




ORIGINAL RESEARCH

Tissue Sodium in Patients With Early Stage Hypertension: A Randomized Controlled Trial

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BACKGROUND: Sodium (Na⁺) stored in skin and muscle tissue is associated with essential hypertension. Sodium magnetic resonance imaging is a validated method of quantifying tissue stores of Na⁺. In this study, we evaluated tissue Na⁺ in patients with elevated blood pressure or stage I hypertension in response to diuretic therapy or low Na⁺ diet.

METHODS AND RESULTS: In a double-blinded, placebo-controlled trial, patients with systolic blood pressure 120 to 139 mm Hg were randomized to low sodium diet (<2 g of sodium), chlorthalidone, spironolactone, or placebo for 8 weeks. Muscle and skin Na⁺ using sodium magnetic resonance imaging and pulse wave velocity were assessed at the beginning and end of the study. Ninety-eight patients were enrolled to undergo baseline measurements and 54 completed randomization. Median baseline muscle and skin Na⁺ in 98 patients were 16.4 mmol/L (14.9, 18.9) and 13.1 mmol/L (11.1, 16.1), respectively. After 8 weeks, muscle Na⁺ increased in the diet and chlorthalidone arms compared with placebo. Skin sodium was decreased only in the diet arm compared with placebo. These associations remained significant after adjustment for age, sex, body mass index, systolic blood pressure, and urinary sodium. No changes were observed in pulse wave velocity among the different groups when compared with placebo.

CONCLUSIONS: Diuretic therapy for 8 weeks did not decrease muscle or skin sodium or improve pulse wave velocity in patients with elevated blood pressure or stage I hypertension.

REGISTRATION: URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02236520.

Key Words: diuretics ■ hypertension ■ prehypertension ■ salt intake ■ sodium ■ sodium MRI ■ tissue sodium

Hypertension is prevalent among >50% of adults in the United States. The health and financial burden of this disease remain massive, rendering preventative measures essential to decrease its incidence and complications.¹ Recent data suggest that the physiology of hypertension extends beyond the neurohormonal system and that a strong correlation exists between elevated blood pressure, vascular injury, inflammatory response, and immune cell activation.²⁻⁴

Recent studies showed that a positive sodium balance exists in the human body, indicating that sodium may be stored in tissue without commensurate water accumulation.^{5,6} Sodium magnetic resonance imaging (²³NaMRI) has been used to visualize and quantify sodium in tissue, validated in chemical analysis in animals.⁶⁻⁸ The accumulation of sodium in the skin is associated with the presence of a local inflammatory state. Increased sodium in skin also creates a

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CLINICAL PERSPECTIVE

What Is New?

- We investigated the impact of race on the quantity of sodium stored in tissue and the effect of diuretic therapy on mobilizing tissue sodium content in patients with early stages of hypertension.
- Dietary salt restriction or diuretic intervention did not decrease skin and muscle sodium content over a period of 8 weeks in patients with early stage hypertension or hypertension.

What Are the Clinical Implications?

- In early stages of hypertension, there does not appear to be any interaction between race and tissue sodium deposition.
- Efforts to mobilize tissue sodium should be targeted to patients who are more likely to be at risk such as ones with impaired kidney function and other comorbidities.

Nonstandard Abbreviations and Acronyms

| | |
|--------------|-----------------------------------|
| NaMRI | sodium magnetic resonance imaging |
| PWV | pulse wave velocity |

hypertonic environment that promotes the expression of vascular endothelial growth factor-C, which in turn increases lymphangiogenesis to promote sodium clearance from the skin compartment.⁶ A disruption in this pathway may lead to hypertension.^{9–12} Using ²³NaMRI, several studies showed that patients with hypertension and patients with kidney disease had higher concentrations of sodium in their tissue compared with controls.^{6,8,13,14} It is also important to note that recent studies suggested that the tissue sodium might potentially reflect the shift in the extracellular-to-intracellular compartments.¹⁵

Black patients in the United States have higher prevalence of hypertension and its complications, compared with White patients.^{16,17} This has contributed to higher mortality and morbidity in Black patients compared with other populations from hypertension and its complications.^{18,19} Evidence has also shown that Black patients are more likely to have salt-sensitive blood pressure, in addition to older patients and patients with hypertension.^{20,21} However, there are limited data on racial differences affecting the quantity or location of tissue sodium.

Despite the limited data on tissue sodium, several studies demonstrated the ability to mobilize tissue sodium by different mechanisms. In a preliminary study,

Kopp et al reported that spironolactone use was associated with reduced Na⁺ storage in a patient with Conn syndrome.⁶ Another randomized trial showed that the use of sodium-glucose cotransporter 2 inhibitors in patients with diabetes resulted in significant reduction of tissue sodium after 6 weeks of dapagliflozin.²² Moreover, hemodialysis was shown to mobilize tissue sodium and water stores in patients with end-stage kidney disease.^{23,24}

In this study, our goals were to evaluate (1) the effects of diuretic therapy on mobilizing tissue sodium content in patients with early stages of hypertension and no concurrent medical problems as part of a preventative goal initiative, and (2) the impact of race on the quantity of sodium stored in tissue. We also examined the association of tissue sodium content with a measure of vascular stiffness, as a marker of vascular health. In this randomized controlled trial, we tested the hypothesis that individual interventions of 8 weeks of reduced salt intake, mineralocorticoid receptor blockade, or thiazide therapy would decrease tissue sodium content and vascular stiffness measured by pulse wave velocity (PWV), compared with a placebo arm. We also tested the hypothesis that Black patients have higher tissue Na⁺ storage compared with age-matched White patients in a cross-sectional study.

METHODS

The data, methods used in the analysis, and materials used to conduct the research will be available to any researcher for purposes of reproducing the results or replicating the procedure.

Study Design

A randomized, double-blind, placebo-controlled clinical trial (NCT02236520) was conducted at Vanderbilt University Medical Center from September 2014 to May 2018. Patients were included if they were between the ages of 30 and 80 years, had systolic blood pressure between 120 and 139 mm Hg, or a diastolic blood pressure 70 and 89 mm Hg on screening day. Patients with acute cardiovascular events within the last 6 months, impaired kidney function (glomerular filtration rate <60 mL/min), impaired liver function, diabetes requiring medical therapy, those currently taking antihypertensive therapy or have taken glucocorticoid systemic therapy in the last month, who were morbidly obese, or ones who had contraindications to undergo a magnetic resonance imaging (metallic implants or mineralocorticoid receptor incompatible devices) were excluded (Figure 1). Informed consent was obtained from all subjects and the study was approved by the institutional review board at Vanderbilt University Medical Center. The study was advertised using flyers and distribution e-mails through Vanderbilt

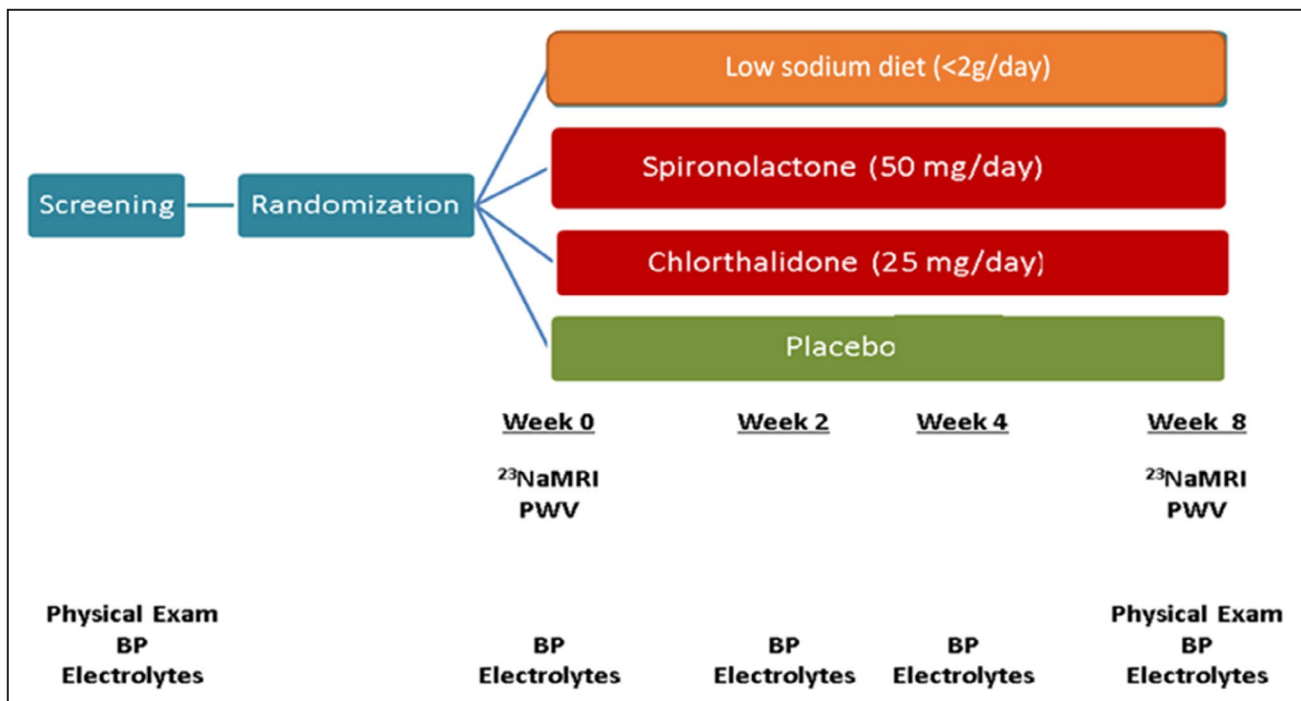


Figure 1. Outline of study procedures.

