Title: Bicarbonate Administration and Cognitive Function in Midlife and Older Adults with CKD

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I. Hypotheses and Specific Aims:

Specific Aims

Chronic kidney disease (CKD) is largely an age-related clinical disorder with accelerated cognitive and cardiovascular aging. Cognitive impairment is a well-documented occurrence in midlife and older adults with CKD and affects multiple domains. Cognitive function worsens as kidney function declines. Twenty to 50% of adults aged 50 or older with moderate CKD have cognitive impairment or dementia. Cognitive impairment in CKD results in increased mortality, functional decline, depression, frailty and reduced quality of life. Additionally, it disqualifies patients from kidney transplantation. **Thus, there is a need to identify novel treatments for cognitive impairment in CKD.**

Acid base homeostasis is very important for neurologic function. Metabolic acidosis may be a contributing factor to the development of dementia through overexcitation and imbalance of cortical pyramidal neurons and GABAergic neurons. Additionally, metabolic acidosis results in increased inflammation, activation of the renin-angiotensin-aldosterone system (RAAS) and oxidative stress, all of which are significant contributors to vascular dysfunction of the peripheral circulation causing blood flow to be delivered to the brain in a higher pulsatile pressure manner. These abnormalities will cause damage of small cerebral vessels creating a vascular pathway to cognitive impairment and dementia in midlife and older adults with kidney disease.

In CKD, the ability of the kidney to excrete the daily dietary acid load progressively declines and patients develop a positive acid balance. The prevalence of metabolic acidosis increases as kidney function declines and is a common complication in patients with moderate CKD. Metabolic acidosis is associated with many complications in CKD including all-cause and cardiovascular mortality, kidney disease progression and vascular dysfunction. Metabolic acidosis results in inflammation and oxidative stress, both of which are associated with vascular endothelial dysfunction, arterial stiffness and decline in cognitive function. Central artery stiffening reduces cerebral blood flow impairing cerebrovascular function. Patients with cognitive impairment have lower mean cerebral blood flow compared to patients with normal cognition.

In our preliminary data, we show that treatment of metabolic acidosis with alkali therapy improves peripheral vascular dysfunction and we demonstrate that metabolic acidosis is associated with cognitive impairment in 2853 older hypertensive participants with and without CKD. Alkali therapy replacement may represent an inexpensive and novel therapeutic option for cognitive impairment in CKD. **However, no interventional trials have been performed examining the effect of alkali therapy on cognitive function in older CKD patients**.

Our primary goal of the present proposal is to perform a pilot study to determine the effect of alkali therapy on cognitive function in older adults (age 50-80 years) with CKD stage 3b-4 and metabolic acidosis (defined as serum bicarbonate level 16-22 mEq/L). Secondary goals are to determine the effect of alkali therapy on cerebrovascular dysfunction and established mediators of urinary acidification. We will conduct a pilot, prospective, randomized, double-blind clinical trial comparing the effect of oral sodium bicarbonate therapy vs. placebo in 50 CKD stage 3b-4 patients with metabolic acidosis to test the following aims:

Hypothesis 1: Treatment with sodium bicarbonate therapy vs. placebo will improve cognitive function in midlife and older adults with CKD stage 3b-4.
Specific Aim 1: To determine domains of cognitive function using the NIH Toolbox Cognitive Battery test and the Trail Making Test before and after 12 months of sodium bicarbonate therapy or placebo.

Hypothesis 2: Treatment with sodium bicarbonate therapy vs. placebo will improve cerebrovascular function in midlife and older adults with CKD stage 3b-4.
Specific Aim 2: To determine changes in cerebrovascular reactivity and pulsatility index of the middle cerebral artery using Transcranial Doppler ultrasound before and after 12 months of sodium bicarbonate therapy or placebo.

Hypothesis 3: Treatment with sodium bicarbonate therapy vs placebo will decrease markers of oxidative stress and inflammation.
Specific Aim 3: To measure circulating markers of oxidative stress (plasma oxidized LDL, total antioxidant status) and inflammation (IL1-β, IL-6, C-reactive protein and TNF-α) before and after 12 months of sodium bicarbonate therapy or placebo.

This novel study will be conducted by an experienced PI and investigative team with expertise in vascular and cognitive function and studies in CKD. The results from this pilot study will inform the design of a larger randomized controlled trial examining the effect of alkali therapy on cognitive and cerebrovascular function in midlife and older CKD patients.

II. Background and Significance:

A. SIGNIFICANCE

1. Cognitive impairment in midlife and older adults with chronic kidney disease (CKD). CKD is largely an age-related clinical disorder with accelerated cognitive and cardiovascular aging. Cognitive impairment is highly prevalent in CKD affecting 20-50% of patients aged 50 or older with CKD stage 3-4.[1-3] Midlife and older adults with CKD have an accelerated risk of cognitive aging equivalent to 3.6 to 7 years compared to the general population.[1-3] Cognitive impairment negatively affects quality of life and other health-related outcomes and contributes significantly to the high cost of CKD.[4-8] Prevention and treatment of CKD-related cognitive impairment is limited, as very few studies have been performed. **It is therefore imperative to identify novel strategies targeting CKD-specific mechanisms to improve cognitive outcomes in midlife and older adults with CKD.**

