Effects of Reduced Dietary Sodium and the DASH Diet on GFR: The DASH-Sodium Trial

Martha Catalina Morales-Alvarez,[1] *Voravech Nissaisorakarn*,[1] *Lawrence J. Appel*,[2] *Edgar R. Miller III*,[2] *Robert H. Christenson*,[3] *Heather Rebuck*,[3] *Sylvia E. Rosas*,[1,4] *Jeffrey H. William*,[1] *and Stephen P. Juraschek*[5]

Key Points

- Sodium reduction over a 4-week period decreased eGFR.
- Combining sodium reduction with the Dietary Approaches to Stop Hypertension diet resulted in larger reductions in eGFR.
- Changes in diastolic BP seem partially responsible for the observed dietary effects.

Abstract

Background A potassium-rich Dietary Approaches to Stop Hypertension (DASH) diet combined with low sodium reduces BP. However, the effects of sodium reduction in combination with the DASH diet on kidney function are unknown. We determined the effects of sodium reduction and the DASH diet, on eGFR using cystatin C.

Methods DASH-sodium was a controlled, feeding study in adults with elevated or stage 1 hypertension, randomly assigned to the DASH or a control diet. On their assigned diet, participants consumed each of three sodium levels for 30 days after a 2-week run-in period of a high sodium-control diet. The three sodium levels were low (50 mmol/d), medium (100 mmol/d), and high (150 mmol/d). The primary outcome was change in eGFR based on cystatin C.

Results Cystatin C was measured in 409 of the original 412 participants, of which 207 were assigned the DASH diet and 202 to the control diet. Compared with control, the DASH diet did not affect eGFR ($\beta = -0.96$ ml/min per 1.73 m^2; 95% confidence interval [CI], −2.74 to 0.83). By contrast, low versus high sodium intake decreased eGFR ($\beta = -2.36$ ml/min per 1.73 m^2; 95% CI, −3.64 to −1.07). Together, compared with the high sodium-control diet, the low sodium-DASH diet decreased eGFR by 3.10 ml/min per 1.73 m^2 (95% CI, −5.46 to −0.73). This effect was attenuated with adjustment for diastolic BP and 24-hour urinary potassium excretion.

Conclusions A combined low sodium-DASH diet reduced eGFR over a 4-week period. Future research should focus on the effect of these dietary interventions on subclinical kidney injury and their long-term effect on progression to CKD.

Clinical Trial registration number ClinicalTrials.gov, NCT00000608.

Kidney360 5: 569–576, 2024. doi: https://doi.org/10.34067/KID.0000000000000390

Hypertension affects nearly half the US population and 1.3 billion adults worldwide.[1] Dietary factors, in particular high sodium and low potassium intake, are believed to be major causes of the global hypertension pandemic. It has been traditionally viewed that increased sodium intake contributes to thirst, excess fluid intake, and intravascular fluid retention, resulting in higher BP, which over time leads to kidney injury and renovascular remodeling.[2] However, recent evidence

[1]Division of Nephrology, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts
[2]The Johns Hopkins Bloomberg School of Public Health, The Welch Center for Prevention, Epidemiology and Clinical Research, The Johns Hopkins University School of Medicine, Baltimore, Maryland
[3]Department of Pathology, University of Maryland School of Medicine, Baltimore, Maryland
[4]Joslin Diabetes Center, Harvard Medical School, Boston, Massachusetts
[5]Division of General Medicine, Department of Medicine, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, Massachusetts

Correspondence: Dr. Stephen P. Juraschek, email: sjurasch@bidmc.harvard.edu

Received: December 6, 2023 **Accepted:** February 1, 2024
Published Online Ahead of Print: February 8, 2024

See related editorial, "Effect of Combined DASH Diet with Sodium Restriction on Renal Function" on pages 487–488.

suggests a larger role for potassium as a potent dietary factor for BP reduction, particularly in the setting of high sodium intake.[3,4] Data on the short-term individual and combined effects of these key micronutrients would inform an understanding of the physiologic effects on fluid regulation with implications for longer-term injury pathways.

The Dietary Approaches to Stop Hypertension (DASH)-sodium trial was a controlled-feeding study designed to test the effects, alone or combined, of the DASH diet and reduced sodium intake on BP. Participants were assigned each of three sodium intake levels (low, medium, or high) in the context of two distinct diets—a typical American diet or a high potassium diet (the DASH diet). Ultimately, the trial demonstrated that both low (versus high) sodium intake and the DASH diet significantly decreased BP.[5] It has been speculated that these improvements in BP might positively affect subclinical kidney function. However, to date, the effects of sodium reduction and/or higher potassium on eGFR have not been assessed in the DASH-sodium trial.[5]

We measured cystatin C in stored specimens of the DASH-sodium trial, to determine the individual and combined effects of sodium reduction and the DASH diet on eGFR. We hypothesized that BP reduction from either intervention would favorably increase kidney function to a magnitude commensurate with the change in BP and that BP would be the primary pathway by which these micronutrients affect kidney function.

Methods

The DASH-sodium study was a multicenter, randomized trial conducted from September 1997 through November 1999 at four clinical centers (Baltimore, MD; Boston, MA; Durham, NC; and Baton Rouge, LA). In brief, DASH-sodium compared the effects of three different levels of sodium consumption in combination with the DASH diet or a typical American diet (control) on BP.[5] This study was determined by the Institutional Review Board of Beth Israel Deaconess Medical Center to be human subjects exempt research.