BP indicates blood pressure ²³NaMRI, ²³Na magnetic resonance imaging; and PWV, pulse wave velocity.

University research distribution list and Research Match (www.researchmatch.org).

Study Visits

After signing informed consent, eligible patients went through a screening visit that included a detailed medical history, physical examination, vital signs, a blood draw for comprehensive metabolic panel, a urine collection for urinalysis, and ²³NaMRI (Figure 1).

At the baseline study visit (week 0), patients were asked to fast for 8 hours before presenting to the Clinical Research Center. Upon arrival, blood samples were drawn for baseline fasting glucose and comprehensive metabolic panel. A baseline ²³NaMRI was obtained for the left lower leg of all participants as explained below. After completion of the baseline study visit, patients were randomized in a 1:1:1:1 ratio to receive 1 of 4 treatments: spironolactone 50 mg/d, chlorthalidone 25 mg/d, low salt diet (<2 g of sodium), or placebo. Study visits at week 2 and week 4 included a urinalysis and comprehensive metabolic panel to assess serum sodium, potassium, and creatinine. Week 8 visit included procedures identical to those performed at the baseline visit (Figure 1).

Randomization and Blinding

Randomization was performed using the stratified permuted-block randomization method based on sex and race, which was generated by the study statistician.

Both the patients and the study staff, including nurses and physicians, were blinded to all study groups, except the diet group. Because of the nature of the intervention, patients assigned to a low sodium diet group were unblinded. These patients met with a dietitian at the beginning of the study for dietary instructions for a diet with <2 g of sodium intake per day. Baseline, midstudy (week 4), and end of study dietary recalls were obtained. The investigational drug team/pharmacy at our medical center was unblinded and was responsible for patient assignment, drug preparation, and dispensation.

Study Procedures

Blood Pressure and Vascular Reactivity

Blood pressure was measured at each study visit with an automated cuff after 10 minutes of resting using the GE CRITIKON Dinamap Pro 1000 Patient Monitor. PWV was measured by the study sonographer at the Clinical Research Center using Sphygmocor AtCor technology, versions 8 and 9.

Blood Samples

All blood sampling was performed at the Clinical Research Center and was processed at Vanderbilt University Medical Center laboratories. All measurements were done at Vanderbilt University Medical Center laboratories using routine laboratory tests and certified methods.

Urine Samples

Random spot urine was collected during the study visit to measure urine Na⁺ concentrations. All urine specimens were centrifuged at 1500 rpm for 20 minutes at 4 °C. Supernatants were aliquoted and samples were stored at –80 °C within 24 hours of collection. Sodium levels were measured using IL 943 flame photometer (from Instrumentation Laboratory, Bedford, MA).

²³NaMRI

Multinuclear ²³NaMRI of the calf was performed using an Na⁺ knee coil at a 3.0 Tesla scanner (Philips Healthcare; Best, The Netherlands) as published before.⁸ Subjects entered the magnetic resonance imaging machine legs first to be scanned where the widest part of the calf was placed on the coil. Four aqueous NaCl reference solutions (10 mmol/L, 20 mmol/L, 30 mmol/L, and 40 mmol/L) were placed in tubes parallel to the patients' leg for calibration. Manual or automated algorithms were implemented to measure the signal intensity from the skin and different muscle compartments in comparison with the known signals from the calibration phantoms. Signal intensities were used to estimate Na⁺ concentrations using a linear model. ²³NaMRI methodology was identical at the beginning and at the end of study. An automated region segmentation MATLAB program (R2015a; MathWorks, Natick, MA) was used to identify muscle and fat quantities on Dixon image acquisitions.²⁵

Pulse Wave Velocity

Aortic PWV was calculated using pressure waveforms from the carotid and femoral arteries in a 3-lead ECG using SphygmoCor (AtCor Medical, Inc.). Patients were placed in a supine position during examination. The mean of 2 aortic pulse wave velocity (aPWV) measurements was calculated and used in the analysis.

Dietary Recall

Dietary intake data were collected and analyzed using Nutrition Data System for Research software version 2017 developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN.²⁶

Statistical Analysis

A total of 98 participants were eligible for the study and were included in the cross-sectional analysis of baseline data. Of these, 60 participants agreed to be randomized to an intervention and were included in the trial. Participant characteristics were described overall, according to muscle sodium quartiles, and according to intervention arm as median (interquartile range) or number (percentage).

The primary outcome of the study was change in tissue sodium content. Since there were no data available at the beginning of the study, a priori power analysis was based on 200 subjects. We assumed a reduction in muscle Na⁺ of 5 mmol/L and SD of 6.0 mmol/L by drug treatment, 85% power, and Bonferroni adjusted 2-sided type I error (significant level) test at level 1% providing a sample size of 41 subjects per group (161 in total).

During the study, an unplanned interim analysis was performed to assess the expected changes after accrual of 60 randomized patients. To guide decision making, the futility probability was calculated for each model and outcome using simulation. For each replicate of the simulation, the data of 100 additional subjects were appended to the data of the initial 60 subjects. Using the full 160 subject data set, the effect of treatment compared with placebo was estimated in each model and outcome. The treatment effect was evaluated with a 1-sided test at a significance level of 0.01. The futility probability was the proportion of analyses (out of 1000 of replicates) that resulted in an inconclusive study result with $P > 0.01$. The covariate data for the additional 100 subjects in each replicate were simulated using the upstrap, a bootstrap-like procedure in which covariate profiles are sampled with replacement from the initial 60 subjects. The outcome data for the 100 additional subjects were sampled from the predictive distribution of the conditional, multivariable model generated from the initial 60 subjects. The combination of the nonparametric upstrap procedure to sample covariate vectors and the model-based outcome-generation procedure to sample conditional outcome vectors resulted in simulated subject data with similar covariate profiles and treatment responses to the initial 60 subjects.²⁷ The simulated futility probabilities for the effect of randomized dietary group on decrease in muscle/skin sodium and PWV are recorded in Table S1. Because of increased likelihood of futility in detecting a significant change in muscle and skin sodium and PWV, recruitment was terminated after enrollment of 60 patients.

The data from the 60 patients were analyzed according to the intention-to-treat principle. A total of 54 participants completed follow-up through week 8 (Figure 2). For participants with missing baseline or week 8 data, single imputation using multivariate normal regression was performed on untransformed outcomes. Proportions of missing for baseline values of muscle, skin, dietary, and urine sodium were 4%, 4%, 6%, and 16%, respectively. Proportions of missing for week 8 values of muscle, skin, dietary, and urine sodium in randomized patients were 10%, 10%, 15%, and 15%, respectively. Muscle, skin, dietary, and urine sodium at baseline and week 8 were imputed using Stata with the `mi impute mvn` command

