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Effects of Sodium Bicarbonate in CKD Stages 3 and 4: A Randomized, Placebo-Controlled, Multicenter Clinical Trial

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Abstract

Rationale & Objective: Metabolic acidosis associated with chronic kidney disease (CKD) may contribute to muscle dysfunction and bone disease. We aimed to test whether treatment with sodium bicarbonate improves muscle and bone outcomes.

Study Design: Multi-center, randomized, placebo-controlled clinical trial.

Setting & Participants: 149 patients with CKD stages 3 and 4 between 7/2011 and 4/2016 at three centers in Cleveland, OH and the Bronx, NY.

Intervention: Sodium bicarbonate (NaBicarb) (0.4 mEq per kilogram of ideal body weight per day) (n=74) or identical placebo (n=75).

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Data Sharing: The authors will share de-identified participant level data collected during the trial that underlie the results reported in this article. The study protocol will also be available upon request. The data will be available 6 months after publication and ending 4 years after publication of this article. The data will be shared with researchers who provide a methodologically sound proposal for analyses pertaining to the aims in the proposal. Proposals should be emailed directly to michal.melamed@einstein.yu.edu. Data requesters will need to sign a data use agreement.

Outcomes: The dual primary outcomes were muscle function assessed by sit-to-stand test and bone mineral density. Muscle biopsies were collected at baseline and 2 months. Participants were seen at baseline, 2, 6, 12 and 24 months.

Results: The mean baseline serum bicarbonate level was 24.0 ± 2.2 (SD) and mean baseline eGFR was 36.3 ± 11.2 ml/min/1.7m². Baseline characteristics did not differ between groups. Mean serum bicarbonate levels in the intervention arm over follow-up were 26.4 ± 2.2 , 25.5 ± 2.3 , 25.6 ± 2.6 , and 24.4 ± 2.8 mEq/L (at 2, 6, 12, and 24 months). These were significantly higher than in the placebo group ($p < 0.001$). Compared to the placebo group, participants randomized to NaBicarb had no significant differences in sit-to-stand time (5 repetitions: $p = 0.1$; and 10 repetitions $p = 0.07$), and bone mineral density ($p = 0.3$). NaBicarb caused a decrease in serum potassium levels that was of borderline statistical significance ($p = 0.05$). There were no significant differences in eGFR, BP, weight, serious adverse events or the levels of muscle gene expression between the randomized groups.

Limitations: Initial mean serum bicarbonate level was in the normal range.

Conclusions: NaBicarb therapy in patients with CKD stages 3 and 4 significantly increases serum bicarbonate and decreases potassium levels. No differences were found in muscle function or bone mineral density between the randomized groups. Larger trials are required to evaluate effects on kidney function.

Funding: National Institutes of Health grant.

Trial Registration: Registered at [Clinicaltrials.gov](https://clinicaltrials.gov) with study number

Keywords

chronic kidney disease (CKD); metabolic acidosis; sodium bicarbonate; alkali therapy; muscle function; bone mineral density; metabolic bone disease; sit-to-stand; randomized controlled trial (RCT)

Introduction

Chronic kidney disease (CKD) affects over 16 million people in the United States and is associated with multiple morbidities and an increased risk of mortality. Currently, there are a limited number of treatments to stop the progression of kidney disease. Chronic metabolic acidosis is a complication of kidney disease but may also cause further kidney damage. Animal data suggests chronic metabolic acidosis may cause further kidney damage by activating the complement system, or upregulating endothelin and aldosterone production.^{1,2} Several observational studies have revealed lower bicarbonate levels are associated with faster progression of kidney disease.^{3,4} Acid retention, even in the absence of overt metabolic acidosis, is associated with poor outcomes.⁵ Several small randomized clinical trials have suggested benefit of alkali therapy in the progression of kidney disease.⁶⁻⁹

Chronic metabolic acidosis may also affect bone and muscles. Experimental studies have shown that chronic metabolic acidosis can directly trigger osteoclast-mediated bone resorption and block osteoblast-mediated bone formation, increase PTH levels, and worsen metabolic bone disease.¹⁰ An analysis of NHANES data revealed an association between

low serum bicarbonate levels and lower bone mineral density in US adults.¹¹ Previous studies in the general population show that potassium citrate and potassium bicarbonate may improve bone mineral density.^{12,13} Animal models show that metabolic acidosis contributes to muscle protein breakdown.¹⁴ A pilot study we conducted showed that treatment with alkali resulted in improved lower extremity muscle performance in a study of 20 adult CKD patients.¹⁵ Two unblinded studies showed improvement in mid-arm muscle circumference.^{6,9}