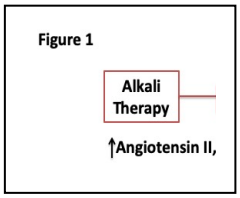
2. Cognitive impairment in midlife and older adults with CKD is related to vascular disease. CKD is a state of increased vascular dysfunction characterized by increased pulse wave velocity resulting in damage to cerebral vessels.[9-11] Patients with CKD are at an increased risk for vascular disease-related cognitive impairment rather than Alzheimer's disease. In a study of over 7800 patients over the age of 65 years, faster estimated glomerular filtration rate (eGFR) decline was associated with global cognitive decline and incident dementia with a vascular component.[12] Older CKD patients have an increased prevalence of subclinical cerebrovascular disease evidenced by more white matter lesions (WML) and silent brain infarcts (SBI) detected on brain imaging.[13] Both

WML and SBI are associated with increased risk for cognitive decline, dementia and stroke in CKD patients.[14,15] Moreover, the pattern of cognitive disorders in older adults with CKD (e.g. impairment in processing and executive function) suggest cerebrovascular disease as the main cause.[16]

3. Arterial stiffness and endothelial dysfunction of peripheral and cerebral arteries create a pathway to cognitive decline in midlife and older adults with CKD. In CKD, studies have found that medial calcification results in higher aortic pulse wave velocity (PWV).[10] Arterial stiffness reduces the capacity of blood vessels to buffer pulsatile flow, resulting in vascular alterations and hemodynamic stress leading to vascular damage in high-volume blood flow organs like the brain.[11] Numerous studies have found an association between arterial stiffness and cognitive decline.[17-19] Higher PWV (a measurement of arterial stiffness) predicts poor cognitive performance and faster cognitive decline. In 4,461 patients from the Atherosclerosis Risk in Communities Study, PWV ≥ 75th percentile was associated with mild cognitive impairment and dementia after adjustment for demographics, education, prevalent cardiovascular disease and cardiovascular risk factors.[18] Individuals with worse brachial artery flow mediated dilation (FMD), a measurement of vascular endothelial function, demonstrate greater WML[20] and worse working memory activation.[21] Adults >60 years old with mild cognitive impairment also demonstrate impaired FMD compared to age-matched controls.[22] Animal studies have shown significant deficits in working memory in mice after carotid calcification.[23] Significant reductions in cerebral blood flow and compromise in the blood-brain barrier (marker of endothelial dysfunction) were present before the cognitive deficits;[23] suggesting that arterial stiffness as a single risk factor, impairs cerebrovascular function and cognition. Patients with cognitive impairment also have lower mean cerebral blood flow in middle cerebral arteries compared to patients with normal cognition.[24] Arterial stiffness is associated with these hemodynamic changes in the middle cerebral artery.[25] Taken together, these studies suggest that peripheral and cerebral endothelial dysfunction and arterial stiffness may be important in the development and progression of cognitive decline. **In our preliminary data, we show that bicarbonate therapy improves vascular dysfunction in CKD and that low bicarbonate is associated with cognitive dysfunction. Sodium bicarbonate therapy may improve cognitive and cerebrovascular function in CKD, which constitute the main aims of the current proposal.**

4. Metabolic acidosis is common in patients with CKD. As kidney function declines, the kidneys progressively lose the ability to synthesize ammonia and excrete hydrogen ions.[26] In general, ammonium excretion decreases in CKD stage 3b-4. Metabolic acidosis is more common in patients with decreasing kidney function and approximately 19%-37% of patients with CKD stage 3b-4 have a serum bicarbonate level <22 mEq/L.[27-30] Recent studies suggest that positive acid balance is present in CKD even with low normal serum bicarbonate levels.[29-31] Metabolic acidosis results in unfavorable effects that can lead to adverse outcomes.

5. Metabolic acidosis results in increased production of angiotensin II (AII), aldosterone and endothelin-1 (ET-1). There are a number of humoral regulatory mechanisms that play a role in increasing urinary acidification in CKD including increased levels of AII, aldosterone and ET-1.[31-35] Experimental and human studies have shown that metabolic acidosis results in increased levels of these factors and increased expression of AII-type 1 receptors which are found in numerous tissues including the blood vessels, kidney and brain.[31-36] Angiotensin II stimulates ammoniagenesis and increases distal nephron acidification.[32,37] It also stimulates ET-1 and aldosterone.[38,39] ET-1 increases both proximal and distal tubule acidification and indirectly increases acidification by stimulating aldosterone.[34] In CKD stage 3 patients, treatment with alkali therapy for 3 years resulted in reduced urinary angiotensinogen (an index of AII), reduced blood pressure (BP) and preserved kidney function.[40] Although all subjects were on angiotensin converting enzyme inhibition (ACEi), urinary angiotensinogen only decreased in those patients on alkali therapy, supporting an important role for dietary acid reduction in the decrease of AII. Alkali therapy has also been shown to reduce ET-1 and aldosterone levels in CKD.[31]



6. Persistent activation of AII, aldosterone and ET-1 by metabolic acidosis in CKD may result in cognitive dysfunction by inducing endothelial dysfunction[41-43] and arterial stiffness.[41,44,45] RAAS activated mice models show declined cognitive function due to decreased cerebral surface blood flow and increased oxidative stress.[46] In humans, RAAS blockade is associated with reduced risks of cognitive decline and dementia.[47,48] **We have previously shown that sodium bicarbonate administration improves peripheral vascular dysfunction in CKD**.[49] To date, no studies have examined whether treatment of metabolic acidosis improves cognitive function or cerebrovascular hemodynamics in CKD. The proposed mechanism of action of the cerebrovascular protective effects of alkali is presented in Figure 1.