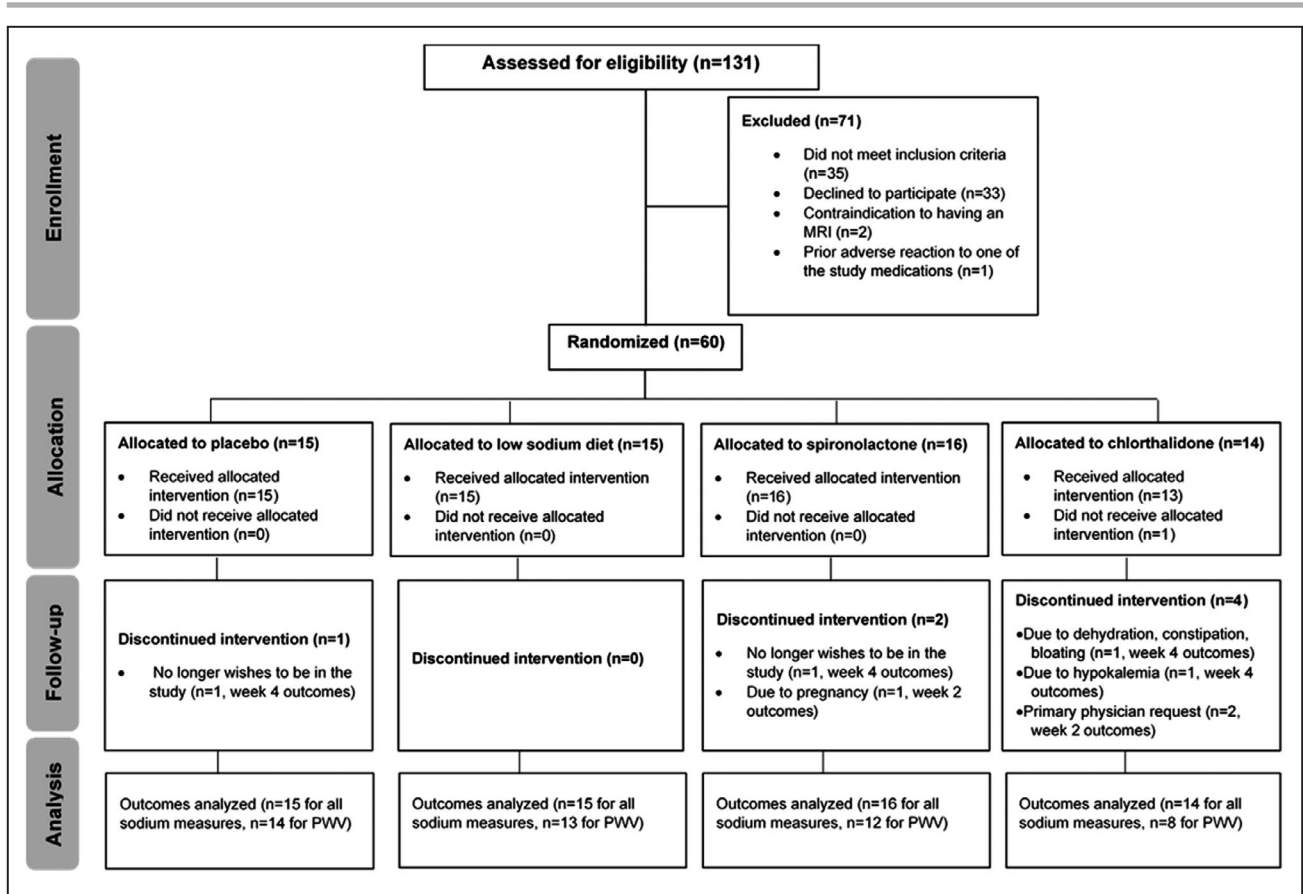


Figure 2. Patient enrollment, randomization, and completion (CONSORT) flow diagram. MRI indicates magnetic resonance imaging; and PWV, pulse wave velocity.

and random seed of 245. The prior distribution was uniform and the burn-in and burn-between periods contained 100 iterations each. The independent variables were age, race, sex, and BMI. A large proportion of participants were missing follow-up pulse wave velocity data; therefore, complete case analysis was used for that outcome (baseline, n=84; week 8, n=47).

Muscle sodium, skin sodium, urinary sodium, dietary sodium, and PWV were described with median (IQR) at baseline. Log-transformed muscle sodium, skin sodium, and PWV were modeled as the primary dependent variables. Additionally, log-transformed urinary sodium and dietary sodium were modeled as secondary dependent variables. Linear regression was used to evaluate differences by race in log-transformed muscle sodium, skin sodium, and PWV at baseline. The first model was adjusted for age and sex. In a second model, we adjusted for BMI and systolic blood pressure (BP) in addition to age and sex. A third model additionally adjusted for baseline dietary sodium and baseline urine sodium for the primary dependent variables of muscle sodium, skin sodium, and PWV.

Among randomized participants, linear regression was used to determine the effect of randomization group on change in log-transformed muscle sodium, skin sodium, urinary sodium, dietary sodium, and pulse wave velocity compared with placebo. The difference between baseline and week 8 values were described as median difference (IQR). The first model was adjusted for age, sex, race, and the baseline measure of the outcome of interest. The second model was further adjusted for BMI and systolic BP. The third model in analyses of muscle sodium, tissue sodium, and PWV was additionally adjusted for baseline, and week 8 dietary and urine sodium values. Secondly, we evaluated whether the effect of each intervention differed by race, by analyzing effects stratified by race and by testing a multiplicative interaction term between race and randomization group via the Wald test. Sensitivity analyses were conducted examining the absolute differences in muscle sodium, skin sodium, and PWV. Leave-1-out sensitivity analyses were also performed excluding the observation with the highest leverage.

Statistical analyses were conducted with Stata version 16.0. The nominal level of significance was defined as $P < 0.05$ (2-sided).

RESULTS

Patients

A total of 131 patients were screened and 98 participants were eligible for enrollment in the study and completed baseline visit. Of those, 60 patients agreed to participate in the trial and 54 completed the 8-week study. Study enrollment, screening, randomization, and follow-up information are displayed in Figure 2.

Baseline Characteristics of the Study Population

The majority of participants who completed the baseline study visit (n=98) were female (65.3%) and White (59.2%). Median (IQR) age was 47.5 years (36.1, 56.3). The participants had normal kidney function at baseline with a median serum creatinine of 0.83 mg/dL (0.74, 0.92). Median baseline BP and BMI did not differ substantially between quartiles of muscle sodium. Participant characteristics by muscle sodium quartiles are shown in Table 1.

Median muscle and skin concentrations at baseline in the 98 subjects were 16.4 mmol/L (14.9, 18.9) and 13.1 mmol/L (11.1, 16.1), respectively. Median muscle sodium at baseline for Black and White participants were 17.3 mmol/L (15.1, 20.0) and 15.8 mmol/L (15.8, 18.1), respectively (Figure 3). Participants with higher muscle sodium were older and more likely to be Black patients (Table 2). After adjustment for age and sex, Black participants had slightly higher muscle sodium than White participants, but this difference was not

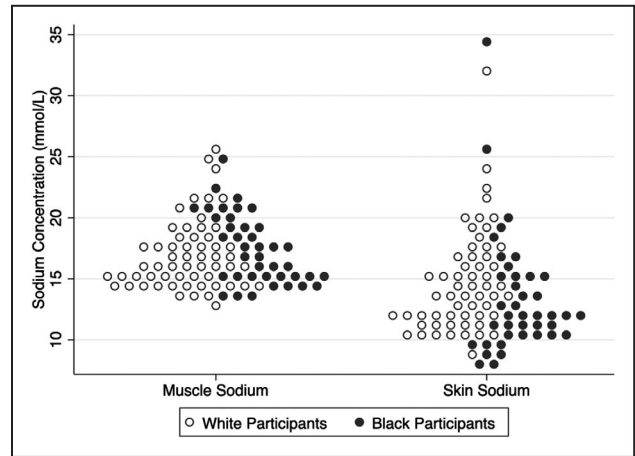


Figure 3. Strip plot of muscle sodium and skin sodium concentrations by race.

significant. This association was similar with further adjustment for BMI and systolic BP (Table 2). There was no statistically significant correlation between baseline muscle or skin Na⁺ and baseline systolic or diastolic BP (data not shown).

At baseline, median skin sodium among White participants was 13.9 mmol/L (11.8, 16.6) compared with 12.2 mmol/L (10.6, 15.1) in Black participants (Figure 3). There was no significant difference in skin sodium in Black participants compared with White participants (Table 2).

Baseline PWV was 7.6 m/s (6.8, 9.0) and 7.5 m/s (6.5, 8.5) for White and Black participants, respectively

Table 1. Baseline Characteristics by Muscle Sodium Quartiles

| | Overall (n=98) | Q1: 12.5–14.8 mmol/L (n=24) | Q2: 14.9–16.2 mmol/L (n=25) | Q3: 16.3–18.8 mmol/L (n=24) | Q4: 18.9–25.6 mmol/L (n=25) |
|--------------------------------|------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Age, y | 47.5 (36.1–56.3) | 42.6 (35.7–54.5) | 47.5 (34.3–53.5) | 46.3 (36.3–55.0) | 51.9 (42.4–59.4) |
| Sex | | | | | |
| Female | 64 (65.3) | 17 (70.8) | 13 (52.0) | 16 (66.7) | 18 (72.0) |
| Race | | | | | |
| White | 58 (59.2) | 17 (70.8) | 15 (60.0) | 14 (58.3) | 12 (48.0) |
| Black | 40 (40.8) | 7 (29.2) | 10 (40.0) | 10 (41.7) | 13 (52.0) |
| Hypertension | 6 (6.1) | 0 (0.0) | 2 (8.0) | 2 (8.3) | 2 (8.0) |
| BMI, kg/m ² | 27.2 (24.4–32.3) | 25.7 (24.0–29.1) | 27.9 (25.4–31.3) | 30.5 (25.2–32.6) | 26.3 (23.8, 31.5) |
| Systolic BP, mm Hg | 126 (119–133) | 123 (115–132) | 126 (122–133) | 125 (122–129) | 127 (118–139) |
| Diastolic BP, mm Hg | 77 (70–83) | 74 (69–83) | 78 (72–84) | 77 (70–81) | 77 (71–81) |
| Serum creatinine, mg/dL | 0.83 (0.74–0.92) | 0.79 (0.68–0.87) | 0.85 (0.76–0.93) | 0.85 (0.76–0.95) | 0.82 (0.75–0.92) |
| Serum Na ⁺ , mmol/L | 139 (138–140) | 138 (137–140) | 139 (138–139.5) | 139 (138–141) | 139 (138–141) |
| Urine Na ⁺ , mmol/L | 36.6 (22.2–72.5) | 37.6 (27.1–72.1) | 35.9 (19.7–51.7) | 39.4 (18.3–79.4) | 38.1 (27.4–74.1) |
| Dietary Na ⁺ , mg | 3233 (2378–4401) | 3274 (2284–4650) | 3069 (2101–4536) | 3832 (3008–4456) | 3209 (2307–3599) |
| SAT volume, mL | 13.2 (9.6–16.8) | 14.0 (9.9–19.9) | 12.3 (7.9–15.3) | 13.8 (10.1–16.6) | 12.5 (8.6–16.3) |
| IMAT volume, mL | 1.3 (1.1–2.1) | 1.2 (0.9–1.4) | 1.4 (1.1–2.1) | 1.4 (1.1–2.1) | 1.6 (1.2–2.2) |

Data shown as n (%) or median (IQR). BMI indicates body mass index; BP, blood pressure; IMAT, intermuscular adipose tissue; IQR, interquartile range; Q, quartile; and SAT, subcutaneous adipose tissue.