Due to a paucity of placebo-controlled data on safety and effects of sodium bicarbonate therapy in CKD, we conducted a randomized, placebo-controlled trial of sodium bicarbonate therapy in patients with CKD stages 3 and 4 (eGFR 15–59 ml/min/1.73m²) to evaluate the effects on bone and muscle function. We hypothesized that treatment with sodium bicarbonate compared to placebo would improve muscle function, measured by the sit to stand test, and decrease bone resorption, as measured by Dual Energy X-ray Absorptiometry. In addition, we collected serial measurements of weight, blood pressure, markers of muscle catabolism (impaired insulin signaling, markers of inflammation, and indicators of proteolysis (levels of muscle atrogen 1 and muscle RING-finger protein 1 (MuRF1) and a 14-kDa actin fragment)¹⁶ plus laboratory data (serum bicarbonate and potassium, estimated glomerular filtration rate) and patient reported outcomes, including quality of life.

Methods

Study Population

We recruited 149 participants with CKD stages 3 and 4 between 7/2011 and 4/2016 to participate in the trial. Participants had to be greater than 18 years old, have an eGFR of 15–59 ml/min/1.73m², and serum bicarbonate levels 20 to 26 mEq/L. Of note, due to low recruitment, half-way through the trial, the upper limit of sodium bicarbonate eligibility was increased from 25 to 26 mEq/L. We used 20 mEq/L as the lower limit due to ethical concerns about not treating patients with serum bicarbonate <20 mEq/L for a long-term study. Exclusion criteria included 1) treatment with alkali therapy in the last 3 months, 2) serum bicarbonate levels < 20 and >26 mEq/L, 3) New York Heart Association Class III or IV heart failure, 4) systolic blood pressure >180 mmHg, 5) initiation of kidney replacement therapy (KRT) planned within 6 months, 6) previous kidney transplantation or 7) treatment with immunosuppressive medications within the last three months. We did not exclude patients with underlying lung disease or on oxygen. The IRBs at the Albert Einstein College of Medicine and at Case Western Reserve University approved the study protocol. All participants provided informed consent. The trial was registered on [ClinicalTrials.gov](https://clinicaltrials.gov) ().

Study Design

Participants were recruited from three study sites: Case Western Reserve University/ University Hospitals Cleveland Medical Center, MetroHealth Medical Center (Cleveland, OH) and Montefiore Medical Center/ Albert Einstein College of Medicine (Bronx, NY). Participants were randomized using a computer-generated randomization protocol administered by the research pharmacy at the respective institutions. Randomization was

stratified by center. Participants were randomized to either 0.4 mEq/d sodium bicarbonate per kilogram of ideal body weight (Watson pharmaceuticals) or identical-appearing placebo capsule. Participants, research coordinators, and investigators were all blinded to the treatment assignment. The typical intervention patient received NaBicarb either 1950 mg or 2600 mg daily. We designed the study to marginally offset the net endogenous acid production (1 mEq/kg/d) while being mindful of the sodium load. Participants were seen at baseline (pre-randomization) and at 2, 6, 12 and 24 months after randomization. Participants were withdrawn from the study if they developed a serum bicarbonate >30 mEq/L or <18 mEq/L, potassium <3.5 mEq/L twice within 2 weeks, or were hospitalized for congestive heart failure.