7. Oxidative stress has been identified as a key driver of aging and development of disease. Oxidative stress and inflammation are associated with cardiovascular pathophysiology and neurodegeneration.[76-78] Several studies have found that oxidative stress and inflammation are associated with a decline in cognitive function.[79-81] Markers of oxidative stress and inflammation are increased in patients with CKD.[82-83] Both oxidative stress and inflammation are associated with cardiovascular disease in CKD patients. Metabolic acidosis results in inflammation and oxidative stress.[84] Plasma oxidized LDL, IL1-β, IL-6, C-reactive protein and TNF-α have been shown to be higher in patients with CKD.[85-86] Our laboratory has experience with these measurements.[87-89]

8. Dietary intake is associated with dietary acid reduction through consumption of fruit, vegetables, and other non-alkaline foods.
Several studies have demonstrated an association of dietary intake among serum bicarbonate, metabolic acidosis, blood pressure, and kidney function.[93-95] Specifically, provision of alkaline fruits and vegetables had effects comparable to sodium bicarbonate on levels of plasma TCO2 in patients with stage 3 CKD with TCO2 levels ranging from 22-24 mmol/l.[93] Patients with CKD provided with alkaline fruits and vegetables had a reduced dietary acid load which resulted in reduced kidney injury events and attenuations in eGFR reduction.[94] These data support the important of evaluating diet in the context of metabolic acidosis in CKD.[93-95]

9. Rigor of the prior research: Compelling data from observational studies position bicarbonate administration as a promising therapy for patients with CKD. Metabolic acidosis is associated with vascular dysfunction and cognitive impairment in CKD. We have shown that treatment of metabolic acidosis improves vascular endothelial function in CKD stage 3b-4. However, key questions regarding the efficacy of bicarbonate administration on cognitive and cerebrovascular function need to be addressed. To date, no randomized controlled studies have been performed examining the effect of sodium bicarbonate treatment on cognitive or cerebrovascular function.

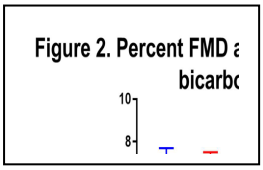
B. INNOVATION. The proposed study will fill critical scientific gaps through 4 innovations:

1. This is the first randomized-controlled study examining the effect of bicarbonate administration on cognitive function and cerebrovascular function in CKD stage 3b-4.
2. This proposal represents the critical first step to establish the efficacy of bicarbonate administration for improving cerebrovascular function and cognitive function.
3. We are combining measures of domains of cognitive function with the NIH Toolbox with cerebrovascular reactivity and pulsatility of the middle cerebral artery using noninvasive measures.
4. We will obtain mechanistic insight into the potential effects of bicarbonate administration on cognitive and cerebrovascular function through measurement of humoral mediators of urinary acidification.

Overall, this work has the potential to inform clinical practice guidelines by establishing a novel, inexpensive, easy to deliver therapy for improving cerebrovascular dysfunction in CKD patients.

III. Preliminary Studies/Progress Report:

a) **Lower serum bicarbonate levels are associated with worse cognitive function.** Dr. Chonchol, a Collaborator of this proposal, examined with other investigators in the Systolic BP Intervention Trial (SPRINT) the association between serum bicarbonate level and cognitive function in 2853 older hypertensive adults with and without CKD.[50] Serum bicarbonate levels were measured at baseline. Serum bicarbonate were analyzed continuously and categorically in clinically relevant groups (≤ 24 mEq/L, 25-28 mEq/L (reference group) and >28 mEq/L). Five cognitive summary scores were measured at baseline. Multivariate linear regression models were used to evaluate the cross-sectional association between serum bicarbonate and cognition. *Results:* The mean age (SD) and mean (SD) eGFR were 68 (8.5) years and 71 ml/min/1.73m^2, respectively. Global cognitive and executive functions were positively associated with serum bicarbonate (Table 1). **These findings suggest that low bicarbonate levels may be detrimental to neuronal activity and support the need for an interventional trial examining whether correction of acidosis has a beneficial effect on cognitive function.**



b) Bicarbonate administration results in improved vascular endothelial function (FMD) in patients with CKD stage 3b-4.[49] We performed a pilot, prospective, open label 14-week crossover study examining the effect of treatment of metabolic acidosis (defined by a low serum bicarbonate level of 16-22 mEq/L), with oral sodium bicarbonate therapy (dose 0.5 mEq/kg-lean body weight/day) in 20 patients with CKD stage 3b-4. The primary endpoint was change in FMD between treatment and control conditions. *Results:* The mean (SD) age and eGFR was 58.5 (12.8) years and 25.3 (8.3) ml/min/1.73m^2, respectively. The mean (SD) bicarbonate level increased after sodium bicarbonate therapy from 19.6 (2.9) mEq/L to 22.4 (3.0) mEq/L. BP control was similar between the two conditions. FMD significantly improved after 6 weeks of sodium bicarbonate therapy compared to control conditions (mean difference in %FMD 1.1% in the treatment arm vs. -0.70% in the control arm, p=0.027), Figure 2. Bicarbonate therapy was well tolerated and there were no significant adverse events.

c) Feasibility of Aim 2 is demonstrated by our groups experience with cerebrovascular hemodynamics. In a small interventional trial of 8 adults over the age of 50 with baseline blood pressure >120 mmHg, 6 weeks of inspiratory muscle strength training (IMST) improved cerebrovascular reactivity compared to control.