Table 2. Effect of Race on Baseline Muscle Sodium, Skin Sodium, and Pulse Wave Velocity

| | Median (IQR) | Model 1 Beta (95% CI)* | P value* | Model 2 Beta (95% CI)† | P value† | Model 3 Beta (95% CI)‡ | P value ‡ |
|---|---------------------|------------------------|----------|------------------------|----------|------------------------|-----------|
| Muscle Na ⁺ (mmol/L) | | | | | | | |
| White | 15.8 (14.7 to 18.1) | 0.0 (ref) | ... | 0.0 (ref) | ... | 0.0 (ref) | ... |
| Black | 17.3 (15.1 to 20.0) | 0.07 (0.001 to 0.13) | 0.05 | 0.06 (−0.004 to 0.13) | 0.07 | 0.06 (−0.003 to 0.14) | 0.06 |
| Skin Na ⁺ (mmol/L) | | | | | | | |
| White | 13.9 (11.8 to 16.6) | 0.0 (ref) | ... | 0.0 (ref) | ... | 0.0 (ref) | ... |
| Black | 12.2 (10.6 to 15.1) | −0.04 (−0.14 to 0.06) | 0.46 | −0.06 (−0.16 to 0.05) | 0.28 | −0.06 (−0.16 to 0.05) | 0.30 |
| Pulse wave velocity [§] (cm/s) | | | | | | | |
| White | 7.6 (6.8 to 9.0) | 0.0 (ref) | ... | 0.0 (ref) | ... | 0.0 (ref) | ... |
| Black | 7.5 (6.5 to 8.5) | 0.04 (−0.04 to 0.11) | 0.31 | −0.003 (−0.07 to 0.06) | 0.93 | −0.01 (−0.07 to 0.06) | 0.87 |
| Urinary Na ⁺ (mEq/L) | | | | | | | |
| White | 36.6 (27.8 to 72.5) | 0.0 (ref) | ... | 0.0 (ref) | ... | ... | ... |
| Black | 39.4 (18.9 to 65.7) | −0.05 (−0.38 to 0.28) | 0.75 | −0.09 (−0.44 to 0.26) | 0.60 | ... | ... |
| Dietary Na ⁺ (mg) | | | | | | | |
| White | 3064 (2459 to 3938) | 0.0 (ref) | ... | 0.0 (ref) | ... | ... | ... |
| Black | 3103 (2162 to 3830) | −0.10 (−0.33 to 0.14) | 0.41 | −0.08 (−0.33 to 0.17) | 0.52 | ... | ... |

Values come from baseline (week 0) study visit, outcomes are log-transformed. BMI indicates body mass index; BP, blood pressure; IQR, interquartile range; and Na⁺, sodium.

*Model 1: adjusted for age and sex.

†Model 2: Model 1+BMI+systolic BP.

‡Model 3: Model 2+baseline dietary sodium+baseline urine sodium.

§N=84 for pulse wave velocity because of missing data, N=98 for all sodium measures including muscle Na⁺, skin Na⁺, urinary Na⁺, and dietary Na⁺.

(Figure 4). No significant difference in PWV was detected between Black and White participants in any of the models (β , −0.01 [95% CI, −0.07, 0.06 for the fully adjusted model]) (Table 2).

There was modest correlation between baseline muscle sodium and baseline skin sodium: $r=0.51$ ($P<0.01$). There was no correlation between muscle or skin sodium with PWV, $r=-0.0450$ ($P=0.69$) and $r=0.042$ ($P: 0.71$), respectively.

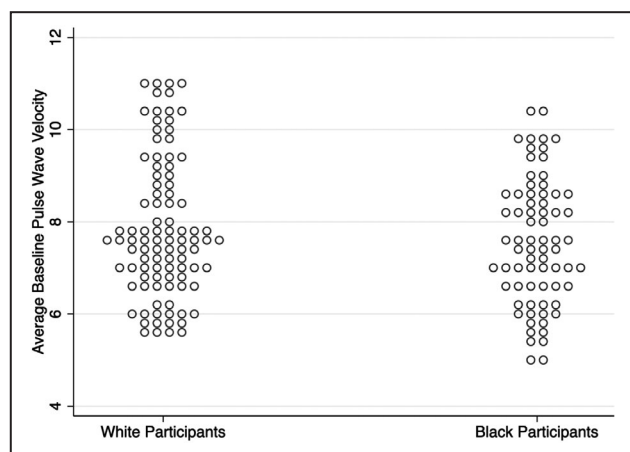


Figure 4. Baseline pulse wave velocity measurements by race.

Effect of Intervention on BP

The changes in systolic and diastolic BP at baseline and after 8 weeks of each intervention are shown in Table S2.

Effect of Intervention on Muscle Sodium

Table 3 depicts participant characteristics at baseline by intervention groups. Of the 60 randomized participants, most were female (66.7%), White (55%), and median age was 49.6 years (39.0, 58.5). Demographic and clinical characteristics were similar across placebo and intervention groups. Median serum sodium at baseline was 139 mEq/L (138, 140) for placebo, diet intervention, spironolactone, and chlorthalidone (Table 3). Median baseline and week 8 muscle sodium, skin sodium, PWV, urine sodium, dietary sodium, subcutaneous adipose tissue, and intermuscular adipose tissue by intervention arms are shown in Table 4.

The median differences between baseline and week 8 in muscle sodium were −0.4 mmol/L (−3.4, 0.2), 0.4 mmol/L (−1.4, 2.4), −0.8 mmol/L (−1.6, 1.1), and 0.3 mmol/L (−1.4, 4.0) for placebo, diet intervention, spironolactone, and chlorthalidone, respectively (Table 5). Compared with placebo, participants in the diet intervention exhibited a statistically significant increase in muscle sodium between baseline and week 8, after adjustment for age, race, sex, baseline

Table 3. Baseline Characteristics of the Study Population by Randomization Group

| | Overall (n=60) | Placebo (n=15) | Diet (n=15) | Spironolactone (n=16) | Chlorthalidone (n=14) |
|-------------------------|------------------|-------------------|------------------|-----------------------|-----------------------|
| Age, y | 49.6 (39.0–58.5) | 48.8 (33.9–61.1) | 53.6 (34.8–60.7) | 49.4 (39.6–58.5) | 50.6 (40.9–54.4) |
| Sex | | | | | |
| Female | 40 (66.7) | 10 (66.7) | 9 (60.0) | 11 (68.8) | 10 (71.4) |
| Race | | | | | |
| White | 33 (55.0) | 9 (60.0) | 7 (46.7) | 9 (56.3) | 8 (57.1) |
| Black | 27 (45.0) | 6 (40.0) | 8 (53.3) | 7 (43.7) | 6 (42.9) |
| Hypertension | 1 (1.7) | 0 (0.0) | 1 (6.7) | 0 (0.0) | 0 (0.0) |
| BMI, kg/m ² | 27.8 (24.8–32.1) | 26.6 (23.2–32.7) | 27.2 (25.3–31.5) | 30.7 (27.2–32.1) | 27.4 (24.9–32.3) |
| Serum creatinine, mg/dL | 0.82 (0.70–0.92) | 0.82 (0.69–0.90) | 0.86 (0.74–0.93) | 0.80 (0.70–0.96) | 0.87 (0.68–0.93) |
| Serum sodium, mmol/L | 139 (138–140) | 139 (138–141) | 139 (138–140) | 139 (138–140.5) | 139 (138–140) |
| Urine sodium, mmol/L | 41.0 (26.9–79.0) | 37.3 (27.8–108.8) | 41.4 (27.4–68.7) | 69.8 (27.8–112.4) | 38.0 (24.9–53.1) |
| Dietary sodium, mg | 3204 (2386–3933) | 3083 (2410–3928) | 3178 (2189–4082) | 3233 (2693–3730) | 3230 (1682–4494) |
| Systolic BP, mm Hg | 127 (121–133) | 126 (120–134) | 129 (125–134) | 122 (117–127) | 129 (123–134) |
| Diastolic BP, mm Hg | 77 (71–82) | 75 (73–83) | 74 (68–81) | 77 (71–82) | 78 (72–86) |
| SAT volume, mL | 13.9 (10.4–22.2) | 14.3 (6.8–29.3) | 12.6 (10.1–15.7) | 15.5 (11.5–26.3) | 14.0 (10.1–22.1) |
| IMAT volume, mL | 1.4 (1.0–2.1) | 1.2 (0.8–2.2) | 1.4 (1.1–2.3) | 1.5 (0.9–1.9) | 1.3 (1.2–1.5) |

