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ORIGINAL ARTICLE

Association between pre hemodialysis serum sodium concentration and blood pressure: results from a retrospective analysis from the international monitoring dialysis outcomes (MONDO) initiative

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A recent study from the United Kingdom indicates an association between pre hemodialysis (HD) serum sodium (SNa^+) and systolic and diastolic blood pressure (SBP and DBP) in chronic HD patients. We extend this analysis to an international cohort of incident HD patients. The Monitoring Dialysis Outcomes initiative encompasses patients from 41 countries. Over 2 years monthly pre-HD SNa^+ levels were used as predictors of pre-HD SBP and DBP in a linear mixed model (LMM) adjusted for age, gender, interdialytic weight gain, diabetes, serum albumin and calcium. Similar models were constructed with DBP as outcome. Analyses were carried out stratified by continent (North and South America; Europe and Asia). LMMs were also constructed for the entire observation period of 2 years, and separately the first and the second year after HD initiation. We studied 17 050 incident patients and found SNa^+ to have a significant slope estimate in the LMM predicting pre-HD SBP and DBP (ranging from 0.22 to 0.29 and 0.10 to 0.21 mm Hg per $mEq\,l^{-1}$, respectively, between the continents). The findings were similar in subsets of SBP and SNa^+ tertiles, and separately analyzed for the first and second year. Our analysis shows an independent association between SNa, SBP and DBP in a large intercontinental database, indicating that this relation is a profound biological phenomenon in incident and prevalent HD patients, generalizable to an international level and independent of SBP and DBP magnitude.

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INTRODUCTION

'Hence if too much salt is used in food, the pulse hardens, tears make their appearance and the complexion changes.' is written in the 'Huangdi Neijing' (The Yellow Emperor's Classics of Internal Medicine), considered to be one of the first medical books, which was firstly mentioned in 111 AD. Often quoted since by researchers in the field of sodium research, this mentioning reflects how well established the association between sodium intake and blood pressure (BP) is. In current days, this association has been confirmed in various epidemiologic studies in the general population[1–3] and the pathophysiologic mechanisms of these associations are better understood. The classical theorem by Guyton suggests that short-term control of arterial BP is primarily a nervous function, whereas the long-term arterial pressure is principally a function of the fluid balance system.[4] Although this is in principle true, sodium has also been determined to affect the cardiovascular system in a fluid-independent manner. Not only does sodium intake (and subsequently higher serum sodium concentrations (SNa^+)) increase arterial stiffness and wall thickness, it also increases blood and pulse pressure[5] over a short observation period,[6] but also over a longer period of time.[7,8] Similar volume-independent effects on the endothelium and the vessel tone have also been reported for glucose.[9,10]

On an epidemiologic level, a recent publication by He *et al.*[11] showed that SNa^+ in 651 chronic hemodialysis (HD) patients was a significant predictor of systolic and diastolic BP (SBP, DBP), which remained true even after adjustment for several relevant parameters with possible effect on the levels of BP.

In the current analysis we extend the findings of He *et al.*[11] to incident and prevalent HD patients in an international database and hypothesize that SNa^+ will be a predictor of both SBP and DBP in incident and prevalent HD patients on an international level.

MATERIALS AND METHODS

The Monitoring Dialysis Outcomes initiative is a database initiated and developed by a consortium consisting of several key persons of international dialysis providers and academic institutions. At the time of writing of this manuscript the database has encompassed HD patients from ~~26~~ countries who started HD between 2000 and 2010.[12] Baseline characteristics of the included subjects have been published recently.[13] For this analysis data of incident patients who started HD between 1 January 2001 and 30 July 2008 was included. The data source were three databases from different continents (Renal Research Institute for North America, Fresenius Europe, Fresenius Asia-Pacific and Fresenius South America) and included patients were followed for an observation period of 12 months and a follow-up period of 6 further months. Database development and all

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Table 1. Demographics in all studied patients and stratified by continents at HD initiation

	All subjects	*North America*	*Asia*	*Europe*	*South America*
Subjects (count)	17 050	4106	1656	9562	1726
Treatments (count)	218 313	74 680	25 203	115 003	3427
Age (years)[a]	62.1 ± 14.7	60.3 ± 14.9	59 ± 13.6	64 ± 14.4	57.7 ± 16.5
Male gender (%)[b]	57	55.2	54.3	58.7	57.3
IDWG (% of post HD body weight)[c]	2.8 ± 1.3	3.2 ± 1	4.1 ± 1.7	2.5 ± 1.2	3 ± 2
Serum potassium (mEq l^{-1})[c]	4.8 ± 0.7	4.6 ± 0.6	4.8 ± 0.8	4.9 ± 0.7	4.7 ± 0.8
Serum albumin (g dl^{-1})[c]	3.8 ± 0.4	3.7 ± 0.4	3.9 ± 0.3	3.7 ± 0.5	3.8 ± 0.5
Diabetes (%)[c]	41.7	56	33.2	34.8	23.9
Serum calcium (mg dl^{-1})[c]	8.8 ± 0.7	8.9 ± 0.6	9.2 ± 0.8	8.7 ± 0.7	8.8 ± 0.7
Serum sodium (mEq l^{-1})[d]	137.8 ± 2.8	138.3 ± 2.4	137.9 ± 2.6	137.6 ± 2.9	136.4 ± 3.6
Dialysate sodium (mEq l^{-1})[c]	138.7 ± 3.2	140.0 ± 1.5	139.6 ± 0.8	138.7 ± 3.5	136.5 ± 5.0
Dialysate potassium (mEq l^{-1})	n/a	2.2 ± 0.4	n/a	2.2 ± 0.4	n/a
Dialysate calcium (mEq l^{-1})	n/a	2.5 ± 0.2	n/a	n/a	n/a
pre-HD SBP (mm Hg)[c]	142 ± 18.8	151.2 ± 18	141.5 ± 18	138.4 ± 17.6	132.2 ± 19.6
pre-HD DBP (mm Hg)[e]	74.5 ± 11	79.1 ± 10.8	77.6 ± 9.5	72.1 ± 10.4	72.6 ± 11
HD treatment time (mins)[a]	231 ± 29	212 ± 23	238 ± 12	235 ± 35	238 ± 13