	ΔCVR (ΔMCA$_{velocity}$/Δend tidal CO2) from baseline Mean (SE)
IMST (Treatment Group) n=4	0.99 (0.31)
Control Group n=4	-0.14 (0.60)

IV. Research Methods

Subjects. After obtaining their written informed consent, 50 patients with CKD stage 3b-4 (defined as estimated GFR (eGFR) 15-44 ml/min/1.73m^2) with metabolic acidosis (defined as a serum bicarbonate level of 16-22 mEq/L, on 2 separate measurements at least 1 day apart), will serve as subjects. **Relevant biological variables:** Men and women 50-80 years old of all races/ethnicities will be included. Major inclusion/exclusion criteria are presented in the table below (Table 1). Only participants aged 50-80 years are included given the high prevalence of cognitive impairment in this age group. We chose a bicarbonate level of 16-22 mEq/L as this defines metabolic acidosis in CKD and safely allows us to have a placebo group since patients with severe metabolic acidosis (<16 mEq/L) are excluded. For additional rationale for inclusion/exclusion criteria, please see the Recruitment and Retention Plan. Patients will undergo screening for eGFR and serum bicarbonate at the Kidney Disease Research Center (KDRC) at the University of Colorado Anschutz Campus. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) prediction equation will be used to calculate eGFR.[51] A race modifier will not be used to correct the eGFR equation (all subjects will be categorized as "other".[52] Patients will be recruited from nephrology clinics at the University of Colorado where the PI has access to over 4,000 CKD patients. We will also recruit

from our CKD database, which contains over 300 CKD patients willing to participate in trials. The Health Data Compass services will also be used to generate a list of potential participants.

Rigorous Experimental Design. A 12-month **pilot, randomized, placebo-controlled, double-blinded study** with sodium bicarbonate will be conducted. The study will include 5 phases: screening, run-in, baseline, randomization and follow-up.

- Screening: Subjects will undergo screening for inclusion/exclusion criteria during a 1-2 week period. The Montreal Cognitive Assessment (MOCA) will be performed, which takes 10 minutes to administer. Participants who score <24, indicating severe cognitive impairment, will be excluded. Due to COVID-19 we are performing telephone/telemedicine consenting and screening to limit the number of patients coming into the research center. We will utilize the MOCA telemed protocol if the patient is able to do a video visit. This protocol has been validated in several studies and is scored the same as the original in-person MOCA. Should a patient not have telehealth video capabilities, we will utilize the phone MOCA (Blind MOCA) protocol, which has been validated in patients with vision issues as the visual abilities have been removed and thus it can be administered over the phone. The scoring is out of a possible score of 22 and adjusting the score to full MOCA, participants with a score <18 (equivalent to <24 on full MOCA) will be excluded. A urine pregnancy test will be performed if indicated. When logistically feasible, an ultrasound probe will be placed in the temporal bone acoustic window to locate the middle cerebral artery to ensure we can perform the cerebrovascular functions testing
- Run-in: A 1-month run-in period will occur if patients do not meet the blood pressure (BP) goal of <140/90 mmHg. The rationale for this run-in phase is to achieve a stable antihypertensive regimen and BP <140/90 mmHg, such that changes in antihypertensive agents throughout the course of the study are minimal. During the run-in phase, an up-titration of patient's current antihypertensive medication(s) will occur to reach a target BP of <140/90 mmHg. The duration of the run-in phase will be 4 weeks with weekly visits to achieve the target BP. If the patient is not able to achieve a BP of <140/90 mmHg during this period, the participant will not be included in the study. This overall approach will allow for inclusion of the typical population of patients with CKD 3b-4 and increase the generalizability of our expected results.
- Resting BP: Arterial BP will be measured in triplicate while seated at rest using an automated oscillometric machine (Omron) at all in person study visits.
- Baseline: During the baseline phase cognitive function, cerebrovascular hemodynamics, grip strength test, pegboard dexterity test, 30 second chair sit stand test, 4 meter walk test, physical functioning scale of the Short Form 36 (SF-36) serum basic chemistry panel, plasma oxidized LDL, total antioxidant status, IL1-β, IL-6, C-reactive protein and TNF-α and venous blood gas will be performed and the GI symptom questionnaire will be assessed. Spot urine will be collected for albumin to creatinine ratio. Demographics, medical history and physical will be performed.
- Randomization: Participants will be randomized with a 1:1 allocation ratio to treatment and placebo group using block randomization. Block randomization will be based on sex, age (within 5 years) and CKD stage (3b or 4). List of randomization will be generated by the study statistician and sent to the study pharmacist (A) Green Mountain Pharmaceutical, Denver, CO, and/or B) University of Colorado Research Pharmacy) blinded to the PI. Study investigators, healthcare providers, participants, data collectors, outcome adjudicators and data analysts will be blinded to treatment assignment.