Data shown as n (%) or median (IQR). BMI indicates body mass index; BP, blood pressure; IMAT, intermuscular adipose tissue; IQR, interquartile range; and SAT, subcutaneous adipose tissue.

muscle sodium, BMI, and systolic BP (β , 0.14 [95% CI, 0.05–0.22]; $P < 0.01$). Participants in the chlorthalidone group also had statistically significant increase

in muscle sodium compared with the placebo group (β , 0.13 [95% CI, 0.05–0.22]; $P < 0.01$) after adjustment for age, race, sex, baseline muscle sodium,

Table 4. Median (IQR) Values of Muscle Sodium, Skin Sodium, Urinary Sodium, Dietary Sodium Intake, Pulse Wave Velocity, IMAT Volume, and SAT Volume by Randomization Group at Each Time Point

| | Overall (n=60) | Placebo (n=15) | Diet (n=15) | Spironolactone (n=16) | Chlorthalidone (n=14) |
|-----------------------|------------------|-------------------|------------------|-----------------------|-----------------------|
| Muscle sodium | | | | | |
| Baseline | 16.8 (14.8–18.9) | 15.7 (14.3–19.8) | 18.1 (14.8–21.1) | 17.1 (15.0–18.8) | 17.1 (14.9–17.6) |
| Week 8 | 16.8 (15.4–18.5) | 15.3 (14.4–16.1) | 17.9 (16.8–19.9) | 16.3 (14.9–18.0) | 17.5 (15.7–20.6) |
| Skin sodium | | | | | |
| Baseline | 12.8 (11.3–17.3) | 12.2 (10.6–17.0) | 12.6 (11.8–16.6) | 13.3 (11.1–17.7) | 13.4 (10.9–17.7) |
| Week 8 | 13.1 (11.2–15.3) | 11.6 (10.1–13.3) | 13.9 (11.3–17.4) | 13.1 (12.6–15.4) | 14.1 (11.1–15.7) |
| Pulse wave velocity* | | | | | |
| Baseline | 7.7 (7.0–9.0) | 8.4 (7.3–10.3) | 7.9 (7.1–9.3) | 7.6 (6.5–8.4) | 7.3 (7.0–7.9) |
| Week 8 | 7.6 (6.9–9.9) | 8.3 (7.0–10.4) | 7.4 (7.1–9.5) | 8.1 (6.9–9.2) | 7.5 (6.9–7.9) |
| Urinary sodium | | | | | |
| Baseline | 41.0 (26.9–79.0) | 37.3 (27.8–108.8) | 41.4 (27.4–68.7) | 69.8 (27.8–112.4) | 38.0 (24.9–53.1) |
| Week 8 | 35.7 (13.5–61.9) | 46.0 (11.6–85.6) | 37.9 (8.4–59.2) | 32.2 (18.4–56.2) | 29.4 (16.0–50.6) |
| Dietary sodium intake | | | | | |
| Baseline | 3204 (2386–3933) | 3083 (2410–3928) | 3178 (2189–4082) | 3233 (2693–3730) | 3230 (1682–4494) |
| Week 8 | 2728 (1863–3507) | 3469 (2292–4387) | 2171 (1028–2489) | 3322 (2826–4354) | 2300 (1555–3396) |
| SAT volume | | | | | |
| Baseline | 13.9 (10.4–22.2) | 14.3 (6.8–29.3) | 12.6 (10.1–15.7) | 15.5 (11.5–26.3) | 14.0 (10.1–22.1) |
| Week 8 | 14.1 (10.7–21.5) | 15.5 (12.5–29.0) | 12.6 (9.7–15.3) | 14.5 (10.7–23.6) | 13.4 (9.8–21.5) |
| IMAT volume | | | | | |
| Baseline | 1.4 (1.0–2.1) | 1.2 (0.8–2.2) | 1.4 (1.1–2.3) | 1.5 (0.9–1.9) | 1.3 (1.2–1.5) |
| Week 8 | 1.4 (1.1–1.8) | 1.1 (0.8–1.7) | 1.7 (1.1–2.3) | 1.7 (1.1–1.8) | 1.3 (1.1–1.7) |

IMAT indicates intermuscular adipose tissue; IQR, interquartile range; and SAT, subcutaneous adipose tissue.

*N=47 for pulse wave velocity.

Table 5. Effect of Randomization on Muscle Sodium, Skin Sodium, and Pulse Wave Velocity From Baseline to Week 8

| | Difference wk 8-wk 0 [median (IQR)] | Adjusted difference Model 1 β (95% CI)* | P Value | Adjusted difference Model 2 β (95% CI)† | P Value | Adjusted difference Model 3 β (95% CI)‡ | P Value |
|--|-------------------------------------|---|---------|---|---------|---|---------|
| Muscle sodium | | | | | | | |
| Placebo | -0.4 (-3.4 to 0.2) | 0.0 (ref) | ... | 0.0 (ref) | ... | 0.0 (ref) | ... |
| Diet | 0.4 (-1.4 to 2.4) | 0.14 (0.05 to 0.22) | <0.01 | 0.14 (0.05 to 0.22) | <0.01 | 0.10 (0.004 to 0.19) | 0.04 |
| Spironolactone | -0.8 (-1.6 to 1.1) | 0.04 (-0.04 to 0.12) | 0.30 | 0.04 (-0.05 to 0.13) | 0.37 | 0.05 (-0.04 to 0.13) | 0.28 |
| Chlorthalidone | 0.3 (-1.4 to 4.0) | 0.13 (0.05 to 0.21) | <0.01 | 0.13 (0.05 to 0.22) | <0.01 | 0.12 (0.03 to 0.20) | <0.01 |
| Skin sodium | | | | | | | |
| Placebo | -1.5 (-3.4 to -0.2) | 0.0 (ref) | ... | 0.0 (ref) | ... | 0.0 (ref) | ... |
| Diet | -0.2 (-1.4 to 1.7) | 0.17 (0.05 to 0.30) | <0.01 | 0.17 (0.05 to 0.29) | <0.01 | 0.15 (0.02 to 0.28) | 0.03 |
| Spironolactone | 0.4 (-3.4 to 1.4) | 0.13 (0.01 to 0.25) | 0.03 | 0.09 (-0.04 to 0.21) | 0.17 | 0.10 (-0.02 to 0.22) | 0.10 |
| Chlorthalidone | -1.3 (-4.2 to 1.3) | 0.11 (-0.01 to 0.24) | 0.08 | 0.11 (-0.01 to 0.23) | 0.08 | 0.11 (-0.01 to 0.23) | 0.08 |
| Pulse wave velocity[§] | | | | | | | |
| Placebo | 0.1 (-0.4 to 0.5) | 0.0 (ref) | ... | 0.0 (ref) | ... | 0.0 (ref) | ... |
| Diet | 0.1 (-0.3 to 0.2) | -0.01 (-0.08 to 0.06) | 0.79 | -0.01 (-0.08 to 0.06) | 0.74 | -0.02 (-0.11 to 0.07) | 0.71 |
| Spironolactone | 0.0 (-0.2 to 0.2) | 0.02 (-0.05 to 0.09) | 0.57 | 0.01 (-0.07 to 0.09) | 0.76 | 0.01 (-0.08 to 0.10) | 0.80 |
| Chlorthalidone | -0.2 (-0.6 to 0.6) | -0.03 (-0.11 to 0.06) | 0.51 | -0.03 (-0.12 to 0.06) | 0.48 | -0.03 (-0.14 to 0.07) | 0.50 |
| Urinary sodium | | | | | | | |
| Placebo | -6.8 (-44.5 to 23.2) | 0.0 (ref) | ... | 0.0 (ref) | ... | ... | ... |
| Diet | -4.0 (-24.0 to 18.6) | -0.51 (-1.25 to 0.23) | 0.18 | -0.57 (-1.29 to 0.14) | 0.11 | ... | ... |
| Spironolactone | -33.8 (-78.8 to 28.3) | -0.15 (-0.86 to 0.55) | 0.66 | 0.03 (-0.69 to 0.76) | 0.92 | ... | ... |
| Chlorthalidone | -10.1 (-32.8 to -2.5) | -0.26 (-1.00 to 0.46) | 0.49 | -0.21 (-0.92 to 0.51) | 0.56 | ... | ... |
| Dietary sodium | | | | | | | |
| Placebo | 172 (-1131 to 1500) | 0.0 (ref) | ... | 0.0 (ref) | ... | ... | ... |
| Diet | -1047 (-2331 to -429) | -0.64 (-0.97 to -0.31) | <0.01 | -0.64 (-0.98 to -0.31) | <0.01 | ... | ... |
| Spironolactone | 447 (-429 to 1154) | 0.03 (-0.29 to 0.36) | 0.85 | 0.10 (-0.25 to 0.45) | 0.58 | ... | ... |
| Chlorthalidone | -911 (-2276 to 442) | -0.30 (-0.64 to 0.03) | 0.08 | -0.29 (-0.63 to 0.05) | 0.10 | ... | ... |

Outcomes are log-transformed. BMI indicates body mass index; BP, blood pressure; and IQR, interquartile range.