Population

The DASH-sodium study enrolled participants age 22 years or older with a mean systolic BP (SBP) of 120–159 mm Hg and diastolic BP (DBP) of 80–95 mm Hg. The study excluded adults with CKD, defined at the time of recruitment as urine protein dipstick level ≥2 or serum creatinine level >1.2 mg/dl in women or 1.5 mg/dl in men, unless the eGFR by creatinine using Cockcroft–Gault formula was >60 ml/min (note cystatin C results were not available at the time of the original study). The study also excluded adults with a prior diagnosis of heart disease (*i.e.*, myocardial infarction, coronary artery bypass graft, angioplasty, symptomatic ischemic heart disease, stroke, or congestive heart failure), poorly controlled dyslipidemia (*i.e.*, total cholesterol >6.8 mmol/L), type 1 or poorly controlled type 2 diabetes mellitus (*i.e.*, daily insulin use or hemoglobin A1c >8.0), or morbid obesity (body mass index >40 kg/m^2).[6] Participants taking antihypertensive agents, insulin, or consuming >14 alcoholic drinks per week were also excluded.

Intervention

Participants of the DASH-sodium trial were randomized to either the DASH diet or a control diet following a parallel design. While consuming their assigned dietary pattern, they were also assigned to each of the three sodium levels, following a crossover design (see Supplemental Table 1 for the nutrient composition of the dietary interventions). The three sodium levels were high (150 mmol/d), medium (100 mmol/d), and low (50 mmol/d) on the basis of their estimated kilocalorie intake. Estimated kilocalorie requirement was monitored throughout the study and was adjusted as needed to maintain weight constant. The five energy levels prepared were 1,600, 2,100, 2,600, 3,100, and 3600 kcal/d. At the 2100-kcal level, the high sodium level was consistent with the average US sodium intake (3450 mg/d), the medium level was based on contemporaneous sodium recommendations (2300 mg/d), and the low sodium intake was based on a level below current recommendations (1150 mg/d). Differences in sodium level were achieved with unsalted or salted varieties of foods or by adding salt to entrees, ensuring similar nutrient profiles. All meals and snacks were provided to participants by the research team.

Over a 2-week, run-in period, all participants were given the high sodium-control diet before they were randomized to the diet and sodium sequence. Each dietary pattern was followed for a mean of 30 days, followed by an average 5-day washout period during which participants could eat their usual diets (Figure 1). Of note, few adverse events were reported during the original trial. The most common side effect was headache reported during the high sodium period.[5]

Outcomes

The primary outcome of this *post hoc* study was eGFR, measured using the CKD Epidemiology Collaboration 2021 cystatin C equation. Cystatin C is advantageous among kidney markers because it is not affected by dietary macronutrients.[7] Cystatin C was measured in stored serum specimens collected at baseline and at the end of each of the three sodium feeding periods, using the Dimension Vista Cystatin C assay (Siemens Healthineers, Malvern, PA). This assay has a within-run coefficient of variation of 3.5% (corresponding mean of 0.98 mg/L). Additional assay details are described elsewhere.[8]

Covariates

Additional covariates were described previously.[9] Age, sex, and race (categorized as Black, yes or no) were self-reported. After the original DASH-sodium trial, seated SBP and DBP were measured by trained and certified observers with random zero sphygmomanometers at three visits during the screening phase and at two visits during the 2-week, run-in period. The average of these five measurements served as a baseline for this study. HDL cholesterol, triglycerides, and total cholesterol were measured using enzymatic colorimetry and used to estimate LDL cholesterol.[10] Body mass index was derived from measured height and weight. Urinary concentration of potassium and sodium as well as urine volume was quantified using a 24-hour urine collection.