Measurements

Participants' demographics, medical and social history, and medication use was obtained via questionnaire. Participant's race/ethnicity was self-reported. Blood pressure was recorded at each study visit as the mean of three measurements at least one minute apart after at least 5 minutes of rest in a seated position with an appropriate blood pressure cuff. Participants' height was recorded at baseline and weights were recorded at each visit. Lower extremity edema was assessed at each visit by a trained investigator (classified as none, 1+, 2+ or 3+). Serum, plasma and urine samples were collected at each visit. Serum chemistry values, including potassium, were measured by routine procedures at the clinical laboratories of the University Hospitals Cleveland Medical Center and Montefiore Medical Center. Serum bicarbonate was measured using the phosphoenolpyruvate carboxylase method. Serum creatinine was measured by a modified kinetic Jaffe reaction. Estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) equation.¹⁷ Participants reported their health status on the Short Form Health Survey, the SF-36, at each time point.¹⁸

Study Outcomes

Sit-to-stand (STS) time was measured by asking participants to sit in a straight-backed, non-cushioned chair and then stand and sit 10 times in succession. The total time and the time after five repetitions were recorded. At each visit, the STS test was performed twice, with a minimum of 30 minutes separating the two measurements. We used the mean of the two measurements for analysis.

Handgrip strength was measured three times with each hand using a handheld dynamometer (North Coast Medical, Inc., Gilroy, CA). The mean of the three measurements in the dominant arm was used for analysis.

Bone mineral density at the femoral neck was measured by Dual Energy X-ray Absorptiometry (DXA) (GE/Lunar Prodigy, Madison, WI) at baseline, 6, 12 and 24 months.

Adverse events were prospectively collected and included laboratory parameters (serum bicarbonate and potassium based), physical exam (edema) and adverse events (hospitalization, emergency department visits, and other self-reported health outcomes).

Muscle biopsies—In a subset of participants, quadriceps muscle biopsies were performed at baseline and at the 2-month timepoint to examine effects of sodium bicarbonate on skeletal muscle insulin signaling, proteolysis, and inflammation. For each biopsy, participants were admitted at 8:00 AM to the Clinical Research Center study room after an overnight fast. Approximately 100mg of tissue was obtained from the vastus lateralis muscle via an incision that was 15cm proximal to the superior border of the patella. Muscle tissue was blotted to remove extraneous blood and immediately frozen in liquid nitrogen and stored at -80°C . These samples were used for analyses of messenger RNA or proteins to determine if there were changes in levels of catabolic markers.

Gene Expression analysis—RNA was isolated from muscle biopsy using RNeasy Fibrous tissue mini kits (Qiagen); complementary DNA (cDNA) was prepared using iScript cDNA synthesis kits (Bio-Rad). Duplicate polymerase chain reaction amplifications were performed using SYBR green (Bio-Rad) on a Bio-Rad CFX96 real-time thermal cycler.^{19,20} Gene expression was calculated from cycle threshold values using expression of the GAPDH gene as an internal control (Ct ; relative expression = $2^{(\text{sample Ct} - \text{GAPDH Ct})}$). Primer sequences used for reverse transcription–polymerase chain reaction will be provided if requested.

Western Blotting—Muscle samples (1 mg per 20 μl of buffer) were homogenized in RIPA buffer containing Complete Mini Protease Inhibitor and PhosStop Phosphatase Inhibitor (Roche Applied Science, Indianapolis, IN). Lysates were centrifuged for 5 min at $16,200 \times g$ at 4°C and equal amounts of protein from the supernatant were separated on SDS-polyacrylamide gels in Tris/SDS buffer, transferred onto nitrocellulose membranes and incubated with primary antibodies overnight at 4°C . After washing with TBST, the membrane was incubated with secondary antibodies conjugated to IRDye (Cell Signaling, Beverly, MA) at room temperature for 1 h. Protein bands were scanned using the Odyssey system (LI-COR, Lincoln, Nebraska). The band density of target proteins was quantified using NIH ImageJ Software.

Statistical Analyses

Sample size calculations were based on the outcome of bone mineral density. Assuming a standard deviation of 0.12 g/cm^2 and with 64 subjects per group, we had greater than 80% power for detecting an effect of 0.06 g/cm^2 with an alpha of 0.05. We aimed to recruit 150 participants (75 in each group) assuming a 15% drop-out to yield a total of 128 participants completing the study. For muscle function, assuming a standard deviation of 1.5 seconds and with 15 subjects per group, there is a greater than 95% power for detecting an effect of 2 seconds (10%). We previously saw a change of 1.6 seconds after 6 weeks of NaBicarb treatment in 20 adults.¹⁵