*Model 1: adjusted for age, sex, race, and baseline outcome value.

†Model 2: Model 1 + BMI + systolic BP.

‡Model 3: Model 2 + urine sodium + dietary sodium.

§N=47 for pulse wave velocity.

BMI, and systolic BP. The change in muscle sodium in participants in the spironolactone group did not differ significantly from that in the placebo group after adjustment for the same variables (β , 0.04 [95% CI, -0.05 to 0.13]; $P=0.37$).

Effect of Intervention on Skin Sodium

Compared with participants in the placebo group, only the dietary intervention resulted in statistically significant increase in skin sodium between baseline and week 8, after adjustment for age, race, sex, baseline muscle sodium, BMI, and systolic BP (Table 5). The difference in skin sodium was 17% higher in the diet intervention group compared with placebo at week 8 (β , 0.17 [95% CI, 0.05, 0.30]; $P<0.01$) (Table 5). Participants in the spironolactone and chlorthalidone groups both had increased skin sodium compared with placebo but neither reached statistical significance.

There was no correlation between the changes in muscle or skin Na⁺ and systolic or diastolic BP (Table S3).

Effect of Intervention on PWV

None of the interventions changed the PWV measurements in 8 weeks compared with placebo. The median differences between baseline and week 8 PWV measurements were 0.1 m/s (-0.4, 0.5), 0.1 m/s (-0.3, 0.2), 0 m/s (-0.2, 0.2), and -0.2 m/s (-0.6, 0.6) for the placebo, diet intervention, spironolactone, and chlorthalidone groups, respectively (Table 5).

Effect of Intervention Stratified by Race

The effects of the interventions on muscle sodium, skin sodium, or PWV did not statistically differ by race. Interaction terms between race and randomization group for muscle sodium, skin sodium, and PWV were not statistically significant (0.94, 0.18, and 0.40, respectively) (Table S4). As seen in the overall analyses, for muscle sodium, the diet intervention and chlorthalidone groups had a larger change in muscle sodium at week 8 compared with placebo in both White and Black participants, even after adjustment (Table S4).

Sensitivity Analyses

Sensitivity analysis examining effect of race on baseline muscle sodium, skin sodium, and PWV did not show notable changes in significance or inference after leave-1-out analysis (Table S5). Similarly, effect of randomization on muscle sodium, skin sodium, and PWV from baseline to week 8 was not different after leave-1-out analysis (Table S6).

Adherence to Intervention

As shown in Table 5, dietary sodium intake was significantly reduced in the diet arm at week 8 compared with placebo. However, in the diet arm, the change in urinary sodium at 8 weeks was not significantly different than placebo. Pill count was done only on 20 patients and adherence to pills was >95% in these patients.

DISCUSSION

In this study, we found that, compared with placebo, dietary salt restriction or diuretic intervention did not decrease skin and muscle sodium content over a period of 8 weeks in patients with early stage hypertension or hypertension. While at baseline higher muscle sodium content in Black patients was observed compared with White patients matched for age and sex, a significant racial difference was not present in the fully adjusted model that included salt intake and BP.

Several studies have suggested that certain medications such as spironolactone and sodium/glucose cotransporter 2 inhibitors could mobilize tissue sodium. In our study, patients in the dietary intervention arm had slight but statistically significant increase in both skin and muscle sodium levels when compared with placebo. Chlorthalidone resulted in a significant increase in muscle sodium while spironolactone had no effect in either compartments. While this finding may be random, it is possible that increased sodium excretion in response to chlorthalidone is compensated through some retention in muscle tissue.

The primary aim for the study was to provide a preventive strategy for BP control. Accordingly, we enrolled individuals with minimal comorbidities, no significant kidney disease, and mild hypertension, which could have impacted the results. Consistent with this preference, the study subjects did not have high tissue sodium concentrations at baseline when compared with other studies where patients with other comorbidities such as advanced kidney disease were included. With such low quantities of sodium at baseline, it is much less likely to ascertain any significant differences in tissue sodium content in response to diuretic therapy or dietary intervention. However, other contributing factors such as insufficient dosing and potency of diuretics, nonadherence with sodium-restricted diet or daily pills could have resulted in null findings. Notably, urinary sodium at baseline or end of study did not correlate with tissue sodium or dietary sodium intake. Patients in the dietary intervention group underwent counseling by a certified dietitian in the beginning of the study and we did dietary recalls in the middle and at the end of the study to assess adherence and provide further guidance. Despite showing a significant

reduction in dietary sodium intake on dietary recalls, urine sodium levels in the low sodium diet group were not altered at week 8 compared with placebo. It is also possible that interventions may have exerted a significant effect if the duration of intervention was extended for a time longer than 8 weeks to reach a new steady state of lower sodium in tissue.

We also hypothesized that decreasing sodium intake or increasing urinary excretion would mobilize sodium from tissue stores that would in turn reduce vascular stiffness assessed by PWV. Our results showed no association between tissue sodium content and PWV and the interventions did not have any noticeable effect either. While these findings would suggest lack of any biological link, a longer treatment period with a more effective reduction in tissue sodium stores might possibly lead to improvements in arterial stiffness. In addition, changes in muscle and skin Na⁺ were in opposite directions. This suggests that the 2 compartments may be regulated by different mechanisms.

Our findings did not fully support our a priori hypothesis that Black subjects would have higher skin and muscle sodium content. Our results suggest that there is no interaction between race and tissue sodium deposition. It is well-established that salt-sensitive hypertension is more common among Black patients.^{28,29} While in the unadjusted analysis, Black patients had slightly higher muscle sodium than White patients, the difference was not significant after adjustment for age, sex, BMI, and systolic BP. Of note, Black patients did not exhibit increased skin sodium content. It is possible that such difference would be highly pronounced in a different patient population with more significant comorbidities or worse BP control. Considering the suggestive finding that there might be a difference in muscle sodium storage in a relatively healthy group of Black patients such as ours, the difference would likely be more pronounced in groups with higher BP or in patients with kidney disease. Notably, median kidney function, systolic BP, and urinary and dietary sodium did not significantly differ between Black and White patients at baseline, further diminishing biological factors that could contribute to differences in sodium storage in tissue.

Our study had several limitations. First, this was a randomized clinical trial with a small sample size and a short duration of treatment. Secondly, whether reducing the tissue sodium content improves cardiovascular mortality remains unknown. A clinically significant target reduction in skin or muscle sodium to improve cardiovascular morbidity or mortality is also unavailable. Hence, despite being an easy and subjective measure, the clinical significance of our primary outcome is not fully established. Finally, sample size for our study could be inadequate to show significant differences between racial groups and interventions. We did not

recruit the original targeted sample size because the interim analysis suggested that a much larger number than initially proposed would be required to find any statistically and clinically significant difference between interventions and placebo. In addition, we did not have data for adherence to pills on some patients. Despite these limitations, data from this clinical trial potentially suggest that efforts to mobilize tissue sodium should be targeted to patients who are more likely to be at risk such as ones with impaired kidney function and other comorbidities. In such populations, sodium stores may be high enough to exert a clinical effect and excreting sodium from tissue then could potentially result in clinically detectable change.

