on HD. Mean daily energy intake (DEI) and daily protein intake (DPI) were also calculated.

The medication-related Na was calculated from the prescribed doses of Na bicarbonate, Na chloride, and Na-based potassium exchange resins.

Urinary Na was measured in a 24-h urine collection that started 24 h before a HD session or 24 h before the visit for PD children. Oligoanuria was defined as a daily urine output (UO) < 0.5 ml/kg/h.

Other Na losses were not considered, in particular those due to skin, feces, and dialysis fluid. However, for ease of reading, we will refer to this simplified model as sNaB throughout the text.

Blood pressure

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) standard deviation score (SDS) was calculated from mean 24-h SBP and DBP obtained by 24-h ambulatory blood pressure monitoring (ABPM) in children ≥ 5 years or from office measurements in those < 5 years. In detail, 24-h ABPM was performed according to current guidelines in the

30 days following the diet diary [18, 19]. ABPM started at the end of a dialysis session for children on HD and at the end of the morning visit for those on PD.

For children < 5 years, the median of six blood pressure readings was considered, measured by oscillometric method before the start of the mid-week HD session or during the morning visit for children on PD.

All ABPM and office measurements were normalized for age, sex, and height according to the available reference values [19, 20].

The number of antihypertensive drugs was recorded. Hypertension was defined as either systolic or diastolic blood pressure > 95th percentile for age, height, and sex or when using antihypertensive medication, while uncontrolled hypertension was defined as either systolic or diastolic blood pressure > 95th percentile for age, height, and sex in patients receiving antihypertensive agents [19, 20].

Biochemical parameters

The following laboratory parameters were measured in the morning after the nocturnal session for children receiving PD or at the beginning of a mid-week session for children on HD, in the 30 days following the diet diary: serum sodium (sNa), potassium (K), creatinine, albumin, bicarbonate, phosphate, hemoglobin, and N-terminal pro-brain natriuretic peptide (NT-proBNP). Three measurements of pre-HD sNa were obtained for each child on HD in the month following the diet diary, and their mean value calculated.

Specific measurements in patients on HD

The following are the specific measurements in patients on HD:

1. IDWG: The median IDWG (defined as the difference between pre-HD body weight and body weight at the end of the preceding session) over the 30 days following the diet diary was calculated as a percentage of estimated optimal dry weight (DW). The estimated DW was assessed by the local clinician.
2. Pre-HD office BP: The median of all the pre-HD SBP and DBP in the 30 days following the diet diary was also collected by oscillometric method; BP was measured by a specialized nurse before starting the HD session according to the standard guidelines [19]. The pre-HD measurements were normalized for age, sex, and height according to the reference values [19].
3. First-hour refill index (1st-h RI): It is a novel index based on blood volume monitoring (BVM) to assess pre-HD fluid overload in pediatric patients, calculated as the ratio between the ultrafiltration rate in the first hour of dialysis, normalized for body weight, and the simultaneous reduction in relative BV during the treatment [21].

In detail, it was calculated according to the following formula:

1st-h RI = ultrafiltration rate in the first hour of dialysis (ml/kg/h)/percent blood volume reduction in the first hour of treatment.

The rationale supporting the use of 1st-h RI as the measure of pre-HD volume overload is that the refill capacity during dialysis is proportional to fluid overload [21]. The median 1st-h RI of each HD patient over the 30 days following the diet diary was calculated. As many centers did not use BVM to regulate ultrafiltration rate during HD, this data was available for a minority of patients only.

Specific variables for patients on PD

Mean ultrafiltration, in ml/kg per night, over the 30 days following the dietary diary was recorded.

Statistical analysis

Descriptive statistics were reported as median and interquartile range (IQR). Student's *t* test or Mann–Whitney test was used to compare the distribution of a continuous variable in two groups, as appropriate according to variable distributions.

Simple linear regression models were used to assess the correlation between sNaB and the variables under study in the overall cohort (PD + HD): SBP SDS, DBP SDS, age, dialysis vintage, UO, daily energy intake, daily protein intake, serum Na, K, creatinine, albumin, bicarbonate, phosphate, hemoglobin, and NT-proBNP. All the correlates with a *p* value < 0.15 at the simple regression model were included in the multiple linear regression model, together with significant interactions. A saturated model was first produced, and a backward stepwise search algorithm, with further manual refinement, was used to identify the best multiple regression model, according to the lowest Akaike information criterion (AIC). ANOVA tests were also performed to compare models, and the adjusted *R*-squared and the model *p* value were also assessed.

