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Variation in Sodium Intake and Intra-Individual Change in Blood Pressure in Chronic Kidney Disease

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Abstract

Background—In the kidney disease clinic setting, higher-than-usual blood pressure is often ascribed to recent dietary sodium indiscretion. While clinical trials demonstrate a clear relationship between salt intake and blood pressure on the population level, it is uncertain whether real-world variation in sodium intake within individual CKD patients is associated with fluctuations in blood pressure.

Methods—We analyzed data from the Phosphorus Normalization Trial, in which participants with CKD eating their usual diets completed at least three 24-hour urine collections over 9 months, from which we measured sodium. Blood pressure was measured at the time of 24-hour urine collections. For each individual participant, we assessed the slope of the relationship between sodium intake and mean arterial blood pressure (MAP).

Results—Among 119 participants (mean age 67 and mean eGFR 31ml/min/1.73m^2), there was substantial variation in sodium intake as measured by 24-hour urine collections (mean intake 3903 mg/day, SD 1037 mg/day). Individual participants had highly variable associations between their sodium intake and their MAP; 47% (n=56) had inverse associations between sodium and MAP, whereas the remainder had positive (salt-sensitive) associations.

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Conclusions—Among CKD patients, there is substantial variation in sodium intake but no predictable relationship between dietary sodium and blood pressure in individuals. The frequent dismissal of elevated blood pressure readings as related to recent sodium intake in clinic may be a misapplication of large-scale population data to explain individual variability, and may contribute to clinical inertia not to change high blood pressure treatment.

Introduction

At the population level, higher dietary sodium intake is associated with higher blood pressure[1] and adverse renal outcomes[2] and hence the 2012 KDIGO (Kidney Disease Improving Global Outcomes) guidelines recommend sodium intake <87 mmol (<2g) per day in patients with CKD.[3] Further, marked reductions in dietary sodium intake from 250 mmol/day (5750 mg/day) to 50 mmol/day (1150 mg/day) over short periods of time in patients with CKD have demonstrated clinically relevant decreases in blood pressure (mean systolic blood pressure reduction of 10mm Hg).[4]

In clinical practice, higher-than-usual blood pressure readings are often ascribed to recent dietary sodium indiscretion by both physicians and patients. However, sodium intake in a group of CKD participants outside the trial setting is virtually always higher than the 1150 mg/d prescribed in a clinical trial, and usually higher than the 2000mg/d suggested by KDIGO. Moreover, the magnitude of the real-world, day-to-day variation in sodium intake is very unlikely to be as extreme as the magnitude achieved in the research setting. Thus, the generalizability of these population-based data to individuals with less extreme variation in sodium intake is unknown; to our knowledge, there is no evidence that real-world day-to-day variation in dietary sodium intake is positively associated with blood pressure in individuals with CKD.

To that end, we evaluated repeated 24-hour urine sodium and blood pressure measurements over 9 months among individuals with stage 3–4 CKD to examine whether, on the individual level, higher sodium intake was associated with higher blood pressure.

Methods

We included participants from the Phosphorus Normalization Trial, a randomized controlled trial conducted in 2009–2010 designed to test the effect of phosphate binders on serum phosphate levels.[5] Trial eligibility required a baseline eGFR between 20 and 45 ml/min/1.73 m^2, a serum phosphate level between 3.6 and 6.0 mg/dl, and a willingness to avoid intentional changes in diet. No recommendations regarding sodium intake were provided through the study protocol. Study participants were evaluated in clinic 7 times over a 9-month study period. At multiple visits, participants were asked to provide 24-hour urine samples, and their blood pressure was measured twice per visit. The average of the 2 blood pressure measurements were used in data analysis. A maximum of four 24-hour urine samples were collected from each patient, and urine sodium (Na) and creatinine (Cr) were measured (Litholink Corp [Chicago, IL]). We used measured body weight and height to calculate BMI. Estimated GFR was calculated using the Modification of Diet in Renal Disease (MDRD) equation.

As our focus was on intra-individual variability in sodium intake, we excluded 29 trial participants with 2 or fewer 24-hour urine samples resulting in an analytic sample of 119 participants. Among these, 18 provided three and 111 provided four 24-hour urine collections during the 9-month study. To minimize bias from over- or under-collected 24-hour urine samples, we normalized each 24-hour urine sodium measurement to the participant's creatinine excretion by calculating urine sodium/creatinine ratios (UNa/Cr). This minimizes over- or under-collection bias by taking advantage of the likelihood that muscle mass, and hence creatinine production, remained stable in any given individual over the 9-month study.