- Follow-up: The follow-up schedule includes:
    - 1, 2, 4, 5, 7, 8, 10, and 11 months: safety check-in call via phone to complete adverse event assessment and GI symptom questionnaire
    - 3 and 9 months: safety visit (basic chemistry panel, adverse event assessment, GI symptoms questionnaire, BP, pill compliance).
    - 6 months: 1) Adverse event assessment, GI symptoms questionnaire, BP, pill compliance; 2) outcome measures: cognitive function, grip strength test, pegboard dexterity test, 30 second chair sit stand test, 4 meter walk test, physical functioning scale of the SF-36, serum basic chemistry panel, plasma oxidized LDL, total antioxidant status, IL1-β, IL-6, C-reactive protein and TNF-α; 3) spot urine for albumin to creatinine ratio.
    - 12 months: 1) Adverse event assessment, GI symptoms questionnaire, BP, pill compliance; 2) outcome measures: cognitive function, cerebrovascular hemodynamics, grip strength test, pegboard dexterity test, 30 second chair sit stand test, 4 meter walk test, physical functioning scale of the SF-36serum basic chemistry panel, plasma oxidized LDL, total antioxidant status, IL1-β, IL-6, C-reactive protein and TNF-α and venous blood gas; 3) spot urine for albumin to creatinine ratio.

Table 1

Inclusion Criteria	Exclusion Criteria
• Age 50-80 years old • Serum bicarbonate 16-22 mEq/L on 2 separate measurements (at least 1 day apart) • CKD stage 3b or 4 at time of screening (eGFR 15-44 ml/min/1.73m^2) • Blood pressure <140/90 mm Hg prior to randomization • Stable anti-hypertensive regimen for at least one month prior to randomization • Montreal Cognitive Assessment Score > or = 24 • No history of stroke • No history of dementia • No history of neurologic disease • Able to provide consent	• Significant comorbid conditions that lead the investigator to conclude that life expectancy is less than 1 year • Use of chronic daily oral alkali within the last 3 months (including sodium bicarbonate, calcium carbonate or baking soda) • Uncontrolled hypertension • Serum potassium < 3.3 or ≥ 5.5 mEq/L at screening • New York Heart Association Class 3 or 4 heart failure symptoms, known EF ≤30%, or hospital admission for heart failure within the past 3 months • Factors judged to limit adherence to interventions • Anticipated initiation of dialysis or kidney transplantation within 12 months • Current participation in another research study • Pregnancy or planning to become pregnant or currently breastfeeding • Chronic use of supplemental oxygen

4. Study Drug Dosing. The study drugs (bicarbonate and the matched placebo) will be prepared by A) Green Mountain Pharmaceutical and B) University of Colorado Research Pharmacy and will be identical in size, color, shape and taste. Each sodium bicarbonate capsule contains 7.7 mEq of bicarbonate and 178 mg of sodium. The matching placebo capsule will contain cornstarch. Green Mountain Pharmaceutical and/or University of Colorado Research Pharmacy will bottle the capsules and label the bottles with code numbers to maintain the study's double blind and Green Mountain Pharmaceutical will ship the bottles directly to the investigative site. Study drug supplied by the on-campus pharmacy will be managed and picked up directly from University of Colorado Research Pharmacy for each study participant.

a) Sodium bicarbonate: Subjects randomly assigned to sodium bicarbonate therapy will receive 0.5 mEq/kg-lean body weight (LBW)/day for the entire 12 months. Participants will take ½ the daily dose in the morning and the other ½ in the evening. The number of capsules will be rounded to the nearest whole capsule. To reduce pill burden and increase compliance the maximum number of pills per day will be six.

Rationale for sodium bicarbonate dose: A dose of 0.5 mEq/kg-LBW/day has been shown to be safe and effective for treatment of metabolic acidosis in patients with CKD.[49,53-54] Previous studies using this dose of sodium bicarbonate have not reported significant changes in edema, body weight or BP.[49,53-55] In our **preliminary data**, sodium bicarbonate administration was not associated with an increase in BP or fluid gain in patients with CKD stage 3b-4.[49] Additionally, we will dose sodium bicarbonate based on LBW, not actual body weight. The volume of distribution of bicarbonate is approximately that of total body water. Total body water is dependent on lean body mass. Standard equations will be used to determine LBW.[56]

b) Placebo: Subjects randomly assigned to placebo will take the same number of capsules as if they were assigned to receive 0.5 mEq/kg-LBW/day of sodium bicarbonate. Participants will take ½ the daily dose in the morning and the other ½ in the evening. The number of capsules will be rounded to the nearest whole capsule. To reduce pill burden and increase compliance the maximum number of pills per day will be six.

Rationale for placebo: A placebo group is necessary to successfully complete our aims. If a placebo group were not included both the investigators and participants would know that they are receiving sodium bicarbonate, which could influence medical management and perception of side effects in the study.

Dose Titration of Study Drug: If at month 3 the serum bicarbonate level not $\geq$ 23 mEq/L, we will increase the dose of sodium bicarbonate to 0.8 mEq/kg/LBW. This dose was recently used in a randomized trial comparing the safety and efficacy of doses of sodium bicarbonate therapy and was found to be well tolerated without any significant differences in adverse events or hospitalization compared with placebo.[57]

5. Rationale for study duration. Changes in cognitive function, cerebrovascular reactivity and pulsatility can be seen within 4-6 weeks in adults 50 years and older but may require longer periods of time and published data use a period of 3 months to 1 year.[57-61] Hence, we are proposing a 12-month intervention.