In conclusion, we were not able to demonstrate any difference in the tissue sodium between Black and White patients. We also report that dietary salt restriction or diuretic intervention with chlorthalidone or spironolactone did not decrease skin or muscle sodium content compared with placebo in 8 weeks among subjects with pre- or mild hypertension. Further studies are needed to investigate other factors that might mobilize tissue sodium, as well as the role of tissue sodium removal in cardiovascular outcomes.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S6

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Supplemental Material

Table S1. Interim analysis.

| Model | Futility probability | | |
|------------------------------|-----------------------------|---------------------|-----------------------|
| | Diet | Spirolactone | Chlorthalidone |
| Muscle sodium: Model 1 | 1.000 | 0.999 | 1.000 |
| Muscle sodium: Model 2 | 1.000 | 1.000 | 1.000 |
| Muscle sodium, Model 3 | 1.000 | 1.000 | 1.000 |
| Skin sodium, Model 1 | 1.000 | 1.000 | 1.000 |
| Skin sodium, Model 2 | 1.000 | 1.000 | 1.000 |
| Skin sodium, Model 3 | 1.000 | 1.000 | 1.000 |
| Pulse wave velocity, Model 1 | 0.994 | 1.000 | 0.918 |

| | | | |
|------------------------------|-------|-------|-------|
| Pulse wave velocity, Model 2 | 0.992 | 1.000 | 0.924 |
| Pulse wave velocity, Model 3 | 0.992 | 0.999 | 0.930 |

Table S2. Blood pressure at baseline and week 8 in each randomization group (median, [interquartile range])

| | Week 0 | Week 8 | P* |
|---------------------------------|----------------|----------------|-----------|
| Systolic Blood Pressure | | | |
| Placebo (n=15) | 126 (120, 134) | 124 (118, 132) | 0.8020 |
| Diet (n=15) | 129 (125, 134) | 127 (119, 136) | 0.9552 |
| Spironolactone (n=16) | 122 (117, 127) | 120 (116, 130) | 0.4920 |
| Chlorthalidone (n=14) | 129 (123, 134) | 117 (115, 124) | 0.0619 |
| Diastolic Blood Pressure | | | |
| Placebo (n=15) | 75 (73, 83) | 75 (72, 77) | 0.5059 |
| Diet (n=15) | 74 (68, 81) | 74 (71, 85) | 0.6070 |
| Spironolactone (n=16) | 77 (71, 82) | 74 (70, 84) | 0.9978 |
| Chlorthalidone (n=14) | 78 (72, 86) | 70 (67, 77) | 0.2018 |

*The difference between baseline and week 8 blood pressure values were calculated using a two-sample t-test

Table S3. Correlations between changes in muscle and skin sodium and changes in systolic and diastolic blood pressure

| | Change in Systolic Blood Pressure | Change in Diastolic Blood Pressure |
|--------------------------------|--|---|
| Change in Muscle Sodium | 0.0862 (p=0.5476) | 0.2625 (p=0.0627) |
| Change in Skin Sodium | 0.2346 (p=0.0976) | 0.2560 (p=0.0699) |

Table S4. Effect of randomization on muscle sodium, skin sodium, and PWV stratified by race

| | Difference [Median (IQR)] | β (95% CI)* | P | β (95% CI) ⁺ | P | β (95% CI) [^] | P |
|------------------------------------|---------------------------|---------------------|-------|-------------------------------|-------|-------------------------------|-------|
| Muscle Sodium | | | | | | | |
| White | | | | | | | |
| Placebo | -0.4 (-1.7, 0.9) | 0.0 (ref) | - | 0.0 (ref) | - | 0.0 (ref) | - |
| Diet | 0.4 (-0.5, 2.6) | 0.12 (0.003, 0.24) | 0.04 | 0.11 (-0.01, 0.24) | 0.07 | 0.08 (-0.05, 0.21) | 0.21 |
| Spirolactone | -0.04 (-0.9, 1.6) | 0.03 (-0.08, 0.14) | 0.59 | 0.02 (-0.10, 0.14) | 0.71 | 0.02 (-0.10, 0.14) | 0.72 |
| Chlorthalidone | 0.3 (-0.01, 5.7) | 0.11 (-0.002, 0.22) | 0.05 | 0.11 (-0.01, 0.22) | 0.07 | 0.11 (-0.002, 0.23) | 0.06 |
| Black | | | | | | | |
| Placebo | -2.0 (-4.2, -0.2) | 0.0 (ref) | - | 0.0 (ref) | - | 0.0 (ref) | - |
| Diet | -0.2 (-1.6, 2.4) | 0.16 (0.03, 0.28) | 0.02 | 0.16 (0.03, 0.30) | 0.02 | 0.12 (-0.02, 0.25) | 0.10 |
| Spirolactone | -1.3 (-2.4, -0.3) | 0.06 (-0.07, 0.19) | 0.35 | 0.06 (-0.07, 0.19) | 0.37 | 0.07 (-0.05, 0.20) | 0.26 |
| Chlorthalidone | -0.5 (-1.9, 2.4) | 0.16 (0.03, 0.29) | 0.02 | 0.16 (0.03, 0.30) | 0.02 | 0.12 (-0.01, 0.26) | 0.08 |
| P for interaction: 0.94 | | | | | | | |
| Skin Sodium | | | | | | | |
| White | | | | | | | |
| Placebo | -0.7 (-1.6, -0.2) | 0.0 (ref) | - | 0.0 (ref) | - | 0.0 (ref) | - |
| Diet | -0.2 (-0.9, 1.7) | 0.14 (-0.03, 0.32) | 0.10 | 0.12 (-0.05, 0.29) | 0.17 | 0.10 (-0.08, 0.27) | 0.27 |
| Spirolactone | 0.2 (-4.7, 0.6) | 0.03 (-0.13, 0.19) | 0.68 | -0.04 (-0.20, 0.12) | 0.63 | -0.02 (-0.18, 0.14) | 0.79 |
| Chlorthalidone | 0.1 (-2.9, 2.0) | 0.09 (-0.08, 0.25) | 0.29 | 0.08 (-0.08, 0.23) | 0.32 | 0.09 (-0.06, 0.25) | 0.23 |
| Black | | | | | | | |
| Placebo | -2.8 (-4.3, -0.7) | 0.0 (ref) | - | 0.0 (ref) | - | 0.0 (ref) | - |
| Diet | -0.5 (-1.8, 3.0) | 0.22 (0.03, 0.40) | 0.02 | 0.25 (0.07, 0.42) | <0.01 | 0.22 (0.03, 0.40) | 0.03 |
| Spirolactone | 0.8 (0.1, 3.0) | 0.16 (0.08, 0.46) | <0.01 | 0.24 (0.06, 0.42) | <0.01 | 0.24 (0.06, 0.41) | <0.01 |
| Chlorthalidone | -2.0 (-6.2, -0.4) | 0.05 (-0.05, 0.34) | 0.14 | 0.14 (-0.04, 0.33) | 0.12 | 0.13 (-0.06, 0.31) | 0.18 |
| P for interaction: 0.18 | | | | | | | |
| Pulse Wave Velocity (PWV)** | | | | | | | |
| White | | | | | | | |

| | | | | | | | |
|-------------------------|-------------------|---------------------|------|---------------------|------|---------------------|------|
| Placebo | 0.1 (-0.6, 0.5) | 0.0 (ref) | - | 0.0 (ref) | - | 0.0 (ref) | - |
| Diet | -0.3 (-0.4, 0.1) | -0.04 (-0.14, 0.06) | 0.44 | -0.04 (-0.15, 0.06) | 0.42 | -0.04 (-0.16, 0.08) | 0.48 |
| Spironolactone | 0.1 (-0.2, 0.2) | 0.03 (-0.06, 0.13) | 0.45 | 0.02 (-0.07, 0.12) | 0.62 | 0.03 (-0.08, 0.14) | 0.63 |
| Chlorthalidone | -0.3 (-0.6, 0.4) | -0.02 (-0.14, 0.10) | 0.73 | -0.02 (-0.14, 0.10) | 0.74 | -0.02 (-0.16, 0.13) | 0.81 |
| Black | | | | | | | |
| Placebo | 0.2 (0.0, 0.5) | 0.0 (ref) | - | 0.0 (ref) | - | 0.0 (ref) | - |
| Diet | 0.4 (0.1, 1.0) | 0.02 (-0.08, 0.12) | 0.72 | 0.02 (-0.09, 0.13) | 0.76 | 0.02 (-0.11, 0.15) | 0.80 |
| Spironolactone | -0.03 (-0.1, 0.6) | -0.01 (-0.12, 0.10) | 0.85 | -0.02 (-0.14, 0.10) | 0.74 | -0.02 (-0.16, 0.12) | 0.75 |
| Chlorthalidone | 0.2 (-0.6, 0.6) | -0.04 (-0.15, 0.08) | 0.52 | -0.04 (-0.16, 0.08) | 0.53 | -0.04 (-0.18, 0.11) | 0.62 |
| P for interaction: 0.40 | | | | | | | |

Urinary Sodium

White

| | | | | | | | |
|----------------|-----------------------|---------------------|------|---------------------|------|---|---|
| Placebo | -32.5 (-50.0, 12.1) | 0.0 (ref) | - | 0.0 (ref) | - | - | - |
| Diet | -19.9 (-63.3, 18.6) | -0.97 (-2.08, 0.13) | 0.08 | -0.78 (-1.88, 0.32) | 0.16 | - | - |
| Spironolactone | -78.3 (-105.7, -34.0) | -0.71 (-1.67, 0.26) | 0.15 | -0.44 (-1.46, 0.57) | 0.38 | - | - |
| Chlorthalidone | -10.1 (-25.3, 18.3) | -0.31 (-1.31, 0.68) | 0.53 | -0.16 (-1.14, 0.82) | 0.74 | - | - |
| Black | | | | | | | |
| Placebo | -2.8 (-6.8, 23.2) | 0.0 (ref) | - | 0.0 (ref) | - | - | - |
| Diet | -3.4 (-15.5, 23.1) | -0.03 (-1.07, 1.01) | 0.96 | -0.31 (-1.37, 0.74) | 0.55 | - | - |
| Spironolactone | 39.5 (-33.5, 66.2) | 0.51 (-0.56, 1.58) | 0.35 | 0.52 (-0.53, 1.57) | 0.32 | - | - |
| Chlorthalidone | -12.4 (-138.0, -4.1) | -0.19 (-1.30, 0.92) | 0.73 | -0.29 (-1.37, 0.80) | 0.60 | - | - |

