Investigations of the optimum serum bicarbonate level in renal disease (placebo)

Protocol Summary

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Sponsor:	VA CLINICAL SCIENCE RESEARCH & DVLPMT
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Background and Introduction

Chronic kidney disease (CKD) is a common complication of diabetes and can progress to end-stage renal disease (ESRD) in many people. Given the high mortality, morbidity, and costs associated with ESRD [1-3], it is important to identify treatment strategies that will slow CKD progression in people with diabetes.

Treatment with a medication called sodium bicarbonate is a promising strategy to slow CKD progression. Sodium bicarbonate is typically prescribed to people with CKD when the serum bicarbonate is low (<22 mmol/L) because of the adverse effects of metabolic acidosis on muscle and bone.

However, a recent study in people with hypertensive CKD with **normal** serum bicarbonate levels also found that sodium bicarbonate treatment might slow CKD progression [4]. It is unknown whether the administration of sodium bicarbonate to people with diabetic CKD with **normal** serum bicarbonate levels might protect long-term renal function.

One means by which sodium bicarbonate might slow CKD progression is by reducing renal ammonia production, intrarenal activation of the complement cascade, and subsequent renal fibrosis [5]. Previous studies have shown that short-term administration of sodium bicarbonate lowers urinary excretion of the complement pathway activation products Bb and membrane attack complex (MAC) [6]. Also, the administration of a different alkalinizing agent, sodium citrate, was also found to reduce urinary excretion of transforming growth factor-β1 (TGF-β1) [7], which is considered to be a marker of renal fibrosis in diabetic CKD.

Furthermore, frailty is a common finding in CKD patients. Limited data suggests that sodium bicarbonate may improve muscle mass, but it's effects on physical function has not been thoroughly investigated.

This study will investigate whether sodium bicarbonate reduces intrarenal complement activation and fibrosis in people with diabetic CKD with normal serum bicarbonate levels, as well as explore whether it improves physical function. Such findings would add insight into our understanding of the mechanisms that accelerate diabetic CKD progression as well as influence the design of future definitive trials of alkaline treatment to slow CKD progression and improve frailty in CKD patients.

Purpose and Objectives

The objective of this double-blind randomized placebo-controlled study is to investigate whether sodium bicarbonate treatment will reduce kidney damage in people with diabetic CKD who have normal serum bicarbonate levels.

Hypothesis. Chronic oral alkaline therapy in people with diabetic CKD and *normal* serum bicarbonate levels reduces renal fibrosis via the inhibition of intrarenal complement activation.

Specific Aim: To determine in a randomized placebo-controlled study of 74 people with diabetic CKD and normal serum bicarbonate levels, the effect of a 6-month oral sodium bicarbonate intervention on:

1. Urinary excretion of **TGF-β1**, a mediator of renal fibrosis, as the primary outcome; and
2. Urinary excretion of **Bb** (a product of alternative pathway of complement activation) and **MAC** (a product of common pathway of complement activation) as secondary outcomes.
3. Physical function.

Study Population

Age of Participants: 18+

Sample Size:

At Utah:	74
All Centers:	74

Inclusion Criteria:

1. Age older than 18 years
2. Type I and Type II diabetes mellitus
3. Serum bicarbonate 22 - 28 mmol/L on the most recent measurement within the past six months
4. Stage 2, 3, or 4 CKD (defined as eGFR 15 - 89 ml/min/1.73m^2 using the MDRD equation)
5. Urinary albumin:creatinine ratio > 30 mg/gm or urinary protein:creatinine ratio > 300 mg/gm on the most recent sample within the past 12 months.

Exclusion Criteria:

1. Lean body weight > 100 kg
2. Use of oral medications typically prescribed to raise serum low serum bicarbonate levels (i.e. sodium bicarbonate, sodium citrate, potassium citrate).
3. Serum potassium < 3.5 meq/L at enrollment visit
4. Use of 5 or more antihypertensive agents, regardless of the indications of each agent
5. Systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg at the enrollment or baseline visit
6. Diagnosis of congestive heart failure with current, active Class III or IV New York Heart Association symptoms.

7. Significant fluid overload such that it is unsafe in the opinion of the PI for the patient to participate in the trial
8. chronic gastrointestinal disorder or any other factors judged to be likely to limit adherence to interventions (i.e. alcoholism, a history of missing clinic visits)
9. Chronic immunosuppressive therapy for transplanted organs or other indications
10. Individuals who are currently a member of a vulnerable population (I.e. incarcerated, pregnant).
11. Currently participating in another interventional research study

Design

Prospective Clinical Research
Double Blind
Placebo Controlled
Randomized

Study Procedures

Recruitment/Participant Identification Process:

Participants will be recruited from clinics at the VA Salt Lake City Healthcare System. The study coordinator and/or PI will screen the medical records of patients with an upcoming clinic appointment. Those who preliminarily meet entry criteria will be approached during the clinic visit and informed of the nature and purpose of the study. If the patient meets enrollment criteria and agrees to participate in the study, after written informed consent, they will be scheduled for the baseline visit and given supplies and instructions to collect the baseline 24-hour urine collection.