Using these values, we plotted sodium intake (as UNa/Cr) versus MAP for each of the 119 individual participants. We then calculated the slope of the relationship between blood pressure and sodium intake for each participant, reported as the difference in blood pressure (in mmHg) for each unit difference in UNa/Cr. Thus, a positive slope for any given individual would suggest that higher sodium intake was associated with higher blood pressure. Mean arterial pressure (MAP) served as the primary measure of blood pressure and systolic blood pressure (SBP) was used as a secondary analysis. We examined the distribution of these slopes, and examined clinical characteristics associated with positive ("salt-sensitive") vs negative slopes. All analyses were conducted using SAS version 9.0. Institutional review board approval for the parent study was obtained by G.A.B. and colleagues at Denver Nephrology.

Results

The mean ± SD for participant age was 66.9 ± 11.2 years, 51% were female, and mean eGFR was 31 ± 8 ml/min/1.73m^2. Diuretics were used by 66% of participants; 50% used ACE inhibitors, 29% used ARBs, and 6% used both. The number of anti-hypertensive medications used was 1.8 ± 0.9. Mean 24-hour urine sodium excretion at baseline was 3,903 mg/day and the mean within-individual standard deviation of 24-hour urine sodium excretion was 1037 mg/day. The mean ± SD for MAP at baseline was 87.8 ± 11.1 mmHg, and the mean within-individual standard deviation of MAP over the 9 months was 6.5 mmHg.

In the 119 participants, the relationship of urine UNa/Cr with MAP was highly variable. Figure 1 shows the relationship between UNa/Cr and mean arterial pressure in each participant, and the average slope is shown in red. Of the participants, 47% (n=56) had negative slopes between UNa/Cr and MAP, whereas the remainder had positive slopes. Across the study population, the slope had a median of 0.26 and interquartile range of (−2.8, 4.7) mmHg per unit change in UNa/Cr. Results were similar when we evaluated SBP (data not shown).

We divided participants into those with positive and negative slopes to determine if clinical factors might help identify those that were apparently more likely to have higher blood pressure with higher sodium intake (i.e., salt sensitive). We found no difference in age, race, gender or CKD severity between those with positive vs. negative slopes (Table 1). Results were the same for SBP (data not shown).

Conclusions

In our analytic sample of individuals with stage 3–4 CKD eating their usual dietary intake, there was high overall sodium intake, and substantial variation in sodium intake within individuals, but no consistent relationship between dietary sodium intake and blood pressure within individuals; nearly half of all participants did not exhibit a slope consistent with salt sensitivity.

Our findings in patients with real-world dietary intake stand in contrast to those of controlled trials where marked reductions in dietary sodium intake lead to ~10mmHg decreases in blood pressure in patients with CKD. Our findings suggest that the more modest variation we observed in sodium intake -- around a high mean intake of nearly 4000 mg of sodium intake per day -- is not a major determinant of blood pressure at the individual clinic visit in these CKD patients.

There are several reasons why this finding may be different from that in clinical trials. First, because of the high average salt intake in this study, there were almost no collections with sodium intake at the level required in clinical trials to demonstrate a lowering of blood pressure; although there was substantial intra-individual variation in sodium intake, few participants had sodium intake even close to the current recommended intake for individuals with CKD. Our observation of sodium intake fluctuation in this study may be more relevant to CKD patients treated in the clinic setting than to that of clinical trials, which test doses consistent with guidelines. Second, we used urinary sodium as a proxy for intake, whereas trials use prescribed diets; although this might affect the precision of the sodium intake estimates, it ought not affect the relationship between sodium variability and blood pressure variability. We acknowledge that new data on a ‘third compartment’ for sodium storage in skin does introduce a level of previously unrecognized de-coupling between intake and 24-hour output, so that 24-hour urine sodium may not be as good a proxy as previously thought. Indeed, Titze and colleagues suggest that in careful experiments in Mars travel simulation participants, the sodium excretion-blood-pressure relationship cycled independent of intake on a seven-day rhythm.[6] If anything, this data supports the idea that ascribing any given day’s blood pressure to intake or excretion from the prior day is generally inappropriate.