Abbreviations: DBP, diastolic blood pressure; HD, hemodialysis; IDWG, interdialytic weight gain; SBP, systolic blood pressure. Analysis of Variance (ANOVA) adjusted for multiple comparisons (North America versus Asia, North America versus Europe, North America versus South America, Asia versus South America and Europe versus South America) was conducted. Categorical comparisons were conducted using χ^2-test. [a]Comparison significant for all comparison except for Asia versus South America. [b]Comparison significant for all comparison except for North America versus Asia, North America versus South America and Europe versus South America. [c]Comparison significant for all comparisons. [d]Comparison significant for all continents except for North America versus Europe and Europe versus Asia. [e]Comparison significant for all continents except for North America versus Asia and Europe versus South America.

subsequent analyses were conducted in compliance with local rules and regulations to protect data privacy and patients' rights.

Subset analyses

Analyses were carried out in the whole data set and after stratification by continent (North America, South America, Europe and Asia-Pacific). Furthermore analyses for all included regions were carried out for the entire observation period, the first year, and the second year to analyze the association for incident and prevalent patients separately.

To confirm our results the analyses were repeated in subsets of SNa^+ concentration tertiles of SNa^+ (Tertile 1: ⩽ 136.8 mEq l^{-1}, Tertile 2: 136.8 to 139.1 mEq l^{-1} and Tertile 3: ⩾ 139.2 mEq l^{-1}), of interdialytic weight gain (IDWG) (Tertile 1: ⩽ 2.26 mm Hg, Tertile 2: 2.27 to 3.28 mm Hg and Tertile 3: ⩾ 3.29% of postdialysis body weight), of SBP (Tertile 1: ⩽ 133.2 mm Hg, Tertile 2: 133.2–149.4 mm Hg and Tertile 3: ⩾ 149.4 mm Hg) and of DBP (Tertile 1: ⩽ 70.0 mm Hg, Tertile 2: 70.0 to 79.0 mm Hg and Tertile 3: ⩾ 79 mm Hg).

Sensitivity analysis

Because glucose levels affect both SNa^+ concentration and may have direct vasoactive effects,[9,10] we have conducted a sensitivity analysis in patients whose glucose levels were available. This was the case only in HD patients from North America. We have developed a separate linear mixed model (LMM) including serum glucose concentration into the initial model as an additional fixed effect.

Statistical analysis

Continuous data are reported as mean ± s.d. and categorical data as fractions of the analyzed population. Monthly pre-HD SNa^+ levels were used as fixed effects of pre-HD SBP and DBP prediction in a LMM with either random intercepts or random intercepts and random slopes, as determined by Likelihood Ratio Test with two degrees of freedom for LMM comparison. According to the parameters included in the analyses of He *et al.*[11] all LMMs were constructed including age, gender, IDWG (in % of post HD body weight), diabetes, serum albumin, potassium and calcium as fixed effects. Similar models were constructed with DBP as the dependent variable. All analyses were repeated in the subsets outlined above. A *P*-value below 0.05 was considered significant. Analyses were conducted with R version 3.0.3 (codename 'Warm Puppy'; R Foundation for Statistical Computing; Vienna, Austria)[14] additionally using the packages *nlme*, *multcomp* and *plyr*.

RESULTS

Patient population

For the current analysis 218 313 HD treatments with available SNa^+ measurements of 17 050 incident HD patients were included, with 4106 from the Renal Research Institute database, 1656 from Asia, 9562 from Europe and 1726 from South America (Table 1). It is of note that there were differences in the reported parameters between the continents (Table 1). Histograms of SBP, DBP and SNa^+ are shown in Supplementary Figures 1 and 2. Figure 1 shows SBP, DBP, SNa^+ and IDWG over the course of the observation period.

SNa^+ concentration as a predictor of BP

Comparison of LMM with (a) random intercept and (b) with random intercept and slope using a likelihood ratio test showed the random slope to be significant and the slope was thus included in the models. Based on the results of the developed models it appears that there is a significant increase of pre-HD SBP and DBP with increasing SNa^+ based on the data of the entire 24-month observation period. Estimates of the SNa^+ slopes in the LMM predicting SBP and DBP are shown in Table 2. The estimate of the slope in the entire population implies that for example in North America with every mEq l^{-1} SNa^+ increase there was an increase of 0.22 mm Hg for SBP and 0.10 mm Hg for DBP. Slope estimates of SNa^+ for the other analyzed continents are shown in Table 2. The association between SNa^+ and BP remained consistent for the LMM developed with DBP as the dependent variable. Full models are shown in Supplementary Tables 1 and 2.