All analyses were performed using the intention to treat principle. Differences in baseline characteristics between the two groups were compared using Student's t-tests or the Wilcoxon rank sum tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. The number of participants with hyperkalemia (defined as potassium $>5.0 \text{ mEq/L}$ at any time over follow-up) was calculated in each group over follow-up. The

groups were compared using chi-square and logistic regression. Linear mixed models with a subject-specific random effect to account for repeated measurements from subjects were used to examine effects of sodium bicarbonate on serum bicarbonate, potassium, eGFR, weight, blood pressure, and sit-to-stand time and whether effects of sodium bicarbonate on these outcome variables varied with time. eGFR was square root transformed. Weight and sit-to-stand time were log-transformed. Gamma regression models with a subject-specific random effect were used to examine effects of sodium bicarbonate on bone mineral density and handgrip strength over time. Generalized linear mixed models (GLMMs) with a random intercept and a cumulative logit link function were used to examine the effect of sodium bicarbonate on quality of life (SF-36) measurements. SF-36 measurements were converted into three level variables based on baseline tertiles. Risk difference and 95% confidence intervals were calculated to compare adverse effects.

Effects of sodium bicarbonate on the expression of muscle proteins and genes were examined using repeated measures ANOVA with terms for treatment and time. All analyses were performed using SAS version 9.4 (Cary, NC) and Stata version 13.1 (College Station, TX). A two-sided p-value <0.05 was considered statistically significant.

Results

Participant Characteristics

There were 283 patients who were assessed for eligibility, of whom 149 were randomized (Figure 1). The baseline characteristics of the 149 participants in the study are shown in Table 1. The study cohort had a mean age of 61 $\pm$ 12.6 (SD); 54% were women, 58% non-Hispanic black, 27% non-Hispanic white, and 13% Hispanic. At baseline, 93% of the participants had hypertension and 62% had diabetes mellitus. The mean serum bicarbonate level at baseline was 24.0 $\pm$ 2.2 mEq/L and the mean eGFR at baseline was 36.3 $\pm$ 11.2 ml/min/1.73 m². There were no statistically significant differences between the placebo and intervention group in any of the baseline characteristics.

Effects on Serum Bicarbonate, Potassium and estimated GFR

The mean follow-up was 1.35 $\pm$ 0.75 years. There was no difference in mean follow-up time between randomized groups, NaBicarb 1.29 $\pm$ 0.76 years vs. placebo 1.42 $\pm$ 0.74 years (p-value = 0.3). Follow-up represented 106 person years on placebo and 95 person years on NaBicarb. A total of 45 participants dropped out over the course of the study. (Figure 1) Serum bicarbonate levels were similar at baseline (24.1 $\pm$ 2.6 mEq/L vs. 24.0 $\pm$ 2.2 mEq/L) between the two study arms. Thereafter, the levels significantly increased in the participants assigned to sodium bicarbonate treatment (p<0.001). At 2, 6, 12, and 24 months, the mean serum bicarbonate levels in the intervention arm were 26.4 $\pm$ 2.2, 25.5 $\pm$ 2.3, 25.6 $\pm$ 2.6, and 24.4 $\pm$ 2.8 mEq/L (Figure 2A). There were 44 participants who achieved a >3 mEq/L rise in serum bicarbonate at any follow-up time point in the sodium bicarbonate group compared to 20 participants in the placebo group (p<0.001). In a finding of borderline statistical significance (P = 0.05), sodium bicarbonate caused a decrease in serum potassium levels by approximately 0.1 mEq/L compared to placebo (Figure 2B).

There were no statistically significant differences in eGFR at any time point between the two groups (Table 2) ($p = 0.7$).

Effects on Bone Mineral Density, Muscle Function and Quality of Life

Participants randomized to alkali therapy had similar bone mineral density at 24 months compared to participants in the placebo arm (Table 2). Bone mineral density decreased in both groups at 24 months compared to baseline ($p=0.03$). There were also no significant differences observed in hand grip strength between the two groups (Table 2). Handgrip strength decreased over time in the placebo group, and increased slightly over time in the sodium bicarbonate group, but the difference was not statistically significant. Sit-to-stand times decreased in both the placebo and sodium bicarbonate groups (p -value <0.001) during follow-up, but there was no difference in the rate of change between the groups. There were no statistically significant differences in weight, blood pressure (Figure 2C), physical function, physical composite score or any other quality of life measurements between the two randomized groups.