Regarding patients on HD, we repeated the same kind of analysis using IDWG as outcome. We first used single linear regression models between IDWG and the abovementioned variables + sNaB. All variables with a *p* value < 0.15, and significant interactions, were included in the saturated model, and a backward stepwise algorithm, with further manual refinement, was used to find the best model, as already described.

Regarding the calculation of the sample size, in the absence of any data available in the literature concerning NaB in children with CKD, the calculation was based on eNa. In detail, the following parameters were considered: alpha level 0.05; power 80%; standard deviation of eNa

Table 1 Main characteristics of the enrolled patients (median and interquartile range)

	All	HD	PD
Number	41	31	10
Age, years	13.3 (10.7–15.8)	13.4 (11.3–15.9)	11.2 (7.6–13.8)
Sex, F (%)	20 (48.8)	18 (58.1)	2 (20)
Dialysis vintage, years	1.0 (0.7–1.6)	0.8 (0.6–1.5)	1.7 (1.4–2.6)
Primary kidney disease			
CAKUT	20 (48.8)	16 (51.6)	4 (40)
Glomerular	11 (26.8)	10 (32.3)	1 (10)
Cystic	5 (12.2)	2 (6.4)	3 (30)
Others	5 (12.2)	3 (9.7)	2 (20)
Body weight, kg	43.0 (28.8–48.0)	45 (29.6–49.7)	27.4 (18.7–43.2)
Height, cm	150.1 (127.6–160.0)	151.6 (138.2–160.0)	127.0 (119–157.9)
Urine output, ml/kg/day	8.9 (1.0–28.8)	8.9 (2.6–25.8)	10.4 (1.5–46.8)
Oligoanuria (%) ^a	22/41 (53.7%)	17 (54.8)	5 (50)

CAKUT congenital anomalies of the kidney and urinary tract

^aDaily urine output < 0.5 ml/kg/h

intake in children with CKD 49.8 mg/kg/day (mean 86.9), calculated from data of the CKiD trial [14]; and standard deviation of SBP and DBP in children on maintenance dialysis 14.5 mmHg and 10.1 mmHg, respectively (personal data, unpublished). With these reference data, using a linear regression model, a sample size of 40 children was appropriate to detect a minimum effect size defined as a slope of 0.12 for SBP and a slope of 0.09 for DBP, corresponding to a mean variation of 1.2 mmHg of SBP or 0.9 mmHg of DBP for an increase of 10 mg/kg/day of eNa.

Open source software R was used for the statistical analysis [22]. A *p* value < 0.05 was considered statistically significant.

Results

Forty-four patients were recruited, but three of them were excluded because of incomplete data, so that 41 patients, with a median age of 13.3 (IQR 10.7–15.8) years, were enrolled from six centers (Supplementary Fig. 1). Thirty-one patients were on HD and 10 on PD. Their characteristics are summarized in Table 1. Four children received exclusive or complementary enteral nutrition through a nasogastric tube (3 patients) or gastrostomy (1 child).

Assessment of Na intake and urinary losses in the whole cohort

The distribution of sNaB values and its components is shown in Table 2. Median eNa was 1.3 (1.0–2.0) mEq/kg/day.

Twelve patients (29.3%) were treated with Na-containing medications, accounting for 0.6 (0.5–1.1) mEq/kg/day, corresponding to 40% of tNa in this group. The prescribed

Table 2 Sodium intake, urinary sodium, and simplified sodium balance, expressed in mEq/kg/day, in the entire population

	Median	IQR	N
Dietary Na (mEq/kg/day)	1.3	1.0 to 2.0	41
Na from medications (mEq/kg/day)	0.6	0.5 to 1.1	12
Total Na (mEq/kg/day)	1.5	1.2 to 2.3	41
Urinary Na (mEq/kg/day)	0.6	0.1 to 1.8	41
Na balance (mEq/kg/day)	0.9	–0.05 to 1.7	41

Na sodium, IQR interquartile range

Na-containing medications were Na bicarbonate (10/41), Na-based potassium exchange resins (1), and Na chloride (1).

Median tNa (diet + medications) was 1.5 (1.2–2.3) mEq/kg/day, corresponding to 60.6% (41–82.5%) of the maximum RDI for healthy children; 7/41 patients (17.1%) exceeded the maximum RDI for healthy children.

As the median uNa was 0.6 (0.1–1.8) mEq/kg/day, the median sNaB was 0.9 (–0.05 to 1.7) mEq/kg/day. sNaB was significantly higher in 22 oligoanuric patients than in those with preserved residual UO: 1.24 (0.9–2.2) mEq/kg/day vs. –0.18 (–0.9 to 0.6) mEq/kg/day, respectively (*p* < 0.0001).