If a member of the study team is unable to speak with a patient during their clinic visit, a letter of invitation will be mailed to the patient and followed up with a phone call.

The study team will also utilize the VINCI serivces. This program will provide a list of potential participants that meet our inclusion/exclusion criteria. Once the study team has the list of patients the study coordinator will approach them at their next clinic appointment or send an opt-out letter.

Also see the attached VINCI document located in the "other"document section.

Informed Consent:

Description of location(s) where consent will be obtained:

Consent will be obtained in private outpatient clinic rooms at the Salt Lake City VA.

Description of the consent process(es), including the timing of consent:
Consent will be obtained at the time of the clinic visit. If a patient asks for additional time to consider participation, then consent will be obtained at a mutually convenient time for the participant and study team.

Requested Waivers/Alterations of Consent:
Waiver of Informed Consent VA Waiver of Consent for Recruitment Purposes Only

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Procedures:
Enrollment: Consented participants who meet entry criteria will be provided with urine collection supplies and instructions on how to collect a 24-hour urine sample and scheduled for the baseline visit.

Baseline/Randomization Visit: Participants will be seen at the VHASLC Dialysis Clinic. Participants will bring in the 24-hour urine collection to the baseline visit. A medical questionnaire will be reviewed with participants and a medication history will be obtained. Height, weight, blood pressure, and heart rate will be measured. Lower extremities will be assessed for edema. Ten mL of blood will be collected in serum separator tubes and 5 mL of blood will be collected in an EDTA tube. Participants will also provide another urine sample at the time of the visit. Participants will be randomized during this visit and be provided with the assigned intervention and instructions on how to take the intervention. Participants will be counseled regarding possible side effects of the active drug. A low sodium diet brochure will be provided for participants. Urine collection supplies and instructions on how to collect a 24-hour urine sample will be provided. The study coordinator will lead the participant through the physical activity assessment tests and administer the physical activity questionnaire. Participants will be scheduled for their 3-month visit.

Intervention: Participants will be randomly assigned to either the active (sodium bicarbonate) or placebo arm of the study. The number of tablets is determined by the participant's weight and height and will not change during the study. The maximum number of tablets a participant might take each day would be 6. Participants will split the total number of tablets such that half the daily dose is taking twice each day. For an odd number of tablets, the larger number of tablets will be taken in the morning. Participants will be encouraged to monitor blood pressure at home and to contact the study team if there are any questions about the blood pressure measurements.

3-month visit: Participants will be seen at the SLCVHA Dialysis Clinic. Participants will bring in the 24-hour urine collection and their assigned medication. A medical questionnaire will be reviewed and a medication history will be obtained. Participants will be asked about any perceived side effects of the intervention. Height, weight, blood pressure, and heart rate will be measured. Lower extremities will be assessed for edema. Ten mL of blood will be collected in serum separator tubes. Participants will also provide another urine sample. Pill counts will be performed to assess for compliance. Participants will again be counseled regarding possible side effects of the active drug. A low sodium diet brochure will again be

provided for participants. Urine collection supplies and instructions on how to collect a 24-hour urine sample will be provided. The study coordinator will lead the participant through the physical activity assessment tests and administer the physical activity questionnaire. Participants will be scheduled for their 6-month visit. The assigned intervention will be dispensed by the Investigational Pharmacy.

6-month visit: Participants will be seen at the SLCVHA Dialysis Clinic. Participants will bring in the 24-hour urine collection and their assigned medication. A medical questionnaire will be reviewed and a medication history will be obtained. Participants will be asked about any perceived side effects of the intervention. Height, weight, blood pressure, and heart rate will be measured. Lower extremities will be assessed for edema. Ten mL of blood will be collected in serum separator tubes. Participants will also provide another urine sample. The study coordinator will lead the participant through the physical activity assessment tests and administer the physical activity questionnaire. Pill counts will be performed to assess for compliance. This is the final visit.

Medical management during the study. Participants will be provided with handouts regarding a low-sodium diet to help prevent weight gain and increases in blood pressure. They will also be asked to contact the study team if worsening edema is noted or if there are concerns about home blood pressure readings. All general medical care, including the management of blood pressure, will be coordinated with the primary physicians. In order to avoid a potential effect of blood pressure changes on the outcomes, blood pressure will be kept as constant as possible during follow-up. Therefore, blood pressure will be targeted to keep it < 140/90 mm Hg. Changes to antihypertensive agents and diuretics will be at the discretion of the investigator. Weight will be monitored at follow-up visits. If weight gain is > 5 pounds and is clinically felt to be due to fluid retention, a diuretic will be added or the dose adjusted. Because the administration of sodium bicarbonate sometimes causes hypokalemia, serum potassium will be monitored and maintained ≥ 3.5 meq/L in all study participants. If hypokalemia requires intervention, additional measurements of serum potassium will be obtained at the discretion of the research team. Serum bicarbonate levels will be monitored during follow-up visits. If the serum bicarbonate is > 32 mmol/L, the medication will be held. Additional measurements of serum bicarbonate will be per the discretion of the research team with reinstitution of study drug when serum bicarbonate returns into the enrollment range. If abdominal discomfort occurs, addition of a proton-pump inhibitor may be recommended to alleviate discomfort allowing the participant to continue taking study medication. Any changes in medications and the rationale for the changes will be recorded for safety monitoring and for comparison between the two randomized groups. Since one follow-up visit will occur between the baseline and the closeout visits, it is not expected that many changes in medications will occur during the course of the study. Thus, patient medications and characteristics (such as blood pressure) are anticipated to remain relatively stable during this short study.