Effects on Muscle Insulin Signaling, Proteolysis, and Inflammation

Muscle biopsies were performed in 12 participants (5 in the sodium bicarbonate group, 7 in the placebo group). The median change in serum bicarbonate between baseline and the 2-month biopsy was +1 mEq/L (interquartile range (IQR), 0 to 2) in the sodium bicarbonate arm and -1 mEq/L (IQR, -3 to +1) in the placebo arm. There were no significant effects of sodium bicarbonate supplementation on insulin signaling (based on Western blotting of phosphorylated Akt and total Akt), an indicator of muscle protein breakdown (14-kDa actin fragment), proteolysis mediators (atrogin 1, MuRF1 messenger RNA), or markers of inflammation (Table 3 and Figure 3).

Safety of the Intervention

There was no statistical difference in the number of serious adverse events between the alkali and the placebo groups (Table 4). There were 14 patients in the sodium bicarbonate group who had a potassium level >5.0 mEq/L over the course of the study compared to 30 patients in the placebo group ($p=0.006$) (Odds ratio, 0.35; 95% confidence interval, 0.17–0.74). There were slightly more total adverse events in the NaBicarb group (45% vs. 32%). There were no other differences in adverse events.

Discussion

In this multi-center, placebo-controlled randomized trial of 149 patients with CKD stages 3 and 4, we found that we were able to significantly raise serum bicarbonate levels and lower serum potassium levels, but found no difference in serum creatinine or estimated GFR, muscle function, or bone mineral density. We also did not find differences in patient-reported quality of life or in muscle breakdown products. Notably, this is to our knowledge the first double-blind, placebo-controlled trial of sodium bicarbonate therapy in patients with eGFR <60 ml/min/1.73m².

Our study differs in several important ways from previous studies of alkali therapy. Participants in our study had significantly higher baseline serum bicarbonate levels than in the de Brito-Ashurst study (24.0 mEq/L in our study versus 19.8 mEq/L).⁶ We also used a slightly smaller dose of alkali than previous studies that had shown a difference in eGFR decline. Mahajan et al used a dose of 0.5 meq per kilogram of lean body mass; de Brito-Ashurst et al, in a non-blinded study, titrated the dose of sodium bicarbonate to achieve a serum bicarbonate level 23 mEq/L. While the de Brito-Ashurst mean dose was lower (1.8 g vs. 2.6 g in our study), they titrated to a sodium bicarbonate level. In our study, 46% (26 out of 57) of participants on alkali therapy maintained a serum bicarbonate level 23 mEq/L at 24 months because we did not titrate the sodium bicarbonate dose. We also tested the effects of alkali in patients with a wide range of causes of CKD, whereas several of the other studies included only patients with hypertension.^{7,21}

While the effect on potassium was small, over follow-up, the likelihood of developing a serum potassium >5.0 mEq/L was significantly less in the sodium bicarbonate group. As new, expensive potassium binders are introduced on the market,²² it may be worthwhile using sodium bicarbonate, a less expensive alternative as a first line agent.

Previous studies have evaluated the effects of sodium bicarbonate on muscle function. In our previous pilot study in 20 participants, we found that after 6 weeks of increasing sodium bicarbonate therapy, sit-to-stand times improved.¹⁵ Observational associations between low serum bicarbonate level and lower physical function are found in both CKD patients²³ and the general population.^{23–25} We did not find a difference in muscle function between the two groups over follow-up. Muscle biopsy results also did not show any differences in muscle protein breakdown or insulin signaling between placebo and sodium bicarbonate groups. This is in contrast to prior studies in people with advanced CKD, which showed that treatment of acidosis reduced muscle protein breakdown,^{26,27} and animal studies, which demonstrated that acidosis-induced muscle proteolysis was mediated by impaired insulin signaling.^{28,29} Our analyses were limited by the small number of biopsy participants, and an effect, if present, would likely have been smaller than expected due to the normal levels of baseline serum bicarbonate in our participants.