Subset analyses

Analysis in tertiles of pre-HD SBP and DBP, respectively, showed a comparable magnitude of the slope estimates for SNa^+ included as fixed effects in the model in all three tertiles of SBP and DBP, respectively (Figure 2; Supplementary Table 3). Repetition of the analysis in tertiles of pre-HD SNa^+ and IDWG also showed comparable slope estimates for pre-HD SNa^+ included as a fixed effect in the prediction of pre-HD SBP (Figures 3 and 4, Supplementary Tables 4 and 5) and DBP (data not shown), both of which increased with an increasing range of SNa^+. The estimation of the slope for SNa^+ showed an increasing trend

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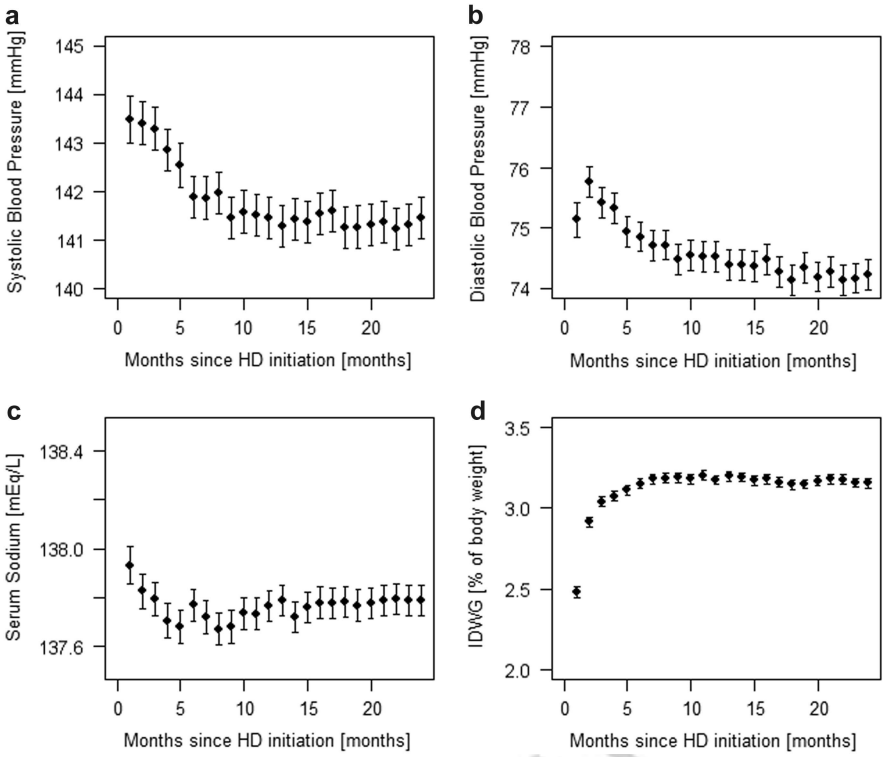

Figure 1. Average values (95% CI indicated) of (**a**) systolic and (**b**) diastolic blood pressure, (**c**) serum sodium and (**d**) interdialytic weight gain for every month during the course of the observation period of 24 months.

Table 2. Slope estimate of serum sodium in a Linear Mixed Effects Model predicting pre HD (a) SBP and (b) DBP over the entire observation period (24 months), based on sodium concentrations and other parameters of relevance

Continent	*SNa^+ slope estimate for Pre HD SBP (mm Hg change per m Eq l^{-1} change)*	*SNa^+ slope estimate for Pre HD DBP (mm Hg change per mEq l^{-1} change)*
All subjects[a]	0.22 (0.19–0.25)	0.09 (0.08–0.11)
NorthAmerica[b]	0.22 (0.17–0.28)	0.1 (0.07–0.13)
Asia[b]	0.29 (0.17–0.41)	0.13 (0.06–0.19)
Europe[b]	0.19 (0.15–0.22)	0.07 (0.05–0.09)
South America[c]	0.25 (0.05–0.45)	0.21 (0.11–0.32)

Abbreviations: DBP, diastolic blood pressure; HD, hemodialysis; SBP, systolic blood pressure; SNa^+, serum sodium. Additional fixed effects in the model were interdialytic weight gain, age at hemodialysis initiation, male gender, serum potassium, serum albumin, diabetes serum calcium and hemodialysis vintage. [a]Includes continents with longitudinal data available (that is, North America, Asia and Europe). In South America only cross-sectional data were available. [b]$P < 0.05$ (comparison of individual slope estimates between North America, Asia and Europe, using analysis of variance). [c]Estimates of a linear model constructed based on cross-sectional data.

with an increasing range of SNa^+ for the prediction of SBP and DBP (Figure 4 and Supplementary Table 4).

Furthermore analyses of the study population stratified into incident and prevalent HD patients in Year 1 and Year 2, respectively, showed virtually identical results (Table 3, Supplementary Table 2a and 2b).