We attempted to correct for over or under collection by using creatinine excretion, so that urine sodium values would be comparable within an individual. Finally, our study participants with CKD were not in an observed clinical research unit and blood pressures were measured twice and averaged, rather than measured with greater frequency or by ambulatory blood pressure; this decreases the precision of the blood pressure readings but is more reflective of clinical practice than a research protocol would be.

In summary, we did not find a strong intra-individual sodium/blood-pressure response in these patients with CKD, in contrast to population-level findings on relationships between salt intake and blood pressure.

Summary and Practical Application

Our study demonstrates the absence of a strong intra-individual sodium/blood-pressure response in patients with CKD. This suggests that the common clinical practice of discounting high blood pressure readings because of the presumed effect of recent high sodium intake may not be supported by data. Moreover, this practice can lead to therapeutic inertia. We advocate that high blood pressure readings be addressed and treated either pharmacologically or through aggressive, sustained reduction of dietary sodium intake, or both, rather than dismissed as an effect of recent sodium indiscretion.

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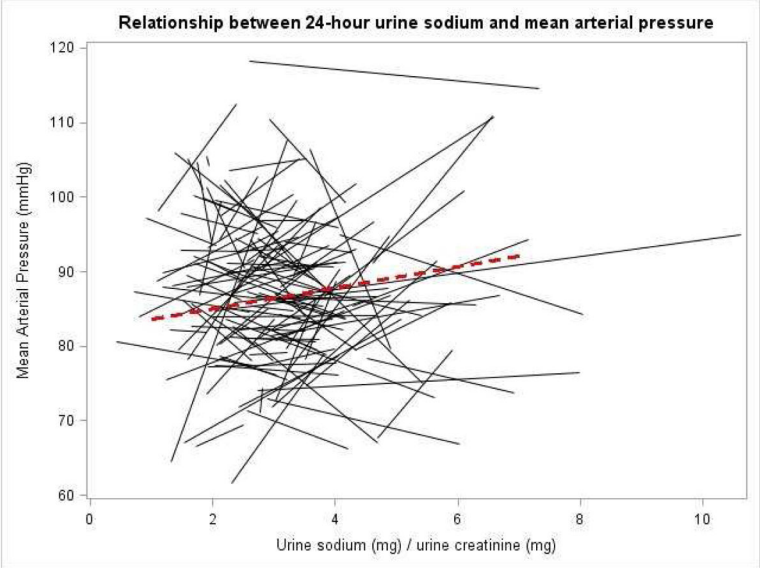

Figure 1.

Relationships between urine sodium/urine creatinine and mean arterial pressure among 119 trial participants with CKD stage 3–4. The black lines denote regression lines (calculated from 3 or 4 data points) for each individual. The red line shows the mean of the slopes of regression lines for all the patients.

Table 1

Characteristics of participants with negative and positive relationships between salt intake and mean arterial pressure

	Negative Slope (n=56)	Positive Slope (n=63)	p-value
Slope (mmHg per UNa/Cr)	−5.21 ± 7.27	7.30 ± 10.76	
Participants randomized to binders vs. placebo	31 (55%)	42 (67%)	0.21
Age (years)	66.7 ± 9.9	67.0 ± 12.3	0.89
Female	29 (52%)	32 (51%)	0.91
Black race	7 (13%)	7 (11%)	0.81
BMI (kg/m^2)	32 ± 8	31 ± 6	0.47
Medication use			
Diuretic Users	38 (68%)	40 (64%)	0.61
ACEi Users	28 (50%)	31 (49%)	0.93
Anti-hypertensive agents (#)	2.0 ± 0.7	1.8 ± 1.0	0.40
eGFR ($ml/min/1.73\ m^2$)	31.3 ± 8.9	31.1 ± 7.6	0.89
Baseline Systolic Blood Pressure (mmHg)	125.3 ± 16.8	128.4 ± 16.8	0.32
Baseline Mean Arterial Pressure (mmHg)	87.1 ± 11.2	88.5 ± 11.0	0.49

Note: Continuous variables shown as mean ± standard deviation, and categorical variables shown as number (percentage).

Abbreviations: eGFR, estimated glomerular filtration rate; BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor