RESEARCH LETTER

Response to Alkali Administration in Women and Men With and Without CKD

To the Editor:

Alkali therapy may limit the progression of chronic kidney disease (CKD)[1-4] or prevent the recurrence of urinary stone disease.[5,6] Proper dosing of alkali is necessary to avoid complications such as metabolic alkalosis or excessive urine alkalinization, which can lead to calcium phosphate kidney stones. There is evidence that women excrete more alkaline urine than men, and this tendency may account for the higher prevalence of calcium phosphate stones in women.[7] Worcester et al reported that women excrete more alkaline urine because they extract more dietary alkali than men.[8] If these findings could be extrapolated to clinical practice, women may need to be prescribed lower doses of alkali salts lest their urine becomes too alkaline. To our knowledge, no studies have directly addressed whether alkali should be dosed differently between women and men. To investigate sex differences in the urine response to alkali treatment, we examined changes in the amount of urine ammonium (NH_4^+) and citrate and the urine pH in response to weight-based dosing of sodium bicarbonate ($NaHCO_3$) in women and men in good health and those with CKD.

The study was approved by the institutional review board of Stanford University, and volunteers provided written informed consent. The BASE Pilot Trial was approved by institutional review boards at each site and study participants provided written informed consent. The BASE Pilot Trial was registered at clinicaltrials.gov (NCT02521181).

In our study of healthy volunteers, age-matched participants (8 women and 7 men) with a median age of 34.3 years (interquartile range, 5.7) received a single daily dose of $NaHCO_3$ 0.5 mEq/kg of body weight for 1 week (Table S1). Participants were asked to complete a 24-hour urine sample collection at baseline and after 1 week of taking the prescribed dosage of $NaHCO_3$ while consuming a similar free-choice diet. Baseline 24-hour urine pH, NH_4^+, and citrate levels were not significantly different between women and men. After the administration of $NaHCO_3$ for 1 week, the 24-hour urine pH increased and 24-hour urine NH_4^+ level decreased for the entire cohort. We noted no sex differences in the change from baseline or the level of 24-hour urine output parameters after treatment with $NaHCO_3$ (Table 1).

We next examined the urine sample response to the administration of $NaHCO_3$ for women and men with stage 3 or 4 CKD in the BASE Pilot Trial[4] (Table S2). Participants received either $NaHCO_3$ 0.5 mEq/kg of lean body weight per day (LD-$NaHCO_3$) or $NaHCO_3$ 0.8 mEq/kg of lean body weight per day (HD-$NaHCO_3$) in divided doses for 28 weeks. Participants were not given any specific dietary instructions other than to limit sodium intake at their discretion. In the BASE Pilot Trial, the level of urine citrate was not measured from 24-hour urine samples as part of the protocol; therefore, we report urine citrate/creatinine level measured from a random BASE urine sample to compare with urine citrate/creatinine level of healthy volunteers. Baseline urine pH, NH_4^+, and citrate/creatinine levels were not significantly different between women and men. After administration of LD-$NaHCO_3$, urine pH and citrate/creatinine levels increased and urine NH_4^+ levels decreased for the entire cohort and urine NH_4^+ level was lower and citrate/creatinine level was higher in women than in men. After administration of HD-$NaHCO_3$, urine pH and citrate/creatinine levels increased and urine NH_4^+ level decreased for the entire cohort, and the level of these urine parameters was not different between women and men. We again found no sex differences in the change from baseline parameters in urine pH, NH_4^+, or citrate/creatinine levels after treatment with $NaHCO_3$ for either dose (Table 1, Tables S3 and S4).

Our data demonstrate that the urine response to alkali therapy is similar for women and men if weight-based dosing is prescribed to either healthy volunteers or persons with CKD while consuming an *ad libitum* diet. A weight-based dosing regimen will lower the level of urine NH_4^+ excretion and raise the level of urine citrate and pH to a similar extent in women and men, which can be particularly important for the treatment of women with calcium phosphate kidney stones and hypocitraturia.[7] Our study has several limitations. First, the sample size was small, and it is possible that the trend toward higher urine pH in women (after treatment with $NaHCO_3$) would have reached statistical significance with a larger sample size. Second, although we included healthy volunteers and patients with CKD, we did not include patients with urinary stone disease. Therefore, we do not know if this dosing regimen would induce equivalent changes in urine pH, NH_4^+, or citrate levels for women and men with urinary stone disease or whether it would induce differences in stone recurrence. Third, although we examined urine parameters that respond to alkali treatment, we did not compare between women and men the effects of alkali dosing on acid-base balance by more quantitative measures such as net endogenous acid production or net acid excretion.

In conclusion, women and men have a similar pharmacodynamic response to weight-based dosing of alkalis, suggesting that a person's sex should not play a major factor in determining the initial dose of prescribed alkali.

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Table 1. Baseline and post-$NaHCO_3$ level of urine pH, ammonium (NH_4^+), and citrate/creatinine in healthy volunteers and BASE participants with chronic kidney disease

	Baseline			Post-$NaHCO_3$		
Healthy Volunteers	**pH**	**NH_4^+ (mmol)**	**Citrate/Cr (mg/mg)**	**pH**	**NH_4^+ (mmol)**	**Citrate/Cr (mg/mg)**
Total (n=15)	6.56 (0.67)	32.4 (9.80)	0.466 (0.131)	7.23 (0.47)[a]	22.0 (8.34)[a]	0.549 (0.217)
Women (n=8)	6.63 (0.71)	29.4 (8.08)	0.524 (0.129)	7.33 (0.43)[a]	17.0 (6.27)[a]	0.703 (0.254)
Men (n=7)	6.49 (0.67)	35.8 (11.1)	0.400 (0.104)	7.17 (0.51)	25.6 (8.10)	0.440 (0.098)
P value for W vs. M[b]	0.70	0.23	0.06	0.58	0.07	0.08
P value for difference in mean change for W vs. M[c]	—	—	—	0.99	0.84	0.19

	Baseline			Post-$NaHCO_3$		
BASE Participants	**pH**	**NH_4^+ (mmol)**	**Citrate/Cr (mg/mg)**	**pH**	**NH_4^+ (mmol)**	**Citrate/Cr (mg/mg)**
Total (n=123)						
LD-$NaHCO_3$ (n=47)	5.86 (0.46)	19.8 (10.8)	0.195 (0.166)	6.61 (0.55)[a]	13.5 (8.1)[a]	0.284 (0.182)[a]
HD-$NaHCO_3$ (n=76)	5.75 (0.46)	22.7 (12.9)	0.151 (0.137)	6.73 (0.56)[a]	13.1 (9.4)[a]	0.262 (0.172)[a]
Women						
LD-$NaHCO_3$ (n=16)	5.96 (0.50)	17.7 (10.4)	0.243 (0.195)	6.65 (0.61)[a]	10.7 (3.7)[a]	0.386 (0.257)
HD-$NaHCO_3$ (n=21)	5.80 (0.49)	19.1 (10.8)	0.177 (0.157)	6.79 (0.61)[a]	11.1 (8.1)[a]	0.302 (0.132)[a]
Men						
LD-$NaHCO_3$ (n=31)	5.79 (0.42)	20.9 (11.0)	0.170 (0.147)	6.58 (0.53)[a]	14.9 (9.3)[a]	0.235 (0.106)[a]
HD-$NaHCO_3$ (n=55)	5.73 (0.45)	24.1 (13.5)	0.141 (0.128)	6.70 (0.55)[a]	13.9 (9.8)[a]	0.248 (0.183)[a]
P value for W vs. M[b]						
LD-$NaHCO_3$	0.20	0.33	0.20	0.66	0.03	0.04
HD-$NaHCO_3$	0.54	0.10	0.36	0.54	0.22	0.17
P value for difference change for W vs. M[c]						
LD-$NaHCO_3$				0.70	0.33	0.20
HD-$NaHCO_3$	—	—	—	0.89	0.36	0.83

Note: Values reported as mean (SD); post-$NaHCO_3$ values are the average of values of urine sample at the week 12 and week 28 visit of participants with chronic kidney disease from the BASE Pilot Trial.
Abbreviations: Cr, creatinine; HD, high dose; LD, low dose; NH_4^+, ammonium; $NaHCO_3$, sodium bicarbonate; pH, potential hydrogen; W, women; M, men.
[a]*P* value <0.05 for comparison between baseline parameters and parameters after administration of $NaHCO_3$.
[b]*P* value is for comparisons between women and men at the same visit.
[c]*P* value is for comparisons of the mean change from baseline parameters in women and men.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1: Baseline characteristics of healthy volunteers.

Table S2: Baseline characteristics of participants in the BASE Pilot Trial.

Table S3: Baseline and post-$NaHCO_3$ level of 24-hour urine sodium (mmol) in healthy volunteers and BASE participants with chronic kidney disease.

Table S4: Baseline and post-$NaHCO_3$ level of 24-hour urine citrate (mg) in healthy volunteers.

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Authors' Contributions: Research idea and study design: AP, KR; data acquisition: AP, SS, KR; data analysis/interpretation: AP, JL,

KR, SRS, CG, SC, PF; statistical analysis: SK; supervision or mentorship: AP, JL, KR, AC, JI, TI, MW, DR, SMS, LF, JG. Each author contributed important intellectual content during article drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

Support: This work was funded in part by the Stanford School of Medicine Women's Health and Sex Differences in Medicine Center. The BASE Pilot Trial was conducted by the National Institute of Diabetes and Digestive and Kidney Diseases Pilot Clinical Trials in Chronic Kidney Disease Consortium (contracts U01DK097093, U01DK099877, U01DK099924, U01DK099930, and U01DK099933). The funders of the study had no role in the study design, collection, analysis, interpretation of data, writing the report or the decision to submit the report for publication.

Financial Disclosure: Dr Isakova reports consulting honorarium from Blueprint Partnership Manchester Ltd. The remaining authors declare that they have no relevant financial interests.

Peer Review: Received January 16, 2023 as a submission to the expedited consideration track with 3 external peer reviews. Direct editorial input by a Statistical Editor and the Editor-in-Chief. Accepted in revised form March 11, 2023.

 Published online May 15, 2023 with doi 10.1016/j.xkme.2023.100670

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