According to the density plot (Supplementary Fig. 2), both tNa and uNa show an asymmetric, right-skewed distribution, while sNaB exhibits a rather symmetric, reasonably normal distribution, due to the interaction of the two components.

As shown in Supplementary Fig. 3, uNa and eNa were not significantly different between patients receiving and those not receiving Na-containing drugs (*p* = 0.63 and *p* = 0.58, respectively), but tNa and sNaB were significantly higher in children prescribed Na-containing medications (*p* = 0.002 and *p* = 0.009, respectively).

sNaB and BP

BP was measured by 24-h ABPM in 37 patients and by office measurements in 4 children < 5 years of age, with a median interval of 3 days (0–7.5) between diet diary and BP assessment. As shown in Fig. 1, neither SBP SDS nor DBP SDS was significantly associated with sNaB ($R^2=0.02$ [$p=0.34$] and $R^2=0.001$ [$p=0.84$], respectively). The same was true for tNa, expressed in mEq/kg/day ($R^2=0.001$ [$p=0.83$] and $R^2=0.001$ [$p=0.84$], respectively), and tNa, expressed in %RDI ($R^2=0.001$ [$p=0.84$] and $R^2=0.005$ [$p=0.66$], respectively).

Since BP was measured by 24-h ABPM in patients aged ≥ 5 years only, as sensitivity analysis, we repeated the test, considering only the 37 patients with 24-h ABPM. The results were absolutely comparable to those obtained in the overall population ($R^2=0.04$ [$p=0.21$] and $R^2=0.005$ [$p=0.68$] for SBP SDS and DBP SDS, respectively).

A total of 27/41 patients (65.8%) were on antihypertensive medications, 30/41 (73.1%) were classified as hypertensive, and uncontrolled hypertension was diagnosed in 14/41 patients (34.1%). sNaB was not different between hypertensive and normotensive patients ($p=0.38$), between patients receiving antihypertensive drugs and untreated patients ($p=0.87$), and between patients with controlled and uncontrolled hypertension ($p=0.73$). No correlation was found between sNaB and the number of antihypertensive drugs/patient.

Associations of sNaB with other variables (whole cohort)

At simple linear regression analysis, sNaB was significantly associated ($p<0.05$) with age, UO, and sNa (inverse association) and with DEI and DPI (direct association) (Fig. 2). There was no significant association with dialysis vintage ($p=0.19$) or with other laboratory parameters (serum K, creatinine, albumin, bicarbonate, phosphate, hemoglobin, NT-proBNP).

We included in the multiple linear regression analysis all the abovementioned parameters (age, UO, sNa, DEI, DPI), together with serum albumin and K (whose p value was <0.15 at simple regression analysis) and the interactions between age, UO, and K (that were significant at an explanatory analysis). As shown in Table 3, a backward stepwise analysis provided a final model which included age, DPI, UO, sNa, and K, plus the interaction between age and UO and the interaction between UO and K. The most significant predictors of sNaB were UO ($p=0.01$) and the interaction between UO and K ($p=0.01$). The model was highly significant (R^2 adj. = 0.64; $p=0.0000003$). According to this model, sNaB decreased when UO increased,

and the negative effect of UO on sNaB was stronger as K increased, as a result of the negative interactions. Serum Na and DPI were weakly related to sNaB, but they contributed to make the model better.

To better explore the correlation between sNaB and serum potassium (sK), we investigated the role of renin–angiotensin–aldosterone system (RAAS) antagonists. We observed a tendency toward higher sK and higher sNaB in patients on RAAS antagonists that did not reach statistical significance; the risk of hyperkalemia ($K>6$ mEq/l) was 53% and 26.9% in patients receiving and not receiving RAAS antagonists, respectively ($p=0.09$), the difference being higher in case of preserved residual kidney function (60% vs. 21%) than in oliguric patients (50% vs. 33%).

sNaB and HD-related variables

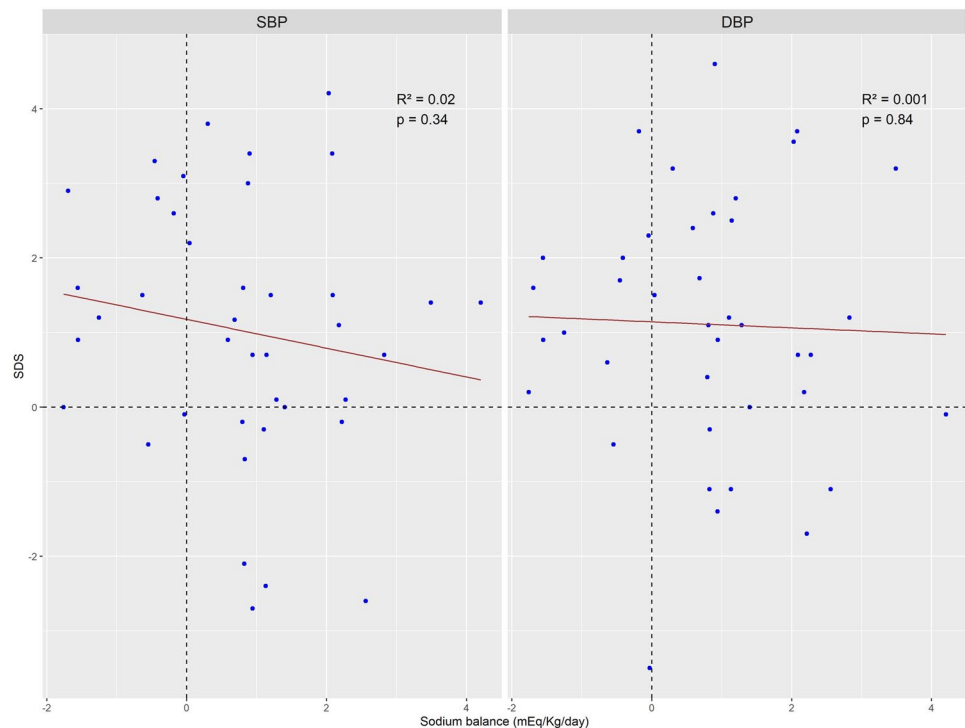
Dialysis details of the 31 patients on HD are summarized in Supplementary Table 1. HDF was the dialysis modality in 67.7% of the patients. No ultrafiltration or dialysate sodium (dNa) profiles were prescribed; in the majority of patients, dNa was kept at 138 mEq/l.

SBP SDS and DBP SDS, obtained by 24-h ABPM in 30 out of 31 patients and by office BP in one patient, were not significantly correlated with sNaB ($R^2=0.02$ [$p=0.49$] and $R^2=0.004$ [$p=0.73$], respectively). sNaB strongly correlated with IDWG ($R^2=0.61$; $p<0.0001$) (Fig. 3), both in patients with oligoanuria ($n=15$; $R^2=0.21$; $p=0.04$) and in patients without oligoanuria ($n=16$; $R^2=0.65$; $p=0.0003$). At the simple regression analysis, IDWG inversely correlated also with UO ($R^2=0.20$; $p=0.007$). We performed a multiple regression analysis including sNaB and UO, but also age, HD vintage, DPI, hemoglobin (which had a p value <0.15 at simple regression analysis), and the interaction between age and UO. As shown in Table 4, the backward stepwise analysis provided a final model where the most significant predictor of IDWG was sNaB, positively related to IDWG (coefficient = 0.63, $p=0.005$), and the other significant predictors were HD vintage ($p=0.04$) and the negative interaction between age and UO ($p=0.02$). The model was highly significant (R^2 adj. = 0.69; $p=0.000001$). Basically, IDWG increased with higher sNaB and longer HD vintage; the negative effect of UO on IDWG was particularly evident in adolescents.

According to a logistic regression model, we observed that both a sNaB ≤ 0.7 mEq/kg/day and a tNa ≤ 1.5 mEq/kg/day were associated with a probability lower than 10% of IDWG $\geq 4\%$.

A significant correlation was observed between sNaB and pre-HD DBP SDS ($R^2=0.19$; $p=0.009$) (Fig. 3), but not with pre-HD SBP SDS ($R^2=0.004$; $p=0.74$). sNaB was also significantly correlated with 1st-h refill index in the 13 patients for which this parameter was available

Fig. 1 Simple linear regression analysis between systolic and diastolic blood pressure standard deviation scores and simplified sodium balance



($R^2 = 0.60$; $p = 0.002$). The correlation between sNaB and dialysis fluid-to-plasma Na gradient did not reach statistical significance ($R^2 = 0.07$; $p = 0.08$). Symptomatic HD sessions were reported in 3/31 patients, without any significant association between the incidence of symptomatic sessions and sNaB.