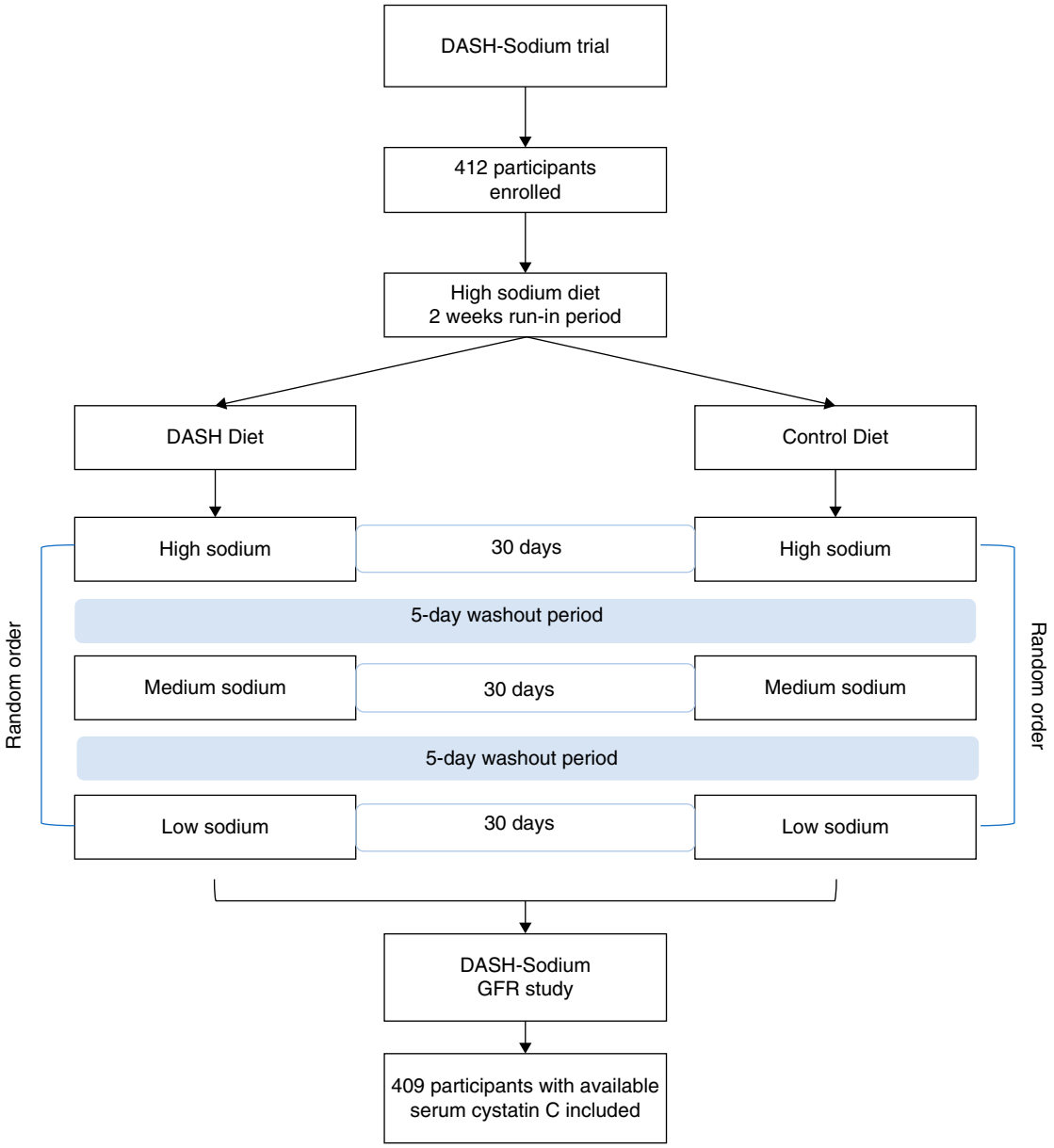

Figure 1. Study overview, participants, and available specimens. DASH, Dietary Approaches to Stop Hypertension.

Weight, BP, total cholesterol, LDL cholesterol, urine volume, urine potassium, and urine sodium were measured at baseline and after each sodium feeding period. After randomization, BP was measured at five clinic visits during the last 9 days (at least two during the final 4 days) of each sodium intervention period.

Statistical Analyses

Baseline characteristics were described by diet assignment using means (SD) and proportions for the complete, randomized population, and the 409 participants with cystatin C measurements. The primary outcome of this study was eGFR. Our analysis had the following three contrasts: (*1*) DASH versus control dietary assignments (a parallel design comparison), (2) low (or medium) sodium intake versus high sodium intake (a crossover design comparison), and (*3*) a combined DASH and low sodium diet versus a combined control and high sodium diet (a parallel design comparison).

Comparisons were performed for eGFR or cystatin C using generalized estimated equation models (normal family, identity link, exchangeable working correlation matrix, and a robust variance estimator). We first plotted mean eGFR or cystatin C by sodium assignment and by study week using a diet-by-sodium interaction term and a diet-by-visit interaction term.

We then assessed for an interaction by sodium and diet (treating sodium assignment as a continuous variable and diet as a categorical variable). After confirming the absence of an interaction, the DASH versus control contrast was performed with a diet-by-visit interaction term (0 for baseline, 1 for a follow-up visit). The sodium contrast was performed within

diet (sodium term only) and across diets (with a sodium-by-diet interaction term). The low sodium-DASH versus high sodium-control was implemented similarly to the dietary contrast above with a diet-by-visit interaction term but restricted to the corresponding sodium periods.

Finally, we assessed for potential pathways contributing to the effects of diet on cystatin C and eGFR by repeating models above with adjustment for related covariates measured concurrently with the serum collections (both at baseline and after each of the three sodium feeding periods), specifically body weight, SBP, DBP, total cholesterol, LDL cholesterol, urine volume, sodium concentration per 24-hour period, and potassium concentration per 24-hour period. In supplemental analyses, we also examined the effect of the interventions on the pathway covariates above.

A two-tailed P value < 0.05 was considered statistically significant without adjustment for multiple comparisons. All analyses were conducted using Stata version 15.1 (Stata Corporation, College Station, TX).

Results

Baseline Characteristics

Baseline clinical and demographic characteristics were similar across randomized dietary assignments even when restricted to the group with cystatin C measurements (Table 1 and Supplemental Table 2).

Effect of the DASH Diet on eGFR

There was no evidence of an interaction between diet and sodium with respect to eGFR or cystatin C (P values both = 0.15). Neither diet significantly changed eGFR from baseline (control diet: β=0.84 ml/min per 1.73 m^2; 95% confidence interval [CI], −0.42 to 2.09; DASH diet: β=−0.12 ml/min per 1.73 m^2; 95% CI, −1.39 to 1.16) (Figure 2 and Table 2). Moreover, there was no significant difference in eGFR from DASH compared with the control diet (−0.96; 95% CI, −2.74 to 0.83).

Effect of Sodium Intake on eGFR

eGFR trended lower across sodium levels among participants assigned the DASH diet: 1.45, 0.14, and −1.97 ml/min per 1.73 m^2 for high, medium, and low sodium levels (P-trend < 0.001), but did not differ across sodium levels among those assigned the control diet (1.18, 1.16, and 0.07 ml/min per 1.73 m^2 for high, medium, and low sodium levels; P-trend = 0.27). There was no evidence of an interaction between dietary assignments. Effects in the overall population were 1.35, 0.65, and −1.01 ml/min per 1.73 m^2 (P-trend < 0.001) (Table 3).