Sensitivity analysis

Inclusion of the serum glucose concentration as an additional fixed effect showed glucose to have a significant slope estimate for pre-HD SBP and DBP (Table 4a and b) and the association between SNa^+ and BP consistent irrespective of the inclusion of serum glucose in the model. Its inclusion also accentuated the effect of SNa^+ on SBP (0.69 (95% confidence interval 0.6–0.78) mm Hg per mEq l^{-1} SNa^+ change) and DBP (0.29 (95% confidence interval 0.24–0.34) mm Hg per mEq l^{-1} SNa^+ change; Table 4a and b) as reflected by the slope estimates in comparison with the initial model (Table 2 and Supplementary Table 2).

DISCUSSION

Statement of principal findings

This longitudinal 2-year study in patients with end-stage renal disease treated with HD indicates that there exists an association between SNa^+ and SBP measured before the actual HD treatment. These associations were found to be independent of relevant covariates (age, gender, IDWG, diabetes, serum albumin, potassium and calcium). In addition, we confirmed the association in analyses conducted in different continents, which, in our opinion, renders this association a pathophysiologic finding somewhat independent of race, ethnicity, laboratory techniques or treatment practices in the respective continents. Furthermore, the analyses were repeated for the periods from HD initiation to Month 12 and for the period from Month 13–24, which is consistent with analyses in incident and prevalent patients. Subset analyses in tertiles of SBP and DBP confirmed the association independent of the magnitude of these potentially relevant parameters and was significant at all studied ranges of SBP and DBP. The analysis in tertiles of SNa^+ showed a clearly increasing slope estimate at higher SNa^+ levels. A sensitivity analysis in patients from North America with serum glucose levels available in the medical records showed that the association between SNa^+ and BP was also independent of serum glucose concentrations.

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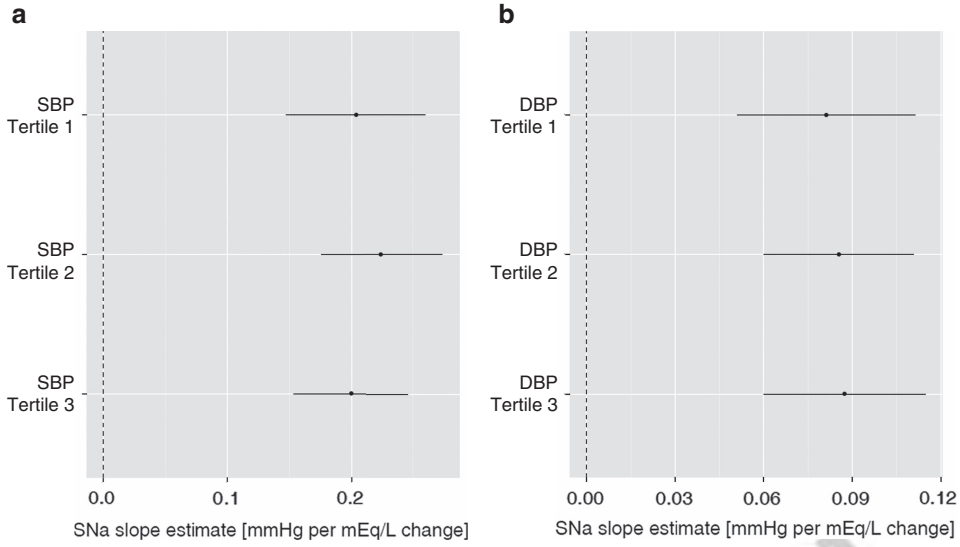

Figure 2. Forest Plot of the slope estimate of serum sodium (SNa^+) in a Linear Mixed Model predicting pre hemodialysis (HD) systolic blood pressure (SBP) after stratification into tertiles of (**a**) SBP and (**b**) DBP. Additional fixed effects in the model were interdialytic weight gain, age at hemodialysis initiation, male gender, serum potassium, serum albumin, diabetes, serum calcium and hemodialysis vintage.

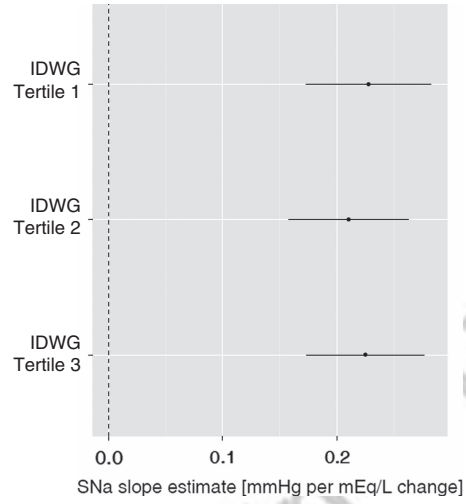

Figure 3. Forest Plot of the slope estimate of serum sodium (SNa^+) in a Linear Mixed Model predicting pre hemodialysis (HD) systolic blood pressure (SBP) after stratification into tertiles of IDWG. Additional fixed effects in the model were interdialytic weight gain, age at hemodialysis initiation, male gender, serum potassium, serum albumin, diabetes, serum calcium and hemodialysis vintage.