5. **Safety monitoring:** Sodium bicarbonate therapy may cause bloating, flatulence and abdominal discomfort. Although previous studies using similar doses of sodium bicarbonate have not reported significant changes in edema, body weight or BP,[49,53-55] sodium bicarbonate may cause edema to develop or worsen thereby increasing BP. Sodium bicarbonate also has the potential for causing metabolic alkalosis and hypokalemia if it is retained rather than excreted in the urine. These expected adverse events will be monitored during the study. Serum bicarbonate may fall due to natural progression of CKD, particularly in the placebo group. Rescue therapy with open-label sodium bicarbonate will be initiated if serum bicarbonate is <16 mEq/L on 2 consecutive measurements until the serum bicarbonate is $\geq$ 16 mEq/L. Participants will not discontinue study medications if open-label sodium bicarbonate is prescribed. Please see the protection of human subjects section for full safety monitoring details.

Medical Supervision and Subject Surveillance. The Kidney Disease Research Center nursing staff will have the responsibility of performing blood draws from participants. The vascular technician will have the responsibility of performing the cerebrovascular function measurements under the supervision of Dr. Kristen Nowak Director of the Vascular Biology Lab at the University of Colorado Anschutz Medical Campus. The research study coordinator will be responsible for performing the cognitive function tests and for collecting information about treatment adverse events. Dr. Kendrick, the PI, will be responsible for supervision of the entire study. Dr. Kendrick will make final decisions regarding subject screening/enrollment and monitor/oversee clinical status and subject safety.

a) Data Safety Monitoring Plan. To ensure the safety of subjects, they will need to meet rigorous inclusion/exclusion criteria, including comprehensive health screening procedures. The participants' personal physicians will also be informed of their patients' participation in the study.

Data Safety Monitoring Board (DSMB). A DSMB including clinicians and a statistician (independent of the study investigators but part of the faculty at the University of Colorado School of Medicine) will be formed to assess potential adverse events. The data will be prepared by the DSMB statistician, ensuring the study statistician remains blinded until the final analysis. The DSMB will meet at least 1 time per year to review the protocol and will follow the guidelines established by the NIH National Center for Research Resources, which include: a) monitoring the progress of the protocol (e.g. reviewing subject recruitment, attrition and minority involvement) and the safety of research participants (e.g. reviewing unblinded data for safety); b) assuring compliance with requirements regarding the reporting of adverse events; c) assuring that any action that results in the temporary or permanent suspension of the protocol is reported to all of the appropriate monitoring bodies (IRB, NIH, etc.) and d) assuring data accuracy and protocol compliance. Any unexpected adverse events will be reported immediately to the Colorado Institutional Review Board, the funding I/C and the NIH Office of Biotechnology Activities. This study is not solidly considered as a confirmatory study and as such no interim analysis has been planned. The PI, Dr. Kendrick, will provide ongoing day-to-day monitoring of the study and the protocol will be reviewed by the IRB on an annual basis.

b) Reporting of Side Effects. Subjects will be instructed to report serious or worrisome side effects to the investigators and their primary care physician (who will have been informed of their patient's participation in and the nature of the study). A subject experiencing side effects during off hours will contact Dr. Kendrick, who is available 24 hours a day. Any unexpected adverse events will be reported immediately to the Colorado Institutional Review Board, the funding I/C and the NIH Office of Biotechnology Activities.

- **Expected adverse events:** Sodium bicarbonate therapy may cause bloating, flatulence and abdominal discomfort. Although previous studies using similar doses of sodium bicarbonate have not reported significant changes in edema, body weight or BP,[49,53-55] sodium bicarbonate may cause edema to develop or worsen thereby increasing BP. As shown in our preliminary data, sodium bicarbonate did not result in increased BP.[49] Sodium bicarbonate also has the potential for causing metabolic alkalosis and hypokalemia if it is retained rather than excreted in the urine. These expected adverse events will be monitored during the course of the study and in general, can be medically managed by

adjusting antihypertensive and/or diuretic agents, providing potassium replacement and by dietary changes. Of note, none of these adverse events were observed in our previous short-term pilot study. Patients will have safety visits and check-in calls to assess side effects and check laboratory values.

- **Dose reduction and discontinuation:**
  - Serum bicarbonate >28 mEq/L: The intervention dose (study drug) will be reduced by 50% and diuretics will be adjusted as appropriate. The participant will return for a visit one week later to have serum chemistries rechecked. If the bicarbonate remains >28 mEq/L the intervention will be stopped and the participant will have serum bicarbonate measured weekly until it is <28 mEq/L. PI will monitor for symptoms of hypocalcemia as an increase in pH can decrease the ionized calcium concentration.[117,118] Management of low calcium will be at the discretion of the PI based on symptoms reported by the patient.
  - Systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 90 mmHg: Potential reasons for uncontrolled BP, such as poor compliance or running out of medications will be evaluated and managed appropriately. If an identifiable cause is not found, the PI will increase anti-hypertensive medications and/or diuretics. The participant will return 1 week later for follow-up. If BP remains >160/90 mmHg at the second visit, medications will again be increased and the intervention dose will be reduced by 50%. The participant will return 1 week later. If BP remains unchanged at the third visit, the intervention will be stopped and medications will again be escalated. Participants will continue to have PRN visits weekly until BP is <160/90 mmHg.
  - Serum potassium < 3.0 mEq/L: The intervention dose will be reduced by 50%, diuretics will be adjusted as appropriate and potassium replacement will be prescribed. The participant will return 1 week later for repeat labs. If serum potassium remains < 3.0 mEq/L, the intervention will be discontinued. The participant will return weekly until serum potassium is > 3.0 mEq/L.
  - Severe edema: If in the opinion of the PI severe edema (4+) is present and another etiology cannot be identified the dose of the intervention will be reduced by 50% and diuretics will be adjusted. If fluid retention remains severe at follow-up visits, the intervention will be discontinued.
  - Rescue therapy with oral sodium bicarbonate: Rescue therapy with open-label sodium bicarbonate will be initiated if serum bicarbonate is <16 mEq/L on 2 consecutive measurements at least 1 week apart since a level <16 mEq/L may be associated with adverse outcomes. In this instance, open-labeled sodium bicarbonate will be given to target serum bicarbonate of ≥ 16 mEq/L. Participants will not discontinue study medications if open-labeled sodium bicarbonate is prescribed.