Among participants assigned the control diet, low sodium intake decreased eGFR by 1.12 ml/min per 1.73 m^2 (95% CI, −3.15 to 0.91) compared with high sodium intake. Meanwhile, participants randomized to the DASH diet and low sodium intake exhibited a net decrease in eGFR from baseline of 3.41 ml/min per 1.73 m^2 (95% CI, −5.03 to −1.79) compared with high sodium intake (Table 3). The overall effect from low *versus* high sodium intake was −2.36 (95% CI, −3.64 to −1.07).

Combined Effects

Compared with the high sodium-control diet, the low sodium-DASH diet changed eGFR by −3.10 ml/min per 1.73 m^2 (95% CI, −5.46 to −0.73) (Table 4).

Table 1. Baseline characteristics according to diet assignment

Characteristic	Control Diet		DASH Diet	
	n	Mean (SD) or *n* (%)	*n*	Mean (SD) or *n* (%)
Age, yr	202	48.9 (10.2)	207	47.3 (9.6)
Women, %	202	55	207	59.4
Black, %	202	56.9	207	57.5
BP, mm Hg				
Systolic	202	135.3 (9.4)	207	134.2 (9.6)
Diastolic	202	85.8 (4.1)	207	85.6 (4.8)
Baseline SBP ≥140 or DBP ≥90 mm Hg, %	202	40.6	207	41.1
HDL cholesterol, mg/dl	202	48.0 (13.1)	207	48.5 (12.6)
LDL cholesterol, mg/dl	200	131.8 (31.7)	203	130.7 (29.8)
Total cholesterol, mg/dl	202	93.5 (67.0–141.0)	207	92.0 (67.0–131.0)
Triglycerides, mg/dl (median, 25th–75th percentile)	202	202.6 (36.1)	207	202.0 (36.5)
BMI, kg/m^2	202	29.5 (5.0)	207	28.8 (4.7)
BMI ≥30, %	202	40.1	207	37.2
Urine volume, ml/24 h (median, 25th–75th percentile)	202	1445.0 (1000.0–1925.0)	203	1410.0 (1000.0–1980.0)
Urine potassium, mmol/24 h (median, 25th–75th percentile)	202	49.0 (36.0–64.0)	203	51.0 (39.0–65.0)
Urine sodium, mmol/24 h (median, 25th–75th percentile)	202	142.5 (97.0–192.0)	203	138.0 (101.0–198.0)
Cystatin C, mg/dl	190	0.8 (0.1)	187	0.8 (0.1)
eGFR (cystatin C), ml/min per 1.73 m^2	190	105.7 (15.2)	187	106.4 (13.8)

BMI, body mass index; DASH, Dietary Approaches to Stop Hypertension; DBP, diastolic BP; SBP, systolic BP.

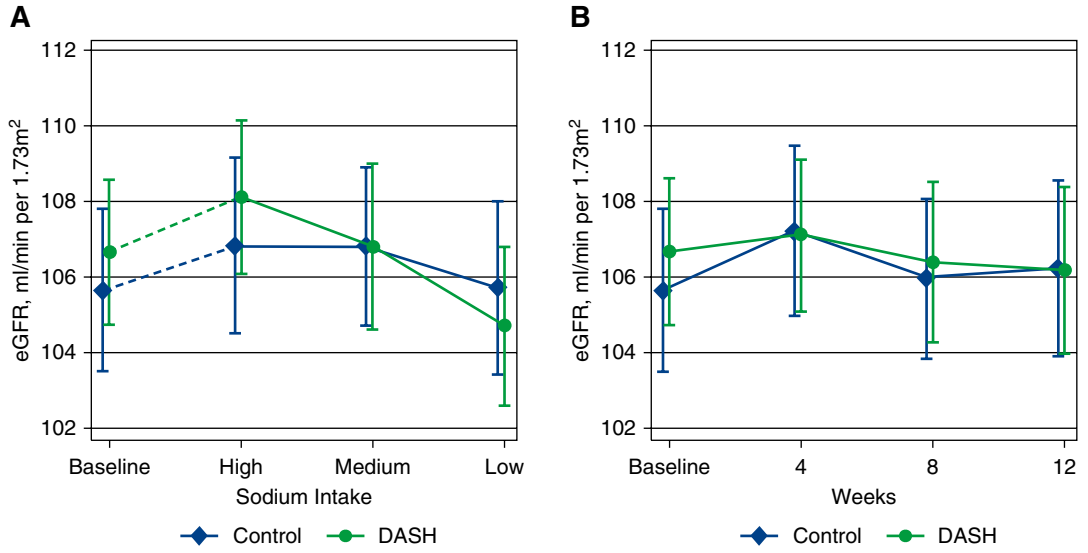

Figure 2. eGFR by sodium level and throughout follow-up. Mean (95% CI) for eGFR on the basis of cystatin C measured at baseline and after each of the 4-week sodium feeding periods, presented by (A) high, medium, and low sodium intake levels and (B) study week (baseline, 4, 8, and 12 weeks). In (B), consistent with the crossover design, about a third of participants would be consuming each of the three sodium levels at each time point among those assigned either the control or DASH diets. The control diet is depicted by the blue diamonds (*N*=202), while the DASH diet is depicted by the green circles (*N*=207). CI, confidence interval.