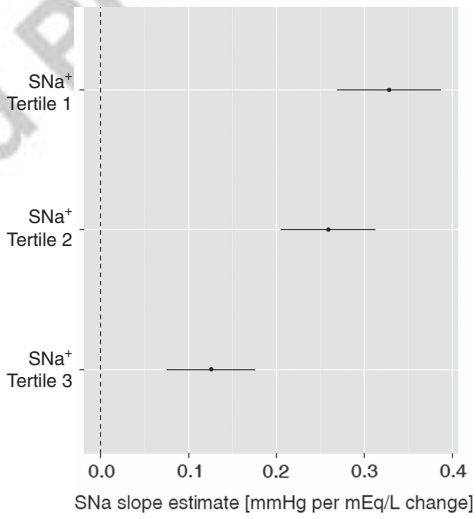

Figure 4. Forest Plot of the slope estimate of serum sodium (SNa^+) in a Linear Mixed Model predicting pre hemodialysis (HD) systolic blood pressure (SBP) after stratification into tertiles of SNa^+. Additional fixed effects in the model were interdialytic weight gain, age at hemodialysis initiation, male gender, serum potassium, serum albumin, diabetes, serum calcium and hemodialysis vintage.

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Comparison with other studies

Our study corroborates the findings by He *et al.*, who were the first to report a positive association between SNa^+ levels and SBP in HD patients. Notably, we found a smaller effect size, but a nevertheless consistent association in a substantially larger sample size as compared with He's double-center study in the United Kingdom (651 prevalent HD patients over 7445 observations).[11] The current data carries these previous findings a step further by choosing incident and prevalent patients as subsets. To allow this analysis, patients' data were stratified into months 0–12 (incident patients) and months 13–24 (prevalent patients) and the results showed a consistent association between SNa^+ and BP independent of HD vintage (Table 3). Furthermore, we extended the findings to several continents and were able to establish this association in four different continents. We also conducted subset analyses in tertiles of SNa^+, SBP and DBP, which confirm that the magnitude of these parameters, which may be considered to have ~~potential~~ influence~~s~~ on the association between SNa^+ and BP. It is of note that, despite significant difference in the slope estimates, an effect size comparable between continents and all analyzed subsets was found in the constructed models. A difference in the effect size between the model constructed by He *et al.* (0.65 (95% confidence interval 0.46–0.84) mm Hg SBP per mEq l^{-1} SNa^+ change and 0.36 (95% confidence interval 0.25–0.46) mm Hg DBP per mEq l^{-1} SNa^+ change, respectively, per mEq l^{-1} SNa^+) may be noted in comparison with our models (Table 2). The reasons for these differences are not clear and remain speculative at this point. Interestingly, inclusion of serum glucose increased the slope estimate of SNa^+ as a fixed effect to a magnitude comparable to

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Table 3. Slope estimate of serum sodium in a Linear Mixed Effects Model predicting pre HD systolic SBP over (a) the first and (b) the second year of the observation period of 24 months, based on sodium concentrations and other parameters of relevance

Continent	*SNa^+ slope estimate for Pre HD SBP (mm Hg change per mEq l^{-1} change) Year 1*	*SNa^+ slope estimate for Pre HD SBP (mm Hg change per mEq l^{-1} change) Year 2*
All continents[a]	0.22 (0.19–0.25)	0.2 (0.16–0.24)
North America[b]	0.24 (0.17–0.32)	0.2 (0.16–0.24)
Asia[b]	0.15 (−0.04–0.33)	0.19 (0.12–0.26)
Europe[b]	0.15 (0.11–0.2)	0.3 (0.14–0.46)
South America[c]	0.33 (0.04–0.62)	0.14 (0.09–0.18)

Abbreviations: DBP, diastolic blood pressure; HD, hemodialysis; SBP, systolic blood pressure; SNa^+, serum sodium. Additional fixed effects in the model were interdialytic weight gain, age at hemodialysis initiation, male gender, serum potassium, serum albumin, diabetes serum calcium and hemodialysis vintage. [a]Includes continents with longitudinal data available (that is, North America, Asia and Europe). In South America only cross-sectional data were available. [b]$P < 0.05$ (comparison of individual slope estimates between North America, Asia and Europe, using analysis of variance). [c]Estimates of a linear model constructed based on cross-sectional data.

Table 4. Slope estimate of serum sodium in a Linear Mixed Effects Model predicting pre HD systolic blood pressure over the entire observation period (24 months), based on sodium concentrations and other parameters of relevance (including serum glucose as a sensitivity analysis)

	North America
Pre HD systolic blood pressure	
Intercept	**26.24 (12.28–40.21)**
Serum sodium (mEq l^{-1})	**0.69 (0.6–0.78)**
IDWG as percent of post-dialytic body weight (%)	**0.42 (0.28–0.56)**
Age at HD initiation (years)	**−0.17 (−0.21 to −0.12)**
Male gender (yes)	**−3.39 (−4.74 to −2.03)**
Serum glucose (mg dl^{-1})	**0.02 (0.02–0.03)**
Serum potassium (mEq l^{-1})	**0.77 (0.39–1.15)**
Serum albumin (g dl^{-1})	**2.89 (2.06–3.72)**
Diabetes (yes)	**4.56 (3.18–5.94)**
Calcium (mg dl^{-1})	**2.12 (1.74–2.5)**
Dialysis vintage (months)	−0.05 (−0.1–0)
Pre HD diastolic blood pressure	
Intercept	**42.95 (34.86–51.04)**
Serum sodium (mEq l^{-1})	**0.29 (0.24–0.34)**
IDWG as percent of post-dialytic body weight (%)	**0.14 (0.05–0.22)**
Age at HD initiation (years)	**−0.38 (−0.4 to −0.35)**
Male gender (yes)	**1.47 (0.75–2.19)**
Serum glucose (mg dl^{-1})	**0.01 (0–0.01)**
Serum potassium (mEq l^{-1})	**0.46 (0.24–0.68)**
Serum albumin (g dl^{-1})	**1.36 (0.88–1.83)**
Diabetes (yes)	−0.14 (−0.87–0.58)
Calcium (mg dl^{-1})	**0.99 (0.76–1.21)**
Dialysis vintage (months)	**−0.06 (−0.09 to −0.03)**