We enrolled 10 patients receiving conventional HD and 21 on HDF, without any significant difference between the two groups for sNaB (0.85 mEq/kg/day vs. 0.88 mEq/kg/day in patients on HD and HDF, respectively), eNa, tNa, and uNa.

sNaB in patients on PD

Ten patients receiving PD were enrolled, whose details are shown in Supplementary Table 2. sNaB was not significantly different between children on HD and PD ($p = 0.30$). Also in this subgroup of patients, sNaB was not correlated with SBP SDS or DBP SDS. The correlation between sNaB and median ultrafiltration (ml/kg/session) did not reach statistical significance ($R^2 = 0.27$; $p = 0.12$).

Discussion

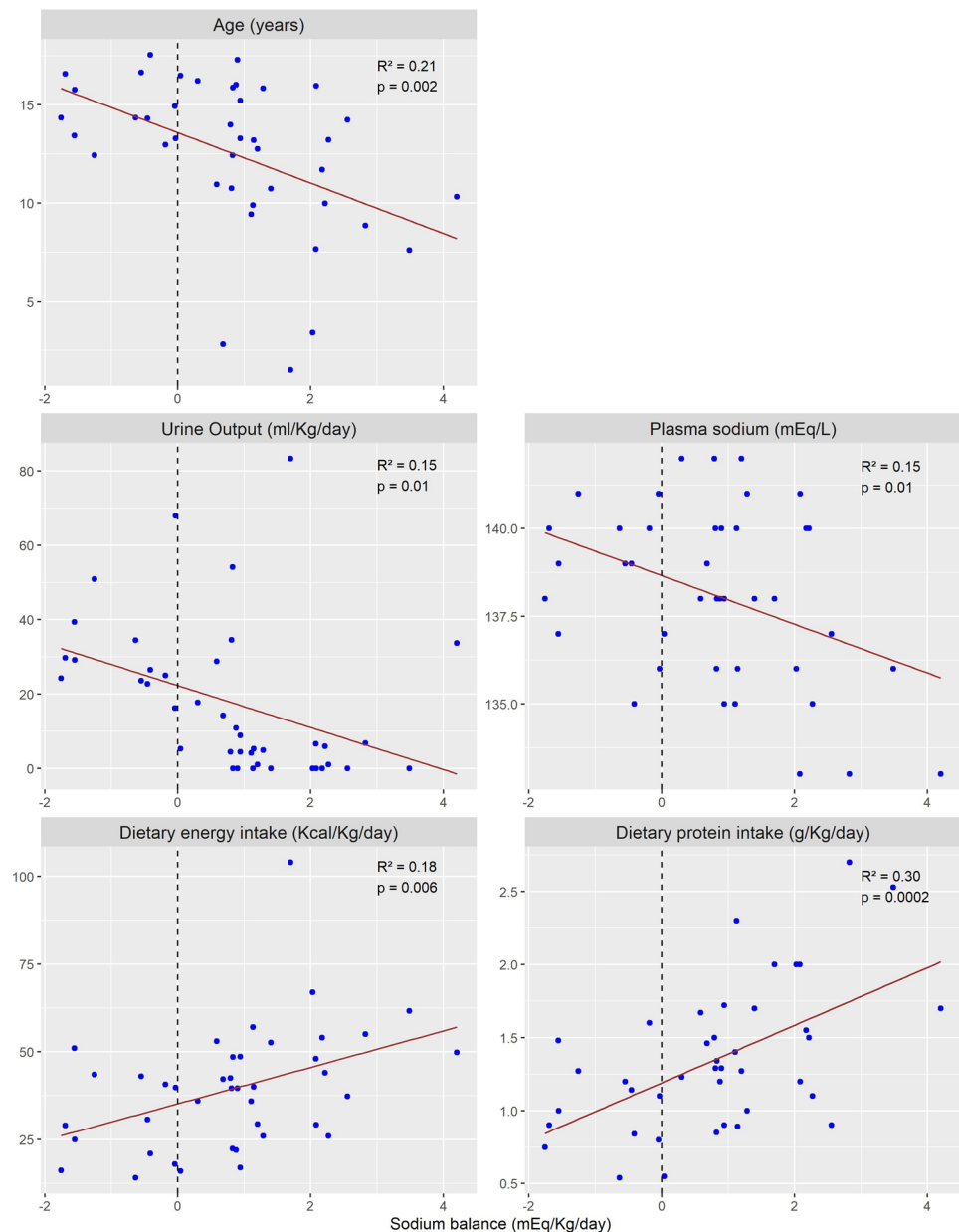
This study provides the first data on Na intake and urinary losses in children on maintenance dialysis. The simplified Na balance did not correlate with BP in the whole population,

but it significantly and independently correlated with IDWG in patients on HD.