Table 2. Mean baseline, follow-up, and difference on eGFR by diet assignment

eGFR, ml/min per 1.73 m^2	Baseline	Follow-Up	Change from Baseline	Between Diet Difference
Control	105.7 (1.09)	106.5 (1.00)	0.84 (−0.42 to 2.09)	Ref
DASH	106.7 (0.99)	106.6 (0.94)	−0.12 (−1.39 to 1.16)	−0.96 (−2.74 to 0.83)

Estimates generated using generalized estimating equations (normal family, identity link, robust variance estimator, exchangeable working matrix). There was no evidence of an interaction between diet and sodium (P = 0.15). DASH, Dietary Approaches to Stop Hypertension.

Effects on Cystatin C

All analyses were replicated using cystatin C values and are available in Supplemental Tables 3–5.

Pathway Analysis

The effects of sodium intake on eGFR were independent of most of the pathways examined with a few notable exceptions (Supplemental Table 6). In the overall population, the decrease in eGFR among the low sodium intake group was attenuated with adjustment for DBP with a similar effect observed among those assigned the DASH diet, and when comparing low sodium-DASH versus high sodium-control. Adjustment for weight seemed to slightly enhance the effect in all groups. Of note, 24-hour potassium urinary concentration did not affect eGFR change, except in the low sodium-DASH versus high sodium-control comparison where the effect was smaller after

Table 3. Effects of sodium reduction on the absolute change in eGFR from baseline and between diets

Dietary Pattern	Absolute Change from Baseline				Low versus High	
	Baseline eGFR ml/min per 1.73 m^2	High Sodium	Medium Sodium	Low Sodium	Difference	P-Trend
Overall	106.2 (0.7)	1.35 (0.20–2.50)	0.65 (−0.49 to 1.79)	−1.01 (−2.18 to 0.15)	−2.36 (−3.64 to −1.07)	<0.001
Control diet	105.6 (1.1)	1.18 (−0.54 to 2.90)	1.16 (−0.27 to 2.60)	0.07 (−1.69 to 1.83)	−1.12 (−3.15 to 0.91)	0.27
DASH diet	106.7 (1.0)	1.45 (−0.10 to 2.99)	0.14 (−1.62 to 1.90)	−1.97 (−3.50 to −0.43)	−3.41 (−5.03 to −1.79)	<0.001
P interaction		0.82	0.38	0.09		

Estimates generated using generalized estimating equations (normal family, identity link, robust variance estimator, exchangeable working matrix). DASH, Dietary Approaches to Stop Hypertension.

Table 4. Mean baseline, follow-up, and difference in eGFR by diet assignment

eGFR, ml/min per 1.73 m^2	Baseline	End of Follow-Up	Change from Baseline	Between Diet Difference
High sodium-control	105.5 (1.10)	106.7 (1.18)	1.17 (−0.59 to 2.93)	Ref
Low sodium-DASH	106.7 (0.99)	104.8 (1.08)	−1.93 (−3.50 to −0.35)	−3.10 (−5.46 to −0.73)

Estimates generated using generalized estimating equations (normal family, identity link, robust variance estimator, exchangeable working matrix). For comparisons between diet across the same sodium levels, see Table 3. DASH, Dietary Approaches to Stop Hypertension.

adjustment. Finally, adjustment for 24-hour urine sodium excretion blunted the individual effect of sodium reduction for both dietary assignments and overall as well as the combined effect of DASH and sodium reduction on eGFR.

The effects of a combined DASH diet and the three sodium intake levels on BP and other covariates (weight, SBP, DBP, total cholesterol, LDL cholesterol, urine volume, urine potassium, and urine sodium) are shown in Supplemental Table 7.

Discussion

In this population of adults with elevated BP or hypertension, we found that a DASH dietary pattern had no effect on eGFR compared with control. By contrast, 4 weeks of a lower sodium diet decreased eGFR compared with a higher sodium diet. Combining both the DASH diet with sodium reduction resulted in larger reductions in eGFR. Beyond adjustment for markers of adherence (24-hour sodium and potassium excretion), adjustment for DBP attenuated, but did not negate the above observations, suggesting that DBP was a partial mediator of these dietary effects.

Hypertension remains one of the strongest risk factors for cardiovascular disease and for progressive CKD. Dietary strategies to prevent hypertension are considered among primary lifestyle approaches to prevent progression to CKD. This is based on observational evidence that DASH adherence and reduced sodium are associated with a lower risk of CKD.[11,12]

Adherence to the DASH diet is inversely associated with risk of ESKD among adults with a history of mild-to-moderate CKD (stage 3 or less) and hypertension.[12] Beyond reducing BP, it is believed that DASH lowers dietary acid load and slows renal injury.[13] DASH is also higher in magnesium, which lowers the production of inflammatory and proatherogenic cytokines in endothelial cells.[14] Finally, the high potassium in DASH has a well-known natriuretic effect potentially mediating some of the reduction in BP, intraglomerular capillary pressure, and acid load.[15] Despite these mechanisms, we did not observe an effect of the DASH diet on eGFR over a 3-month period. It is possible that the study duration was too short for eGFR to change and that markers of renal injury would better reflect the short-term effects of diet on autoregulation of afferent arterioles during BP reduction rather than long-term CKD pathways. Longer-term feeding studies and markers of injury beyond eGFR should be the focus of subsequent work.