Bone is the primary long-term buffer of acidity in the body and animal studies have consistently shown metabolic acidosis causes a decrease in osteoblast activity, increase in osteoclast activity and decreased cortical bone mass.^{10,30,31} Ours is the first study of patients with CKD evaluating the effects of bicarbonate therapy on bone mineral density, but there have been several studies in the general population that have shown a positive effect of alkali therapy on bone. Several studies in post-menopausal women have shown improved bone resorption parameters including positive calcium and phosphate balance and decreased hydroxyproline and amino-terminal telopeptides.^{13,32,33} Two trials by Jehle et al in older adults (n=201) and post-menopausal women (n=161) have shown improvement in BMD after 12–24 months, in participants starting with normal serum bicarbonate levels.^{12,34} One of these studies used HR-pQCT, a more precise measure than DXA, to evaluate bone microarchitecture.¹² Interestingly, these studies used potassium salts while in our study we used sodium bicarbonate. Whether the sodium load may have led to more calcium excretion should be explored. Notably, a recent review suggested that the sodium load in sodium

bicarbonate may also lead to fluid retention and higher blood pressures.³⁵ Although not statistically different, more participants in our sodium bicarbonate group had an increase in their blood pressure medications.

We did not observe a statistically significant difference in eGFR between the two groups. Several non-placebo controlled trials have shown that alkali therapy decreased the progression of kidney disease. de Brito-Ashurst et al. in a non-placebo controlled, unblinded study showed that the rate of decline of creatinine clearance was 1.88 ml/min/1.73m² in the alkali group compared to 5.93 ml/min/1.73m² in the control group.⁶ In a more recent study that was also not blinded and not placebo controlled, Dubey et al showed that the eGFR was higher in the alkali group (32.7 ml/min/1.73m²) compared to the control group (28.2 ml/min/1.73m²) at the end of 6 months (p<0.001).⁹ Both these studies have inherent limitations as they are unblinded, and therefore, investigators and/or participants may inadvertently control other risk factors in the active group.

Our study has several limitations including that it was not powered to evaluate kidney function outcomes. We had a greater than expected number of participants drop out of the study and the bicarbonate levels of the two groups did not achieve consistently large separation over the 24 months of the study. Our population also had fairly normal serum bicarbonate levels at enrollment, which may have limited the effect of the intervention. It appeared that many clinicians at our centers treated patients with mild metabolic acidosis (serum bicarbonate levels 20–22 mEq/L), thereby limiting recruitment of these patients into the study. We did not collect arterial or venous blood gases or perform any urine measurements, thus, we did not have a complete picture of participant acid/base status or sodium or calcium balance. However, our study has several strengths including the randomized, placebo-controlled and multi-center design. We also had a large representation of minorities and women. Repeated measurements allowed for greater power to detect differences.

In this multi-center, randomized, placebo-controlled trial of sodium bicarbonate in participants with CKD stages 3 and 4, there was no significant difference between the randomized groups in muscle function, as measured by sit-to-stand-to-sit test or bone mineral density. Although not powered for the outcome, there were no differences in kidney function over 2 years. A larger, randomized clinical trial of sodium bicarbonate therapy, possibly with a larger dose of sodium bicarbonate, is required to evaluate whether treatment of with sodium bicarbonate is beneficial for kidney function.

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Figure 1.
Participant flow diagram.

Figure 2. Effects of sodium bicarbonate versus placebo administration on bicarbonate, potassium and blood pressure.
Changes in serum bicarbonate (A), serum potassium (B) and blood pressure (C) over 2 years of treatment with either sodium bicarbonate or placebo.

Figure 3. Protein and gene expression within the m. vastus lateralis muscle of CKD patients with sodium bicarbonate versus placebo administration.

Western blotting of muscle lysates (Visit 1 and 2 correspond to Baseline and 2 months, respectively) (A), expression of phosphorylated Akt (normalized to total Akt) (B), 14-kDa actin fragment density (C), and messenger RNA for the E3 ubiquitin ligases MuRF1 (muscle RING-finger protein 1) (D), and atrogin 1 (E), IL-6 (F), TNF-α (G), and CD68 (H), before and after 2 months of sodium bicarbonate (n=5) or placebo (n=7). For IL-6 and CD68, one outlier in the placebo group was excluded due to values >3 standard deviations above the mean at both baseline and 2 month visits. P>0.05 for all comparisons.

Table 1.

Baseline characteristics of 149 participants in a randomized clinical trial of sodium bicarbonate versus placebo.