Data concerning Na intake in children with CKD are scarce, and totally lacking for those on dialysis. In a cross-sectional analysis of the CKiD study in children with CKD 2 to 3, with a median age of 11 years, the median daily Na intake was 3089 mg (134 mEq), exceeding the maximum RDI in all age groups. The median Na intake in our study was much lower compared to the CKiD data and only 17.1% of our patients showed a tNa above the maximum RDI. Other than for geographical location and different modalities to assess dietary intakes (3-day diet diary vs. food frequency questionnaire), the two populations were different in many clinical characteristics: in particular, 54% of our patients were oligoanuric (thus needing fluid restriction) and 73.1% hypertensive, while many patients in the CKiD cohort were categorized as salt losers [14].

This is the first study investigating the role of Na contained in medications in children with CKD 5. Na-containing drugs were prescribed to 30% of patients, and they accounted for 40% of tNa in this group. Our results are consistent with two adult studies on Na-based K exchange resin [23, 24]. No significant effect of Na bicarbonate on BP was found in two studies on adults with CKD, but no trials on this drug were performed in patients on dialysis [25, 26]. Even considering the bias due to possible non-compliance and the possible incomplete absorption of drug-related Na observed in some experimental trials [27], our study reinforces the importance

Fig. 2 Significant correlates of simplified sodium balance at simple linear regression analysis in the whole cohort



of being cautious when prescribing Na-containing drugs to children on dialysis.

The lack of correlation between our sNaB and BP is unexpected considering the huge body of literature linking Na excess and hypertension both in the general pediatric population and in adult CKD patients [28–30]. Some possible explanations could be hypothesized, first of all the cross-sectional design, as it can be assumed that patients with the highest BP values had a more restrictive eNa prescription. Second, for logistic reasons, 24-h ABPM started immediately after the HD session, but a progressive increase in BP was reported during the interdialytic interval in both adult and pediatric patients: given the risk of BP underestimation by 24-h ABPM, 44-h ABPM could have been much more

informative of the actual BP status of the patients [31, 32]. Third is the confounding effect of antihypertensive agents. The lag phenomenon and the role of tissue Na [33] should also be considered, as skin Na is significantly correlated with BP and left ventricular mass in adults with CKD [34, 35]. Moreover, even if the observed effect was so small that it seems difficult to imagine that increasing the number of patients could have led to significantly different results, we cannot exclude that sample size was too low to demonstrate a significant association between sNaB and BP.

The significant role of UO in predicting sNaB was expected. The inverse correlation between sNaB and plasma K, which was stronger at higher values of residual UO, is of interest: we could simply hypothesize that some drugs, in

Table 3 Best multiple regression model for simplified sodium balance (mEq/kg/day) in the entire cohort

Predictors	Coefficients	SE	<i>t</i> value	<i>p</i> value
Age (years)	−0.01	0.06	−0.19	0.853
Urine output (ml/kg/day)	0.14	0.05	2.7	0.011
DPI (g/kg/day)	0.69	0.38	1.82	0.077
Plasma Na (mEq/l)	−0.09	0.06	−1.52	0.139
Plasma K (mEq/l)	0.10	0.35	0.29	0.775
Age:urine output	−0.002	0.001	−1.92	0.064
Urine output:K	−0.04	0.01	−2.65	0.012
R^2/R^2 adjusted	0.707/0.645			
Model <i>p</i> value	0.00000031			

Other variables included in the starting saturated model are dietary energy intake, serum albumin, interaction between age, urine output, and K

DPI dietary protein intake, *Na* sodium, *K* potassium

particular RAAS antagonists, Na-based K exchange resins, and Na bicarbonate, could have played a role, but this finding deserves further confirmation. We observed an interesting inverse association between sNaB and serum Na at univariable analysis; given that this association disappeared at multivariable analysis, we might hypothesize that this finding was due to the confounding effect of some covariates, i.e., IDWG or UO.