The effects of sodium intake on kidney function have been reported with conflicting findings. Previous small interventional studies described an increase in eGFR after a high sodium diet over a short period of time.[16,17] Similarly, others reported slower progression of CKD among patients with restricted sodium intake primarily mediated by reduced BP and proteinuria.[18] In a systematic review of eight studies, McMahon and colleagues evaluated the short-term effects of low sodium intake (up to 26 weeks) on kidney function. None of these studies reported a significant change in eGFR or creatinine clearance, but two studies showed an increase in plasma renin activity and aldosterone levels.[11] Another recent systematic review assessed the association between sodium intake and change in GFR. Pooled data from 11 cross-sectional and five longitudinal observational studies along with 20 intervention trials showed a higher GFR among individuals exposed to high sodium intake.[19]

In line with the existing literature and our *a priori* hypothesis, our study demonstrated a strong positive relationship between higher sodium and eGFR. We speculate that this may be a maladaptive response resulting in glomerular hyperfiltration. While the hyperfiltration observed in our study was reversible, similar states of hyperfiltration have been observed in other populations and forebode more rapid progression to CKD over time.[20,21] Current therapeutic approaches targeting this maladaptive response by reducing intraglomerular pressure often result in an acute and acceptable reduction in eGFR. In the long term, this reduced eGFR slows CKD progression, a phenomena demonstrated with the use of angiotensin-converting-enzyme inhibitors, angiotensin II receptor blockers, aldosterone antagonists, and sodium–glucose cotransporter inhibitors.[22–24] However, there may be important mechanistic differences between sodium reduction and the agents above. For example, sodium reduction may solely reduce intravascular volume without directly affecting regulatory systems in the afferent and efferent arteries. Additional work on the long-term effects of sodium reduction on kidney function over time represents an important area for future research.

We observed the greatest reduction in eGFR from the low sodium-DASH diet compared with the high sodium-control diet. This effect was attenuated with adjustment for DBP, 24-hour urine sodium, and 24-hour urine potassium. While adjustment for 24-hour urine sodium and 24-hour urine potassium (both markers of intervention adherence) was expected, attenuation after adjustment for DBP implies that DBP may partially mediate the effects of the two dietary interventions on eGFR. Whether these findings extend to populations of adults with CKD is unclear. In one trial of adults with hypertension and advanced CKD, sodium

reduction affected peripheral DBP, but not central DBP.[25] Moreover, the observation that the dietary interventions significantly reduced eGFR independent of DBP questions whether these effects purely reflect changes in intraglomerular pressure or are secondary to additional tubuloglomerular feedback effects. Notably, while higher urine volume and body weight were generally observed in response to higher sodium intake, these factors seemed to be more important in the context of the control diet than the DASH diet, suggesting that hemodynamic changes in volume may not fully explain the observations above.

Our study has strengths. First, both dietary contrasts and sodium levels were tightly controlled and randomized. Moreover, nearly all the original trial participants were included in this study, allowing for unbiased estimates of the effect of diet on eGFR. Second, we used cystatin C to estimate eGFR. This marker is advantageous because it is not affected by diet composition, a limitation of creatinine.[26,27] Third, the diets were isocaloric, which limits the effect of weight change on the interventions. Fourth, repeated measurements with high follow-up rates allowed for an examination of change over time. Finally, the study population was over 50% Black, a group disproportionately affected by kidney disease.

However, our study has limitations. While the dietary feeding period lasted 12 weeks, the sodium periods only lasted 4 weeks. As a result, we were unable to observe the long-term effects of the interventions on eGFR. Similarly, a 5-day washout period might be insufficient to eliminate the effect of the previous sodium intake level. Moreover, our population included mostly individuals without CKD, severe hypertension, cardiovascular disease, uncontrolled diabetes, or morbid obesity limiting the generalizability of our findings. In addition, eGFR may not reflect subclinical kidney injury preventing us from detecting an effect of dietary patterns on eGFR. We also acknowledge the intrinsic limitations of the CKD Epidemiology Collaboration equation, including less representation of specific populations such as older or Black adults with higher GFR during the development and validation process. More direct measures of injury pathways, such as albuminuria, are important for future research on diet and CKD progression.

In conclusion, in this population of adults with high BP, sodium reduction lowered eGFR in the short-term with greater effects when combined with the DASH diet. DBP was a partial driver of these effects. Future research should focus on the effect of these dietary interventions on subclinical kidney injury and whether these acute changes in eGFR prevent progression to CKD over time.

Disclosures

L.J. Appel reports the following: Consultancy: Wolters Kluwer for chapters in UpToDate; Honoraria: Wolters Kluwer; and Other Interests or Relationships: Bloomberg Philanthropies. R.H. Christenson reports the following: Consultancy: Babson Diagnostics, Beckman Coulter, Becton Dickenson, PixCell, Quidel, Roche Diagnostics, Siemans Healthineers, and Sphingotec; Ownership Interest: Babson Diagnostics; Research Funding: Abbott Diagnostics, Astute, Beckman Coulter, Becton Dickenson, Critical Care Diagnostics, Ortho Clinical Diagnostics, Quidel, Roche Diagnostics, and Siemens Healthcare Diagnostics; Honoraria: Babson, Beckman Coulter, Roche Diagnostics, Siemens Healthcare Diagnostics, and Sphingotec; I am also Editor in Chief of the *Journal of Applied Laboratory Medicine*. S.P. Juraschek reports the following: Research Funding: American Heart Association and National Institutes of Health. S.E. Rosas reports the following: Consultancy: Astra Zeneca and Bayer honorarium; Research Funding: Astra Zeneca, Bayer, and NIH-NIDDK; Honoraria: AstraZeneca and Bayer honorarium; and Advisory or Leadership Role: AKHD, *American Journal of Kidney Diseases*, *CJASN* Editorial Board; NKF-NE Medical Adivisory Board; and NKF Scientific Advisory Board, NKF President; All positions are voluntary and without payment. All remaining authors have nothing to disclose.