Abbreviations: HD, hemodialysis; IDWG, interdialytic weight gain.

the results reported by He *et al.* (0.69 mm Hg in our model; 0.65 mm Hg reported by He *et al.*).[11] Although the exact reasons remain unclear because of the lack of specific information in this retrospective analysis, it is known that glucose affects vascular tone via the generation of vasoconstricting prostaglandins,[15] an attenuation of endothelin-1 effects[10] or insulin-mediated glucose uptake affecting cellular calcium influx. To what extent this explains the current findings remains to be elucidated.

It is intriguing to speculate that our findings may be related to the clinical phenotype of salt sensitivity in the general population. In brief, salt sensitivity describes the presence of BP following an increase in salt intake[16–18] and vice versa. To the best of our knowledge there is no data indicating elevated SNa^+ levels in salt-sensitive subjects, in particular, Skrabal *et al.*[18] reported no difference in SNa^+ between salt-sensitive and salt-resistant subjects. It is interesting to note through, that acute salt loading in the form of a soup in 15 healthy subjects resulted in an increase of both SNa^+ and SBP,[6] supporting a link between SNa^+ and BP. Although the authors did not perform a formal test (for example, by giving a high-salt diet over an extended period) to what extent the subjects were salt sensitive, this finding is intriguing and deserves further investigation, including healthy subjects and patients at various stages of chronic kidney disease. However, it is important to appreciate that sodium excretion is compromised in chronic kidney disease.

Most remarkably, all our results were consistent across all continents (Table 2a and b), equally for incident and prevalent patients (Supplementary Table 1) and also in the subset analyses (Figure 2; Supplementary Tables 2 and 3). Furthermore, we believe that the adjustment for IDWG in the models accounts to some extent for the effects of intradialytic sodium loading and the ensuing thirst. Keen and Gotch[19] have shown that dialysate sodium concentration (DNa^+) does not affect SNa^+. Hecking *et al.*[20] have recently shown that subjects treated in dialysis facilities with higher DNa^+ prescription present with higher IDWG and predialysis SBP, whereas SNa^+ levels did not differ between the three pre-defined DNa^+ groups. Of note, higher DNa^+ prescriptions would result in more positive DNa^+ to SNa^+ gradients and thus diffusive intradialytic sodium transfer into the patient. Taken together, these findings corroborate the concept that intradialytic sodium loading results in a transient increase in SNa^+, which results in thirst and subsequent postdialysis water intake, which causes the SNa^+ to return back to predialysis levels.[19] Thus, we believe that inclusion of IDWG should sufficiently address this effect on BP.

Overall, these data support direct vasoactive effects of circulating SNa^+ on the endothelium. The exact reasons for these dynamics may only be speculated, however, work by Oberleithner *et al.*[21–25] suggested direct effects of circulating SNa^+ on endothelial cells in the presence of aldosterone, resulting in cell swelling and cell stiffening and strongly affecting the deformability and elasticity of endothelial cells. Although many aspects are yet unclear, it was shown that increases in extracellular sodium concentration lead to derangement of the endothelial glycocalyx, a negatively charged biopolymer surface layer (known to also act as a sodium buffer), and to an increased abundance of sodium channels on the endothelial membrane.[25] Normal endothelial function underlies the control of the release of nitric oxide,[26] which acts as a vasodilator and the presence of sodium channels and entry of sodium into the extracellular space was shown to influence nitric oxide synthase activity and nitric oxide production.[27,28] This in agreement with further data that showed a relationship between nitric oxide and BP during salt loading and restriction, respectively, and an increase in asymmetric dimethyl-arginine, which is an inhibitor of nitric oxide production, during periods of higher salt intake[29]

Implications of this research

The association is of pathophysiologic importance as it sheds further light on the complex relation between sodium, fluid overload and BP in dialysis patients. It also shows, for the first time, this relation at a global level in a large-scale database.

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The clinical importance of the results of this study might be addressed by interventional study of HD treatment, such as the dialysate prescription, as well as study of antihypertensive agents, which might influence this association, with due regard to the analyses conducted by He *et al.*[11] in subsets with and without a prescription of antihypertensive. The estimate of the effect size in the longitudinal analysis conducted by these authors was comparable between both groups, thus the effects of sodium may possibly be of importance in BP management.