The strong association between sNaB and IDWG in patients on HD, never previously demonstrated in pediatrics, is probably the most important result of the study, given the critical role of IDWG in these patients [4, 5, 32]. This finding is fully consistent with the few adult studies looking at the role of salt intake in patients on HD [8–10]. On the same line, other trials demonstrated that a reduction of Na load by decreasing dialysis Na was associated with lower IDWG [36–38]. Although the cross-sectional design does not allow us to establish a cause-and-effect relationship between sNaB and IDWG, the multiple regression analyses

confirmed that such an association is not confounded by other factors, like age and urine output. The significant correlations between sNaB and two markers of pre-dialysis fluid overload, that is 1st-h refill index and pre-HD DBP, although weaker, appear to have the same meaning. Based on a logistic regression model, both an sNaB ≤ 0.7 mEq/kg/day and an Na intake ≤ 1.5 mEq/kg/day were associated with a probability $< 10\%$ of IDWG $\geq 4\%$, which seems an acceptable target in pediatrics [4]. Although the study was not designed to provide recommendations for Na intake, this data could be of some help in clinical practice and in planning future studies on this topic. Interestingly, HD vintage was an independent predictor of IDWG in our cohort, although this finding needs to be confirmed in future trials and it is difficult to give it a full explanation. It might point out the risk of non-compliance in patients with longer dialysis duration.

The results of our study should be interpreted in the context of several limitations, first of all its cross-sectional design, as the effect of Na on BP could be not immediate and a longitudinal study could have been more sensitive in exploring the association between sNaB and BP. Notably, we calculated a partial Na balance, based only on intakes and urinary losses, without considering the losses of Na in sweat and feces: even if we excluded patients with known diseases causing pathologic extrarenal Na losses, this remains an important limitation. More importantly, we did not consider the dialytic Na losses, but we limited the analysis to the interdialytic interval. Although it is obvious that Na and fluid removal during dialysis is critical to keep total Na and fluid balance under control, an extensive amount of literature suggests that high ultrafiltration rate during treatment is associated not only with higher incidence of intradialytic events, but also with a higher risk of myocardial stunning and organ hypoperfusion, which makes it important to act on interdialytic factors in order to reduce the ultrafiltration needs. Moreover, a precise assessment of intradialytic Na kinetics is really challenging in daily clinical practice.

The assessment of eNa by diet diary can be unreliable, mainly due to the large variation in the Na content of processed foods and the difficulty in correctly quantifying the amount of salt added at the table or during cooking. Although we enrolled patients in stable clinical conditions only, the assumption that the 3-day diary was representative of the intake in the following 30 days is not necessarily correct. It should, however, be considered that “discretionary salt intake” accounts for a minor part of eNa in children, that diet diary is more accurate than other dietary assessment methods, and that it cannot be replaced by uNa, which is not an index of intake in CKD 5.

The small number of children on PD limits the possibility to extend to this modality what is found in patients receiving HD. The lack of information on mean 24-h BP is another significant limitation, as ABPM devices use the

Table 4 Best multiple regression model for percentage interdialytic weight gain in patients on hemodialysis

Predictors	Coefficients	SE	<i>t</i> value	<i>p</i> value
Sodium balance (mEq/kg/day)	0.63	0.20	3.09	0.005
Age (years)	0.14	0.07	2.02	0.054
Dialysis vintage (years)	0.31	0.15	2.15	0.042
Urine output (ml/kg/day)	0.18	0.07	2.38	0.025
Age:urine output	−0.02	0.006	−2.56	0.017
R^2/R^2 adjusted	0.738/0.686			
Model <i>p</i> value	0.000001			

Other variables included in the starting saturated model are dietary protein intake, serum albumin, and hemoglobin