Funding

S.P. Juraschek: NHLBI Division of Intramural Research (R21HL144876 and K23HL135273). S.E. Rosas: NIDDK (P30 DK03836).

Acknowledgments

We are indebted to the study participants for their sustained commitment to the DASH-sodium trial.

Author Contributions

Conceptualization: Lawrence J. Appel, Robert H. Christenson, Stephen P. Juraschek, Edgar R. Miller, Martha Catalina Morales-Alvarez, Voravech Nissaisorakarn, Heather Rebuck, Sylvia E. Rosas, Jeffrey H. William.

Data curation: Lawrence J. Appel, Stephen P. Juraschek, Edgar R. Miller.

Formal analysis: Lawrence J. Appel, Stephen P. Juraschek, Edgar R. Miller, Martha Catalina Morales-Alvarez.

Funding acquisition: Lawrence J. Appel, Stephen P. Juraschek, Edgar R. Miller.

Investigation: Lawrence J. Appel, Robert H. Christenson, Stephen P. Juraschek, Edgar R. Miller, Heather Rebuck, Sylvia E. Rosas, Jeffrey H. William.

Methodology: Lawrence J. Appel, Robert H. Christenson, Stephen P. Juraschek, Edgar R. Miller, Martha Catalina Morales-Alvarez, Voravech Nissaisorakarn, Heather Rebuck, Sylvia E. Rosas, Jeffrey H. William.

Project administration: Lawrence J. Appel, Stephen P. Juraschek, Edgar R. Miller.

Resources: Lawrence J. Appel, Stephen P. Juraschek, Edgar R. Miller.

Software: Stephen P. Juraschek.

Supervision: Lawrence J. Appel, Stephen P. Juraschek, Edgar R. Miller.

Validation: Lawrence J. Appel, Robert H. Christenson, Stephen P. Juraschek, Edgar R. Miller, Martha Catalina Morales-Alvarez, Heather Rebuck, Sylvia E. Rosas, Jeffrey H. William.

Visualization: Lawrence J. Appel, Robert H. Christenson, Stephen P. Juraschek, Edgar R. Miller, Martha Catalina Morales-Alvarez, Heather Rebuck, Sylvia E. Rosas, Jeffrey H. William.

Writing – original draft: Lawrence J. Appel, Robert H. Christenson, Stephen P. Juraschek, Edgar R. Miller, Martha Catalina Morales-Alvarez, Voravech Nissaisorakarn, Heather Rebuck, Sylvia E. Rosas, Jeffrey H. William.

Writing – review & editing: Lawrence J. Appel, Robert H. Christenson, Stephen P. Juraschek, Edgar R. Miller, Martha Catalina Morales-Alvarez, Voravech Nissaisorakarn, Heather Rebuck, Sylvia E. Rosas, Jeffrey H. William.

Data Sharing Statement

Partial restrictions to the data and/or materials apply. DASH-sodium data are available with an approved proposal from the NHLBI BioLincc repository.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/KN9/A444.

Supplemental Table 1. Nutrient composition of the dietary interventions.

Supplemental Table 2. Population characteristics of the original DASH-sodium trial.

Supplemental Table 3. Effects of the DASH diet on cystatin C.

Supplemental Table 4. Effects of sodium reduction on cystatin C.

Supplemental Table 5. Combined effects of the DASH diet and sodium reduction on cystatin C.

Supplemental Table 6. Effects adjusted for concurrent changes in potential mediating covariates.

Supplemental Table 7. Effects of sodium reduction on the absolute change in mediating covariates from baseline and between diets.