We would like to emphasize that a close observation of SNa^+ is also of importance given the direct effects of SNa^+ on cardiovascular structures. Previously published findings of left atrial enlargement associated with SNa^+ levels independent of BP levels in chronic kidney disease patients were explained by the pro-fibrotic effects of sodium and a proliferative effect on myocardial tissue.[30] The well-established association (independent of BP) between left ventricular mass, salt intake and urinary sodium excretion, in the general and the chronic kidney disease population, has been proposed to be caused by direct effects on cardiomyocytes, modulation of the neurohumoral system and effects of the intravascular volume state.[31,32]

Strengths and weaknesses

A great strength of the current analysis is the large sample size, the long observation period of 24 months for each patient and we infer generalizability from high numbers of patients from international HD populations. The long observation period particularly allows separate analyses in incident and prevalent patients, and the separate confirmation of findings in explicit analyses of data from different continents strengthen the conclusions drawn from our data. Limitations mainly comprise, as all retrospective analyses, a possible lack of documentation for some parameters (particularly an objective assessment of volume status, which may have also affected BP) and the unavoidable probability of documentation errors. Information on comorbidities, residual renal function and volume status may also be of additional interest, but have also not been available for the current analysis. Of note, it is important to appreciate that IDWG is at best a poor indicator of volume status.[33]

Because of unavailable documentation of oral drugs, we were not able to conduct any analyses of antihypertensive medication effects. This limits the comparability of the current study to the previous work.[11] He *et al.* identified an association between SNa^+ and BP, which was modified by the use of antihypertensive drugs. Including antihypertensive drug use in their analysis reduced the slope estimates of the SNa^+ to SBP association from 0.82 to 0.65 mm Hg per mmol SNa^+. Based on this observation it is conceivable that also in our population the magnitude of the SNa^+ to SBP relations would be weakened by the inclusion of antihypertensive medication. Although the observational nature of He's and our data precludes statements about causality, we speculate that mitigation of the SBP to SNa^+ slope by the use of antihypertensive drugs is likely to be related to a more pronounced BP-lowering efficacy in patients with higher BP and not to their effect on SNa^+.

CONCLUSIONS

In summary our data (in concert with previous data) suggest that many factors such as SNa^+ affect BP. In summary the data of this study suggest that the longitudinal observation of SNa^+ and its dynamics over time do provide information gain and may be helpful to aid diagnosis and disease management strategies. Future research on the exact pathophysiologic mechanisms is needed whether this association could also be a therapeutic target.

What is known about the topic?

- Several vasoactive effects of sodium, either direct or indirect, have been reported over the last decades.
- Evidence suggests that these mechanisms are also effective in dialysis patients relating the pre hemodialysis serum sodium concentration to blood pressure in a single-center study from the United Kingdom.
- In the light of current evidence that serum sodium concentrations and their dynamics in longitudinal observations (variability and systematic trends) are of substantial importance in the prediction of outcomes the association, a more detailed understanding of this association is necessary, however, consequences of this association on outcomes and on blood pressure management remain speculative.

What this study adds?

- In the light of the study from the United Kingdom, which analyzed data of patients from one dialysis network, the association appears confirmed; however, the current study provides evidence of the association between serum sodium and blood pressure in a data set of substantially larger sample size in patients commencing treatment in four different continents, thus substantially increases statistical robustness.
- The numerous subset and sensitivity analyses we have conducted add to the currently available evidence by confirming the association to be present in different settings.
- Analysis of data from patients commencing in different continents and dialysis provider networks does increase the generalizability of the association between serum sodium concentration and blood pressure, and does, in particularly, render the finding independent from dialysis treatment and local blood pressure management practices.

CONFLICT OF INTEREST

Drs Bernard Canaud, Peter Kotanko and Nathan W Levin hold stock in Fresenius Medical Care. The remaining authors declare no conflict of interest.

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REFERENCES

1 Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. *BMJ* 1988; **297**(6644): 319–328.
2 Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM *et al.* A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997; **336**(16): 1117–1124.
3 Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D *et al.* Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med* 2001; **344**(1): 3–10.
4 Guyton AC, Hall JE. *Textbook of Medical Physiology* 11th edn. Elsevier Saunders: Philadelphia, PA, USA, 2006.
5 du Cailar G, Mimran A, Fesler P, Ribstein J, Blacher J, Safar ME. Dietary sodium and pulse pressure in normotensive and essential hypertensive subjects. *J Hypertens* 2004; **22**(4): 697–703.
6 Suckling RJ, He FJ, Markandu ND, MacGregor GA. Dietary salt influences postprandial plasma sodium concentration and systolic blood pressure. *Kidney Int* 2012; **81**(4): 407–411.
7 Komiya I, Yamada T, Takasu N, Asawa T, Akamine H, Yagi N *et al.* An abnormal sodium metabolism in Japanese patients with essential hypertension, judged by serum sodium distribution, renal function and the renin-aldosterone system. *J Hypertens* 1997; **15**(1): 65–72.
8 Wannamethee G, Whincup PH, Shaper AG, Lever AF. Serum sodium concentration and risk of stroke in middle-aged males. *J Hypertens* 1994; **12**(8): 971–979.
9 DeVan AE, Eskurza I, Pierce GL, Walker AE, Jablonski KL, Kaplon RE *et al.* Regular aerobic exercise protects against impaired fasting plasma glucose-associated vascular endothelial dysfunction with aging. *Clin Sci* 2013; **124**(5): 325–331.