Characteristic	All (n=149)	Placebo (n= 75)	Sodium bicarbonate (n= 74)	p-value
Age in yrs, mean (SD)	61.0 (12.6)	61.6 (10.9)	60.3 (14.1)	0.5
Female sex, n (%) (F=1)	80 (54)	42 (56)	38 (51)	0.6
Race/ethnicity, n (%)				0.5
Non-Hispanic black	86 (58)	47 (62)	39 (53)	
Non-Hispanic white	40 (27)	16 (21)	24 (32)	
Hispanic	19 (13)	10 (13)	9 (12)	
Other	4 (3)	2 (3)	2 (3)	
High school graduate, n (%)	121 (82)	61 (81)	60 (82)	0.9
Income <\$25,000, n (%)	62 (42)	30 (30)	32 (43)	0.6
Married, n (%)	43 (30)	21 (29)	22 (31)	0.7
Hypertension, n (%)	139 (93)	71 (95)	68 (92)	0.5
Diabetes mellitus, n (%)	92 (62)	43 (57)	49 (66)	0.3
Congestive heart failure, n (%)	16 (11)	8 (11)	8 (11)	1.0
Current smokers, n (%) (n=146)	31 (21)	18 (24)	13 (18)	0.6
Former smokers, n (%) (n=146)	43 (29)	20 (27)	23 (32)	0.6
ACE inhibitor/ARB use, n (%)	116 (78)	58 (77)	58 (78)	0.9
Diuretic use, n (%)	92 (62)	50 (67)	42 (57)	0.2
Beta blocker use, n (%)	83 (56)	43 (57)	40 (54)	0.7
Weight, kg, mean (SD)	95 (34)	96 (35)	95 (33)	0.9
Body mass index (kg/m ²)	33.6 (7.7)	33.8 (8.4)	33.4 (7.7)	0.8
Edema (2+ or more), n (%)	23 (15)	11 (15)	12 (16)	0.8
Systolic BP (mmHg), mean (SD)	137 (17)	136 (16)	138 (18)	0.4
Diastolic BP (mmHg), mean (SD)	76 (10)	76 (11)	75 (9)	0.3
Bicarbonate (mEq/L), mean (SD)	24.0 (2.2)	24.1 (2.6)	24.0 (2.2)	0.9
Potassium (mEq/L), mean (SD)	4.6 (0.5)	4.6 (0.5)	4.5 (0.5)	0.2
Creatinine (mg/dL), mean (SD)	2.0 (0.9)	2.0 (0.7)	2.0 (1.1)	0.8
eGFR, (ml/min/1.73 m ²), mean (SD)	36.3 (11.2)	36.2 (11.1)	36.4 (11.4)	0.9

Values for continuous variables expressed as mean $\pm$ SD; for categorical variables as count (percentage).

Table 2.

Sit-to-stand-to-sit, handgrip strength, bone mineral density, weight, blood pressure, eGFR and quality of life results by randomized group.