References

1. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of cardiology/American Heart Association Task Force on clinical practice guidelines. *Hypertension.* 2018; 71(6):1269–1324. doi:10.1161/HYP.0000000000000066
2. Stanhewicz AE, Kenney WL. Determinants of water and sodium intake and output. *Nutr Rev.* 2015;73(suppl 2):73–82. doi: 10.1093/nutrit/nuv033
3. Neal B, Wu Y, Feng X, et al. Effect of salt substitution on cardiovascular events and death. *N Engl J Med.* 2021;385(12): 1067–1077. doi:10.1056/NEJMoa2105675
4. Wade JB, Fang L, Liu J, et al. WNK1 kinase isoform switch regulates renal potassium excretion. *Proc Natl Acad Sci U S A.* 2006;103(22):8558–8563. doi:10.1073/pnas.0603109103
5. Sacks FM, Svetkey LP, Vollmer WM, 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. doi:10.1056/NEJM200101043440101
6. Svetkey LP, Sacks FM, Obarzanek E, et al. The DASH diet, sodium intake and blood pressure trial (DASH-sodium): rationale and design. DASH-sodium Collaborative research group. *J Am Diet Assoc.* 1999;99(8 suppl l):S96–S104. doi:10.1016/s0002-8223(99)00423-x
7. Juraschek SP, Appel LJ, Anderson CA, Miller ER III. Effect of a high-protein diet on kidney function in healthy adults: results from the OmniHeart trial. *Am J Kidney Dis.* 2013;61(4):547–554. doi:10.1053/j.ajkd.2012.10.017
8. Siemens Healthineers. *N Latex Cystatin C Assay. Assay for Early Detection of Decline in Renal Function.* 2017. Accessed April 4, 2024. https://www.siemens- healthineers.com/en-us/plasma-protein/assays/n-latex-cystatin- c-assay
9. Juraschek SP, Miller ER III, Weaver CM, Appel LJ. Effects of sodium reduction and the DASH diet in relation to baseline blood pressure. *J Am Coll Cardiol.* 2017;70(23):2841–2848. doi: 10.1016/j.jacc.2017.10.011
10. Obarzanek E, Sacks FM, Vollmer WM, et al. Effects on blood lipids of a blood pressure-lowering diet: the dietary approaches to stop hypertension (DASH) trial. *Am J Clin Nutr.* 2001l;74(1): 80–89. doi:10.1093/ajcn/74.1.80
11. McMahon EJ, Campbell KL, Bauer JD, Mudge DW, Kelly JT. Altered dietary salt intake for people with chronic kidney disease. *Cochrane Database Syst Rev.* 2021;6(6):CD010070. doi:10.1002/14651858.CD010070.pub3
12. Banerjee T, Crews DC, Tuot DS, et al. Poor accordance to a DASH dietary pattern is associated with higher risk of ESRD among adults with moderate chronic kidney disease and hypertension. *Kidney Int.* 2019;95(6):1433–1442. doi:10.1016/j.kint.2018.12.027
13. Banerjee T, Crews DC, Wesson DE, et al.; Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance Team. High dietary acid load predicts ESRD among adults with CKD. *J Am Soc Nephrol.* 2015;26(7):1693–1700. doi:10.1681/ASN.2014040332
14. Maier JA, Malpuech-Brugère C, Zimowska W, Rayssiguier Y, Mazur A. Low magnesium promotes endothelial cell dysfunction: implications for atherosclerosis, inflammation and thrombosis. *Biochim Biophys Acta.* 2004;1689(1):13–21. doi:10.1016/j.bbadis.2004.01.002
15. Clegg DJ, Headley SA, Germain MJ. Impact of dietary potassium restrictions in CKD on clinical outcomes: benefits of a plant-based diet. *Kidney Med.* 2020;2(4):476–487. doi:10.1016/j.xkme.2020.04.007
16. Roos JC, Koomans HA, Dorhout Mees EJ, Delawi IM. Renal sodium handling in normal humans subjected to low, normal, and extremely high sodium supplies. *Am J Physiol.* 1985; 249(6 Pt 2):F941–F947. doi:10.1152/ajprenal.1985.249.6.F941
17. Kirkendall AM, Connor WE, Abboud F, Rastogi SP, Anderson TA, Fry M. The effect of dietary sodium chloride on blood pressure, body fluids, electrolytes, renal function, and serum lipids of normotensive man. *J Lab Clin Med.* 1976;87(3): 411–434
18. He J, Mills KT, Appel LJ, et al.; Chronic Renal Insufficiency Cohort Study Investigators. Urinary sodium and potassium excretion and CKD progression. *J Am Soc Nephrol.* 2016;27(4): 1202–1212. doi:10.1681/ASN.2015010022
19. Nomura K, Asayama K, Jacobs L, Thijs L, Staessen JA. Renal function in relation to sodium intake: a quantitative review of the literature. *Kidney Int.* 2017;92(1):67–78. doi:10.1016/j.kint.2016.11.032
20. Pavkov ME, Knowler WC, Hanson RL, Nelson RG. Diabetic nephropathy in American Indians, with a special emphasis on the Pima Indians. *Curr Diab Rep.* 2008;8(6):486–493. doi: 10.1007/s11892-008-0083-1
21. Wuerzner G, Pruijm M, Maillard M, et al. Marked association between obesity and glomerular hyperfiltration: a cross-sectional study in an African population. *Am J Kidney Dis.* 2010;56(2): 303–312. doi:10.1053/j.ajkd.2010.03.017
22. Mukoyama M, Kuwabara T. Role of renin-angiotensin system blockade in advanced CKD: to use or not to use? *Hypertens Res.* 2022;45(6):1072–1075. doi:10.1038/s41440-022-00902-7
23. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. *N Engl J Med.* 2020;383(23):2219–2229. doi:10.1056/NEJMoa2025845
24. Herrington WG, Staplin N, Wanner C, et al.; The EMPA-KIDNEY Collaborative Group. Empagliflozin in patients with chronic kidney disease. *N Engl J Med.* 2023;388(2):117–127. doi: 10.1056/NEJMoa2204233
25. Campbell KL, Johnson DW, Bauer JD, et al. A randomized trial of sodium-restriction on kidney function, fluid volume and adipokines in CKD patients. *BMC Nephrol.* 2014;15:57. doi: 10.1186/1471-2369-15-57
26. Kovell LC, Yeung EH, Miller ER III, et al. Healthy diet reduces markers of cardiac injury and inflammation regardless of macronutrients: results from the OmniHeart trial. *Int J Cardiol.* 2020; 299:282–288. doi:10.1016/j.ijcard.2019.07.102
27. Juraschek SP, Miller ER 3rd, Selvin E, et al. Effect of type and amount of dietary carbohydrate on biomarkers of glucose homeostasis and C reactive protein in overweight or obese adults: results from the OmniCarb trial. *BMJ Open Diabetes Res Care.* 2016;4(1):e000276. doi:10.1136/bmjdrc-2016-000276