P for interaction: 0.21

Dietary Sodium

White

| | | | | | | | |
|----------------|---------------------|----------------------|-------|----------------------|------|---|---|
| Placebo | 143 (-1131, 504) | 0.0 (ref) | - | 0.0 (ref) | - | - | - |
| Diet | -944 (-2493, 81) | -0.69 (-1.16, -0.21) | <0.01 | -0.64 (-1.13, -0.14) | 0.01 | - | - |
| Spironolactone | -56 (-765, 744) | -0.02 (-0.46, 0.41) | 0.92 | 0.06 (-0.41, 0.53) | 0.81 | - | - |
| Chlorthalidone | -659 (-1791, 671) | -0.16 (-0.61, 0.28) | 0.47 | -0.14 (-0.60, 0.31) | 0.53 | - | - |
| Black | | | | | | | |
| Placebo | 335 (-119, 1500) | 0.0 (ref) | - | 0.0 (ref) | - | - | - |
| Diet | -1205 (-1997, -884) | -0.61 (-1.12, -0.11) | 0.02 | -0.66 (-1.19, -0.14) | 0.01 | - | - |
| Spironolactone | 1142 (-40, 1255) | 0.09 (-0.42, 0.61) | 0.72 | 0.13 (-0.40, 0.66) | 0.62 | - | - |

| | | | | | | | |
|-------------------------|---------------------|---------------------|------|---------------------|------|---|---|
| Chlorthalidone | -1158 (-2862, -592) | -0.49 (-1.02, 0.04) | 0.07 | -0.49 (-1.03, 0.05) | 0.08 | - | - |
| P for interaction: 0.50 | | | | | | | |

Notes: outcomes are log-transformed.

*Model 1: adjusted for age, sex, and baseline outcome value

+Model 2: Model 1 + BMI + systolic BP

^Model 3: Model 2 + dietary sodium + urine sodium

Abbreviations: CI, confidence interval; IQR, interquartile range

**N=47 for pulse wave velocity

Table S5. Effect of race on baseline muscle sodium, skin sodium, and pulse wave after leave-one-out analysis

| | Model 1 | p-value | Model 2 | p-value | Model 3 | p-value |
|------------------------------|-----------------------|----------------|-----------------------|----------------|-----------------------|----------------|
| | Beta (95% CI)* | | Beta (95% CI)+ | | Beta (95% CI)^ | |
| Muscle Na⁺ | | | | | | |
| (mmol/L) | | | | | | |
| White | 0.0 (ref) | | 0.0 (ref) | | 0.0 (ref) | |
| Black | 0.05 (-0.01, 0.12) | 0.10 | 0.03 (-0.04, 0.10) | 0.41 | 0.05 (-0.02, 0.12) | 0.13 |
| Skin Na⁺ | | | | | | |
| (mmol/L) | | | | | | |
| White | 0.0 (ref) | | 0.0 (ref) | | 0.0 (ref) | |
| Black | -0.04 (-0.14, 0.06) | 0.44 | -0.08 (-0.19, 0.02) | 0.11 | -0.06 (-0.16, 0.05) | 0.29 |
| Pulse Wave | | | | | | |
| Velocity** | | | | | | |
| (cm/s) | | | | | | |
| White | 0.0 (ref) | | 0.0 (ref) | | 0.0 (ref) | |
| Black | 0.04 (-0.04, 0.11) | 0.31 | -0.01 (-0.08, 0.06) | 0.85 | -0.004 (-0.07, 0.06) | 0.90 |

Urinary Na⁺

(mEq/L)

| | | | | | |
|-------|---------------------|------|---------------------|------|---|
| White | 0.0 (ref) | | 0.0 (ref) | | - |
| Black | -0.04 (-0.36, 0.29) | 0.83 | -0.05 (-0.40, 0.30) | 0.77 | - |

Dietary Na⁺

(mg)

| | | | | | |
|-------|--------------------|------|--------------------|------|---|
| White | 0.0 (ref) | | 0.0 (ref) | | - |
| Black | 0.05 (-0.14, 0.25) | 0.58 | 0.02 (-0.19, 0.23) | 0.85 | - |

Note: Values come from baseline (week 0) study visit, outcomes are log-transformed

Abbreviations: CI, confidence interval; IQR, interquartile range; Na⁺, sodium.

*Model 1: adjusted for age and sex

+Model 2: Model 1 + BMI + systolic BP

^Model 3: Model 2 + baseline dietary sodium + baseline urine sodium

** N=84 for pulse wave velocity due to missing data, N=98 for all sodium measures including muscle Na⁺, skin Na⁺, urinary Na⁺ and dietary Na⁺

Table S6. Effect of randomization on muscle sodium, skin sodium, and pulse wave velocity from baseline to week 8 after leave-one-out analysis

| | Adjusted Difference | P | Adjusted | P | Adjusted Difference | P |
|----------------------|----------------------------|----------|--------------------|----------|----------------------------|----------|
| | Model 1 | | Difference | | Model 3 | |
| | β (95% CI)* | | Model 2 | | β (95% CI)^ | |
| | | | β (95% CI)+ | | | |
| Muscle Sodium | | | | | | |
| Placebo | 0.0 (ref) | - | 0.0 (ref) | - | 0.0 (ref) | - |
| Diet | 0.17 (0.09, 0.26) | <0.01 | 0.18 (0.09, 0.27) | <0.01 | 0.15 (0.05, 0.25) | 0.01 |
| Spironolactone | 0.09 (0.003, 0.17) | 0.04 | 0.09 (-0.02, 0.17) | 0.06 | 0.09 (0.00, 0.18) | 0.05 |
| Chlorthalidone | 0.17 (0.08, 0.25) | <0.01 | 0.17 (0.08, 0.25) | <0.01 | 0.15 (0.06, 0.24) | <0.01 |
| Skin Sodium | | | | | | |
| Placebo | 0.0 (ref) | - | 0.0 (ref) | - | 0.0 (ref) | - |
| Diet | 0.20 (0.06, 0.33) | <0.01 | 0.18 (0.05, 0.31) | <0.01 | 0.18 (0.04, 0.32) | 0.01 |
| Spironolactone | 0.14 (0.02, 0.27) | 0.03 | 0.14 (0.01, 0.27) | 0.03 | 0.11 (-0.01, 0.24) | 0.07 |
| Chlorthalidone | 0.12 (-0.01, 0.26) | 0.07 | 0.12 (-0.01, 0.25) | 0.07 | 0.14 (0.00, 0.27) | 0.05 |
| Pulse Wave | | | | | | |
| Velocity | | | | | | |

| | | | | | | |
|----------------|---------------------|------|---------------------|------|----------------------|------|
| Placebo | 0.0 (ref) | - | 0.0 (ref) | - | 0.0 (ref) | - |
| Diet | 0.002 (-0.07, 0.07) | 0.94 | 0.01 (-0.06, 0.08) | 0.79 | -0.003 (-0.10, 0.09) | 0.95 |
| Spirolactone | 0.03 (-0.04, 0.10) | 0.44 | 0.05 (-0.02, 0.12) | 0.19 | 0.02 (-0.07, 0.12) | 0.61 |
| Chlorthalidone | -0.03 (-0.12, 0.05) | 0.40 | -0.02 (-0.10, 0.06) | 0.57 | -0.03 (-0.14, 0.07) | 0.51 |

Urinary Sodium

| | | | | | | |
|----------------|---------------------|------|---------------------|------|---|---|
| Placebo | 0.0 (ref) | - | 0.0 (ref) | - | - | - |
| Diet | -0.52 (-1.23, 0.19) | 0.15 | -0.65 (-1.36, 0.05) | 0.07 | - | - |
| Spirolactone | -0.20 (-0.87, 0.46) | 0.54 | 0.02 (-0.65, 0.70) | 0.94 | - | - |
| Chlorthalidone | 0.18 (-0.90, 0.53) | 0.61 | -0.19 (-0.90, 0.52) | 0.60 | - | - |

Dietary Sodium

| | | | | | | |
|----------------|----------------------|-------|----------------------|-------|---|---|
| Placebo | 0.0 (ref) | - | 0.0 (ref) | - | - | - |
| Diet | -0.63 (-0.95, -0.31) | <0.01 | -0.65 (-0.98, -0.31) | <0.01 | - | - |
| Spirolactone | 0.04 (-0.28, 0.35) | 0.82 | 0.10 (-0.23, 0.43) | 0.55 | - | - |
| Chlorthalidone | -0.39 (-0.73, -0.05) | 0.03 | -0.40 (-0.76, -0.05) | 0.03 | - | - |

Notes: outcomes are log-transformed

Abbreviations: CI = confidence interval; IQR = interquartile range

*Model 1: adjusted for age, sex, race, and baseline outcome value

+Model 2: Model 1 + BMI + systolic BP

^Model 3: Model 2 + urine sodium + dietary sodium

**N=47 for pulse wave velocity