	Placebo			Sodium bicarbonate					p	
	BL	Mo 2	Mo 6	Mo 12	Mo 24	BL	Mo 2	Mo 6	Mo 12	Mo 24
Sit to stand time (sec)										
5 repetitions	11.7 (1.4)	11.3 (1.4)	10.9 (1.4)	11.1 (1.4)	10.3 (1.3)	12.6 (1.3)	11.9 (1.3)	11.8 (1.3)	11.6 (1.3)	10.8 (1.3)
10 repetitions	25.9 (9.8)	24.9 (9.9)	24.0 (7.7)	24.7 (7.8)	22.9 (6.5)	27.4 (8.0)	26.2 (7.6)	25.6 (7.6)	25.0 (6.9)	23.8 (5.8)
Handgrip Strength (kg)*	26.9 (9.9)	26.5 (10)	26.2 (10)	24.5 (9.5)	24.9 (10.2)	26.6 (10.6)	26.9 (9.6)	27.0 (9.3)	26.2 (8.7)	27.3 (9.8)
BMD (g/cm ²)	0.74 (0.16)	NA	0.74 (0.18)	0.74 (0.16)	0.73 (0.17)	0.76 (0.20)	NA	0.79 (0.22)	0.76 (0.20)	0.75 (0.23)
Weight (kg)	92.9 (26.1)	92.8 (26.3)	93.1 (26.4)	91.3 (27.3)	89.4 (28.5)	93.4 (22.7)	94.1 (23.6)	94.4 (22.7)	93.5 (22.9)	91.9 (23.0)
SBP (mmHg)	132 (17)	132 (21)	133 (19)	131 (19)	131 (17)	134 (21)	138 (20)	135 (19)	135 (24)	131 (17)
DBP (mmHg)	75 (12)	76 (13)	74 (13)	72 (11)	71 (10)	73 (11)	76 (11)	74 (13)	74 (12)	72 (10)
Quality of Life (SF-36)										
Physical function	43 (10)	42 (11)	42 (11)	41 (11)	43 (11)	42 (12)	41 (12)	41 (12)	41 (11)	40 (12)
Role physical	24 (3.6)	24 (4.1)	24 (3.5)	24 (3.9)	24 (4.0)	23 (4.3)	24 (4.0)	23 (4.0)	23 (4.2)	23 (4.1)
Body pain	48 (12)	48 (10)	48 (11)	48 (12)	49 (11)	48 (12)	47 (11)	45 (11)	46 (12)	46 (11)
Vitality	55 (13)	53 (12)	55 (12)	54 (12)	56 (13)	54 (13)	56 (12)	55 (12)	53 (11)	52 (12)
General health	43 (10)	44 (9)	44 (10)	42 (10)	43 (11)	41 (10)	42 (11)	43 (10)	43 (10)	45 (9)
PCS	39 (8.3)	40 (8.6)	40 (8.9)	39 (9.0)	40 (8.3)	39 (8.9)	38 (8.7)	38 (8.2)	38 (8.5)	38 (8.7)
MCS	48 (9.1)	46 (9.1)	46 (9.7)	46 (9.8)	47 (9.1)	46 (9.4)	47 (8.1)	47 (9.2)	46 (9.8)	47 (9.4)
eGFR (ml/min/1.73m ²)	37.1 (12.2)	37.3 (12.6)	37.2 (12.5)	35.4 (13.7)	36.3 (12.9)	39.2 (14.5)	38.2 (15.0)	37.2 (15.8)	36.1 (13.5)	38.5 (17.7)
										0.7

Values presented as mean (SD). BMD, Bone mineral density; SBP, Systolic Blood Pressure; DBP, diastolic Blood Pressure; PCS, Physical Composite Score; MCS, Mental Component Score

Table 3.

Effects of sodium bicarbonate on muscle protein and gene expression

	P value
Ratio of phosphorylated to total Akt	0.4
14-kDa actin fragment	0.2
MuRF1	0.07
Atrogin 1	0.09
TNF- α	0.3
CD68	0.3
IL-6	0.3

P-values calculated using repeated measures ANOVA with terms for treatment and time.

Table 4.

Adverse outcomes over the 24 months of the study comparing placebo to sodium bicarbonate treatment groups.

Outcome over follow-up	Placebo (n=75)	Sodium bicarbonate (n=74)	Risk difference (95% CI)
Serum bicarbonate 30 mEq/L, n(%)	5 (7)	9 (12)	0.05 (−0.04, 0.15)
Serum bicarbonate 18 mEq/L, n(%)	4 (5)	2 (3)	−0.03 (−0.09, 0.04)
Serum potassium 3.5 mEq/L, n(%)	2 (3)	4 (5)	0.03 (−0.04, 0.09)
Serum potassium 5.0 mEq/L, n(%)	30 (40)	14 (19)	−0.21 (−0.35, −0.07)
Edema 2+, n(%)	35 (47)	35 (48)	0.01 (−0.15, 0.17)
Increase in diuretics, n(%)	4 (5)	6 (8)	0.03 (−0.05, 0.11)
Increase in other BP medications, n(%)	7 (9)	14 (19)	0.10 (−0.02, 0.21)
CHF hospitalizations, n(%)	2 (3)	3 (4)	0.01 (−0.04, 0.07)
All-cause hospitalizations, n (%)	15 (20)	20 (27)	0.07 (−0.07, 0.21)
Worsening of CHF, n (%)	3 (4)	5 (7)	0.03 (−0.04, 0.10)
All-cause adverse events, n (%)	24 (32)	33 (45)	0.13 (−0.03, 0.28)

BP, blood pressure; CHF, congestive heart failure; CI, confidence interval