c) Exit Criteria. The primary exit criteria will include:

- Completion of the study
- Failure to comply with the requirements of the study
- The development of side effects described above as determined by the PI, Dr. Kendrick
- Subjects will have the option of withdrawing from the study at any time for personal

reasons.

The number of subjects exiting the study and the reason for the exit will be carefully documented.

7. Outcome Measures

a) Primary Outcome

- **Cognitive Function:** Cognitive function will be assessed using the NIH Toolbox-Cognition Battery computerized tests[62] at baseline, 6 months, and 12 months. The NIH Toolbox-Cognition Battery entails seven computerized tests that assess five major cognitive subdomains including: 1) attention, 2) episodic memory, 3) working memory, 4) language, 5) executive function, and 6) processing speed. Administering the NIH Toolbox cognitive battery will yield the following summary scores, in addition to individual measure scores: Cognitive Function Composite Score ('g' factor, or general cognitive ability based on performance of each subdomain), Fluid Cognition Composite Score (includes tests of attention, executive function, working memory, and processing speed) and Crystallized Cognition Composite Score (includes Picture Vocabulary and Reading Recognition measures). These instruments have been validated in 476 participants ranging in age from 3 to 85 years, with representation from both sexes, 3 racial/ethnic categories and 3 levels of education.[62] In addition, the Trail Making Test (TMT) parts A and B will be administered to determine processing speed and executive function, respectively.[63] The investigative team has experience administering these assessments.[64]
- **Justification for primary outcome:** Our preliminary data suggests that correction of acidosis may improve cerebrovascular function. The use of the NIH Toolbox and the TMT parts A and B allow for assessing cognitive function in approximately 30-45 minutes and has been validated in numerous patient populations. Our research group has experience with these cognitive function measurements.[64]

b) Secondary Outcomes

- **Cerebrovascular hemodynamics***: 1) Cerebrovascular reactivity* will be measured using Transcranial Doppler US by assessing the change in mean blood flow velocity of the middle cerebral artery (MFV_{MCA}) in response to a vasodilatory hypercapnic challenge (i.e. via CO_2 breathing) at baseline and 12 months.[65] An ultrasound probe will be positioned at the temporal window and held in place by an adjustable headband. This location offers an ideal exposure for Doppler ultrasonography of the middle cerebral artery since the temporal window is the thinnest part of the temporal bone. After baseline recordings at room air, subjects will breathe room air supplemented with 5% CO_2 to induce mild hypercapnia. Each condition is recorded for at least 5 minutes to achieve a steady state velocity. MFV_{MCA} will be determined for each condition by calculating the average velocity over each cardiac cycle for the last minute of each condition. ΔMFV_{MCA} will be calculated as: hypercapnic MFV_{MCA} – normocapnic MFV_{MCA} and used to compare cerebrovascular reactivity between sodium bicarbonate and placebo. Breath-by-breath end-tidal partial pressures of CO_2 ($ETCO_2$) will be continuously monitored and will be used to normalize the MFV_{MCA} response to changes in this arterial blood gas.[65] The assessment of ETCO2 is noninvasive and correlates strongly with (invasive) serial blood measures of arterial

blood gases.[65] The hypercapnia protocol used in this study has been used in the research setting for many years without any adverse events.[65-67] Brachial arterial BP will also be measured during these assessments for correction due to any changes during hypercapnia. 2) *Cerebrovascular Pulsatility Index and Resistance:* Pulsatile cerebrovascular velocity will be determined using the Gosling Pulsatility index = ($MCA_{V(systolic)}$- $MCA_{V(diastolic)}$/MFV_{MCA}) and baseline and 12 months.[68] The mean, systolic and diastolic velocity of the MCA will be measured.

- 9-Hole Pegboard Dexterity Test (NIH Toolbox): This test records the time required for the participant to accurately place and remove 9 plastic pegs into a plastic pegboard. The protocol includes 1 practice and 1 test trial with each hand. Raw scores are recorded as time in seconds that it takes the participant to complete the task with each hand (a separate score for each).
- Grip Strength Test (NIH Toolbox): Participants are seated in a chair with their feet touching the ground. Participants are instructed to squeeze the Jamar Plus Digital Dynamometer as hard as they can for a count of three. A practice trial at less than full force and 1 test trial are completed with each hand.
- 30-second chair sit stand test: The patient will be seated in the middle of a chair with their hands on the opposite shoulder crossed at the wrists. Feet will be flat on the floor. On "Go", the patient will rise to a full standing position, then sit back down again. This will be repeated for 30 seconds and the number of times the patient stands in 30 seconds will be recorded. IF the patient must use his/her arms to stand, the test will be stopped and a 0 will be recorded for the number and score.
- 4-meter walk test: 4-meter walk test will be performed using protocol from NIH Toolbox. Patient will be asked to walk 4 meters at their usual pace. The patient will complete one practice and then two timed trials. The time in seconds to walk 4 meters on each of the two trials will be recorded. The test take approximately 3 minutes to administer.
- Physical Functioning Scale from the SF-36: Participants will complete the short questionnaire on their physical functioning. This is a validated scale that has been used in several CKD studies. The scale takes approximately 3-5 minutes to complete.
- **Oxidative stress and inflammation:** Oxidized LDL will be measured with Mercodia ELISA kit at the University of Colorado CTRC. Total antioxidant status will be measured at the CTRC with Randox Laboratories assay. C-reactive protein will be measured by immunoturbideimetric (Beckman Coulter) at the CTRC.