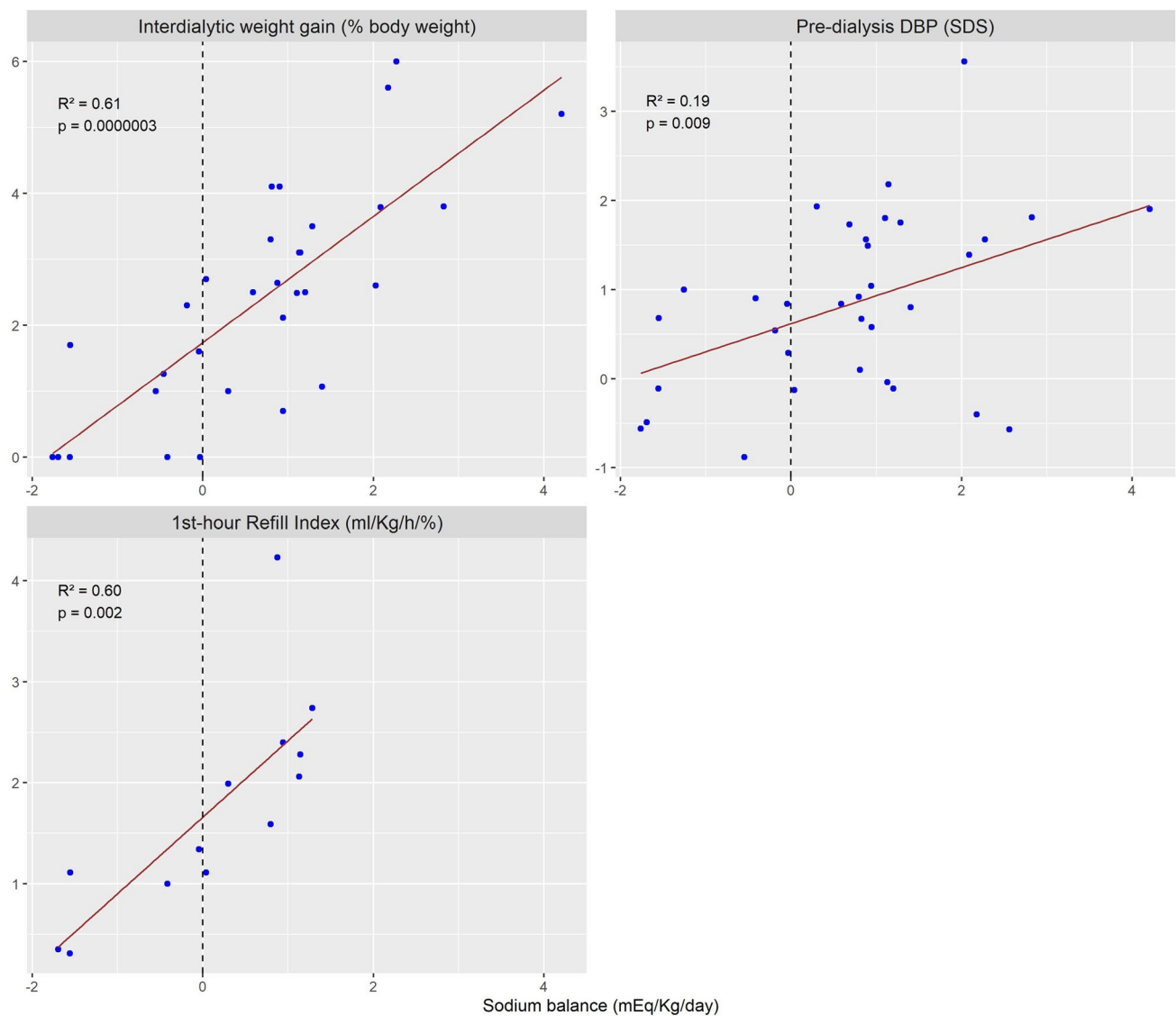


Fig. 3 Significant correlates of simplified sodium balance at simple linear regression analysis in patients on hemodialysis

oscillometric technique, with systolic and diastolic BP values being back-calculated from mean arterial pressure and not directly measured. The lack of data concerning actual fluid intake, the choice of assessing UO and uNa on a 24-h urine collection instead of a full interdialytic interval, and the bias potentially originating from the multicenter design, i.e., different modalities of dry weight assessment by the local clinicians and different maximum ultrafiltration rate prescriptions, should also be considered. Finally, a selection bias, with a lower participation of less compliant patients, cannot be excluded.

Notwithstanding these limitations, this is the first pediatric study investigating Na intake and losses in patients on dialysis. It maintains the value of a real-life trial, and it emphasizes the importance of a simplified but feasible

Na balance, based on Na intake and urinary losses, without the need for more complex measurements, usually not performed in daily clinical practice. The population size and the sound methodology, including 24-h ABPM and 24-h urine collection, are other major strengths.

In conclusion, our study provides the first data concerning Na intake and urinary losses in pediatric patients on maintenance dialysis. Given the low urinary losses, the median simplified Na balance is positive, despite a median Na intake lower than that in healthy children and children with CKD. Medications may be an important source of Na. Urine output is the best predictor of sNaB in the whole population, and simplified Na balance is a significant and independent predictor of IDWG in children on HD. Simplified Na balance is a relatively easy parameter to assess, which could be of

help in adjusting Na intake according to urinary losses, thus avoiding an excessive interdialytic Na load and reducing the intradialytic ultrafiltration needs. Further studies are needed to better explore the effect of Na on BP in this population.

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Author contribution R. S., I. Z., S. A. B., A. Z., A. J., S. C., M. R. G., L. M., A. S., and B. Y. contributed patients to the study. F. P. is the principal investigator. F. P., A. E., and S. C. designed the study. G. P. performed the statistical analyses. F. P., R. S., and A. E. drafted the paper. All authors read and approved the final manuscript.

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Data availability Data available on request.

Declarations

Conflict of interest The authors declare no competing interests.

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