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10 Diehl KJ, Templeton DL, Ma J, Weil BR, Greiner JJ, Stauffer BL *et al.* Impaired fasting blood glucose is associated with increased endothelin-1 vasoconstrictor tone. *Atherosclerosis* 2013; **229**(1): 130–133.
11 He FJ, Fan S, Macgregor GA, Yaqoob MM. Plasma sodium and blood pressure in individuals on haemodialysis. *J Hum Hypertens* 2013; **27**(2): 85–89.
12 Usvyat LA, Haviv YS, Etter M, Kooman J, Marcelli D, Marelli C *et al.* The MONitoring Dialysis Outcomes (MONDO) initiative. *Blood Purif* 2013; **35**(1-3): 37–48.
13 von Gersdorff GD, Usvyat L, Marcelli D, Grassmann A, Marelli C, Etter M *et al.* Monitoring Dialysis Outcomes across the World - The MONDO Global Database Consortium. *Blood Purif* 2013; **36**(3-4): 165–172.
14 R Development Core Team. *R: A Language and Environment for Statistical Computing*, In: R Foundation for Statistical Computing: Vienna, Austria, 2010.
15 Tesfamariam B, Brown ML, Deykin D, Cohen RA. Elevated glucose promotes generation of endothelium-derived vasoconstrictor prostanoids in rabbit aorta. *J Clin Invest* 1990; **85**(3): 929–932.
16 Luft FC, Weinberger MH, Grim CE. Sodium sensitivity and resistance in normotensive humans. *Am J Med* 1982; **72**(5): 726–736.
17 Rankin LI, Luft FC, Henry DP, Gibbs PS, Weinberger MH. Sodium intake alters the effects of norepinephrine on blood pressure. *Hypertension* 1981; **3**(6): 650–656.
18 Skrabal F, Herholz H, Neumayr M, Hamberger L, Ledochowski M, Sporer H *et al.* Salt sensitivity in humans is linked to enhanced sympathetic responsiveness and to enhanced proximal tubular reabsorption. *Hypertension* 1984; **6**(2 Pt 1): 152–158.
19 Keen ML, Gotch FA. The association of the sodium "setpoint" to interdialytic weight gain and blood pressure in hemodialysis patients. *Int J Artif Org* 2007; **30** (11): 971–979.
20 Hecking M, Karaboyas A, Rayner H, Saran R, Sen A, Inaba M *et al.* Dialysate sodium prescription and blood pressure in hemodialysis patients. *Am J Hypertens* 2014; **27**(9): 1160–1169.
21 Oberleithner H, Ludwig T, Riethmuller C, Hillebrand U, Albermann L, Schafer C *et al.* Human endothelium: target for aldosterone. *Hypertension* 2004; **43**(5): 952–956.
22 Oberleithner H, Riethmuller C, Ludwig T, Hausberg M, Schillers H. Aldosterone remodels human endothelium. *Acta Physiol* 2006; **187**(1-2): 305–312.
23 Oberleithner H, Riethmuller C, Ludwig T, Shahin V, Stock C, Schwab A *et al.* Differential action of steroid hormones on human endothelium. *J Cell Sci* 2006; **119**(Pt 9): 1926–1932.
24 Oberleithner H, Riethmuller C, Schillers H, MacGregor GA, de Wardener HE, Hausberg M. Plasma sodium stiffens vascular endothelium and reduces nitric oxide release. *Proc Natl Acad Sci USA* 2007; **104**(41): 16281–16286.
25 Warnock DG, Kusche-Vihrog K, Tarjus A, Sheng S, Oberleithner H, Kleyman TR *et al.* Blood pressure and amiloride-sensitive sodium channels in vascular and renal cells. *Nat Rev Nephrol* 2014; **10**(3): 146–157.
26 Fleming I, Busse R. Molecular mechanisms involved in the regulation of the endothelial nitric oxide synthase. *Am J Physiol Regul Integr Comp Physiol* 2003; **284**(1): R1–12.
27 Li J, White J, Guo L, Zhao X, Wang J, Smart EJ *et al.* Salt inactivates endothelial nitric oxide synthase in endothelial cells. *J Nutr* 2009; **139**(3): 447–451.
28 Perez FR, Venegas F, Gonzalez M, Andres S, Vallejos C, Riquelme G *et al.* Endothelial epithelial sodium channel inhibition activates endothelial nitric oxide synthase via phosphoinositide 3-kinase/Akt in small-diameter mesenteric arteries. *Hypertension* 2009; **53**(6): 1000–1007.
29 Fujiwara N, Osanai T, Kamada T, Katoh T, Takahashi K, Okumura K. Study on the relationship between plasma nitrite and nitrate level and salt sensitivity in human hypertension: modulation of nitric oxide synthesis by salt intake. *Circulation* 2000; **101**(8): 856–861.
30 Yee-Moon Wang A, Lu Y, Cheung S, Hiu-Shuen Chan I, Wai-Kei Lam C. Plasma sodium and subclinical left atrial enlargement in chronic kidney disease. *Nephrol Dial Transplant* 2013; **28**(9): 2319–2328.
31 Du Cailar G, Ribstein J, Daures JP, Mimran A. Sodium and left ventricular mass in untreated hypertensive and normotensive subjects. *Am J Physiol* 1992; **263**(1 Pt 2): H177–H181.
32 Kupari M, Koskinen P, Virolainen J. Correlates of left ventricular mass in a population sample aged 36 to 37 years. Focus on lifestyle and salt intake. *Circulation* 1994; **89**(3): 1041–1050.
33 Hecking M, Karaboyas A, Antlanger M, Saran R, Wizemann V, Chazot C *et al.* Significance of interdialytic weight gain versus chronic volume overload: consensus opinion. *Am J Nephrol* 2013; **38**(1): 78–90.

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