- **Food frequency questionnaire (FFQ):** This FFQ was developed for use in CKD/ESKD (end-stage kidney disease) to investigate highly/ultra-processed food consumption patterns that are typically high in sodium, potassium, and phosphorus. It was modified to include categories of alkaline fruits/vegetables and other acid/alkaline ash foods in the diet.

Justification for secondary outcomes: Transcranial Doppler Ultrasound is a noninvasive and safe way to examine cerebrovascular hemodynamics. Cerebrovascular reactivity (the vasodilation of cerebral arterioles in response to hypercapnia) is a surrogate marker of endothelial function in cerebral arteries and the pulsatility index is positively associated with arterial stiffness,[69] correlates with white matter hyperintensities,[70] and predicts cognitive impairment in patients.[70] Our research group has experience with these measurements (Dr. Seals and Nowak) and Dr. Nowak has established a cerebrovascular

laboratory in the KDRC. Oxidative stress has been identified as a key driver of aging and development of disease. Oxidative stress and inflammation are associated with cardiovascular pathophysiology and neurodegeneration.[78-80] Several studies have found that oxidative stress and inflammation are associated with a decline in cognitive function.[81-83] Markers of oxidative stress and inflammation are increased in patients with CKD.[84-85] Both oxidative stress and inflammation are associated with cardiovascular disease in CKD patients. Metabolic acidosis results in inflammation and oxidative stress.[86] Plasma oxidized LDL, IL1-β, IL-6, C-reactive protein and TNF-α have been shown to be higher in patients with CKD.[87-88] Our laboratory has experience with these measurements.[89-91] The FFQ will inform if there were any changes in self-reported food consumption throughout the study. The FFQ will also inform if changes in study outcomes / measures were associated with changes in self-reported food consumption throughout the study (association, correlation, differences, confounding between study measures and outcomes). Additionally, it will be for participant stratification and for exploratory categorization of participants by self-reported foods consumed. This data will elude at categories of diets: alkaline, acidic, processed, high-sodium/potassium/phosphorus, and high–protein.

8. Power and Statistical Analysis: Briefly, in this pilot study a total of 50 patients will be enrolled and equally randomized to the two groups. The two-sample t-test is applicable to compare the change between the two groups for each cognitive function subdomain and is the basis for power analysis. This sample size was determined based on feasibility and availability, not a specified statistical power. With a two-sided type I error rate of 0.05, the study will have a power of 79% to detect an effect of 0.80 if 25 patients per group can be included in the final analysis. This power calculation applies to the secondary and other outcome variables. For Aim 1, we will assess the treatment effect on each of the six subdomains of cognitive function by a linear regression model with the measure at end of study regressed on treatment along with the baseline measure of the subdomain, sex, age, and baseline eGFR. Conclusion will be subdomain specific. For Aims 2 and 3, the linear regression model will be used to examine the treatment effect on the secondary and other outcomes. Particularly, the measure of an outcome variable at end of study will be regressed on intervention indicator and baseline measure of the outcome variable plus sex, age and baseline eGFR for adjustment purpose.

9. Potential Problems and Alternative Strategies

- Although subject recruitment and retention are always challenging, we should be able to complete the study in the proposed timeline given our groups excellent track record in recruiting participants in clinical trials.
- We should have few difficulties with the proposed experimental procedures and protocols as they are already established in the vascular laboratories at the KDRC by Dr. Nowak.
- We recognize that alternative approaches exist for examining the effects of alkali therapy on cognitive function in patients with CKD. For example, one alternative would be to undertake a larger study to examine structural changes with brain MRIs rather than the investigation proposed in the current application. However, our proposed study is the most cost-effective approach to obtain confirmation of the study hypotheses.

- We recognize that different dosages of sodium bicarbonate therapy can be used. However, the proposed dose in the current study has been shown to be safe and effective in treating metabolic acidosis in CKD 3-4.
- Systolic BP is an important determinant of vacular function and cognitive impairment and could be a theoretical confounder. However, we do not expect this to be an issue as all participants must have their BP controlled prior to entering the study and all patients must be on an ACEi or ARB or spironolactone. We will adjust for BP if differences in BP control is observed between the groups.
- We acknowledge that there may be other potential mechanisms by which acid retention results in cerebral vessel dysfunction. Acidosis induces inflammation and oxidative stress and net calcium and phosphate efflux from bone. We will collect plasma and serum to store for future analyses of these other mechanisms.

G. Summarize Knowledge to be Gained:

The new knowledge generated from this proposal will facilitate planning of future clinical trials in CKD patients that will aim to reduce the burden of cognitive dysfunction.

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