Venous blood gas

Venous blood gas measurements will be obtained in participants at all three study visits to evaluate the effect of sodium bicarbonate on acid-base status indicators. All active and new participants at Salt Lake City VA will be included. The details of the collection and measurement processes are in the MOP. Briefly, venous blood will be collected 2 minutes after release of the tourniquet. Blood gas measurements will be obtained using the Abbott iSTAT handheld device with CG8+ cartridge, which measures pH, pO_2, pCO_2,

total CO_2, HCO_3^- (calculated), base excess, oxygen saturation, ionized calcium, sodium, potassium, glucose, hematocrit, and hemoglobin.

Participants will be called by the study team at months 1, 2, 4, and 5 to monitor safety (AEs, SAEs), compliance, and medication changes.

Treatment Endpoints: Since the primary and secondary outcomes are biomarkers, rather than hard clinical end-points, we do not anticipate having to stop the study based on the biomarker results. Temporary cessation of therapy will occur if SBP is > 180 mmHg or DBP is > 120 mmHg. If SBP is > 180 mmHg or DBP is > 120 mmHg, the study medication will be held in addition to adjusting anti-hypertensive medications. Reinstitution of the assigned intervention will be determined at twice-monthly intervals and restarted only if blood pressure returns to the enrollment range. If the serum bicarbonate level is > 32 mmol/L at the 3-month follow-up visit, the medication will be held. Follow-up serum bicarbonate values will be measured at the discretion of the study team and drug reinstituted when the serum bicarbonate falls back into the enrollment range.

Procedures performed for research purposes only:

Statistical Methods, Data Analysis and Interpretation

I. **Sample size.** The primary outcome in this study is the change in log-transformed urinary TGF-β1. Sample size calculations are based on prior data (7) in which sodium citrate (another oral alkaline treatment) reduced urinary TGF-β1 by 16.3 ng/g Cr, or 17.3%, from the mean baseline level of 94.0 (SD 28.7) ng/g Cr. We were not able to find data from the literature on the standard deviation of changes over time in log-transformed TGF-β1. However, Song et al reported a pooled standard deviation of 24.7% in the percent change in urinary TGF-β1 over 16 weeks in 21 subjects, allowing us to apply a first-order approximation to estimate the required sample size based on the approximate relationships between standard deviations of percent change and standard deviations of the log-transformed values (12). If the average correlation among the percent changes in the urinary TGF-β1 levels from baseline to the two follow-up assessments does not exceed 0.90, the estimated standard deviation of the average percent change over the two assessments would not exceed 24.1%. Under these assumptions, 32 patients with complete follow-up in each treatment group will provide 81% power at a 2-sided $\alpha = 0.05$ in the primary analysis to detect a 17.3% difference in the average percent change between the treatment groups. In order to allow for loss to follow-up, we have designated a sample size of 37 enrolled patients in each group, allowing for a loss to follow-up of up to 13.5%. Thirty-two patients with complete data in each group will also provide 79% power to detect treatment effects in secondary analyses of the change in urinary TGF-β1 of 17.3% to each individual follow-up visit, although the primary analysis will compare the mean values across both the 3-month and 6-month assessments between the treatment groups.

Power calculations for the secondary outcomes of urinary Bb/Cr and urinary MAC/Cr are based on data from Morita et al in which the coefficients of variation (CVs) for 17 proteinuric diabetic CKD patients were 0.794 for Bb/Cr and 0.705 for MAC/Cr (6). After adjustment for the baseline levels, 32 patients per group will provide ≥ 80% power at a 2-sided $\alpha = 0.05$ to detect 33% and 30% greater reductions in the geometric means over the two follow-up visits of Bb/Cr and MAC/Cr, respectively, for the sodium bicarbonate vs. placebo groups assuming approximately lognormal data and equal Pearson correlations among the baseline and follow-up measurements of 0.50 or greater.

II. STATISTICAL METHODS

The statistical methods will address the hypothesis that compared to placebo, the sodium bicarbonate intervention reduces urinary TGF-β1 (as the primary outcome) and urinary Bb and MAC (each as secondary outcomes).

A. Descriptive analyses: Descriptive summaries will be presented according to the randomized group. Between groups comparisons will be done using t-test or Fisher‘s exact test as appropriate. Standard descriptive summaries, such as box plots, will be performed on the baseline and follow-up levels of each outcome in the study. Outcomes exhibiting substantial skewness may be transformed prior to subsequent statistical analyses to better approximate normality.

B. Analytic strategy for primary and secondary outcomes: The primary treatment comparison will be performed using a mixed effects model to relate the change in log-transformed TGF-β1 from baseline to 3 and 6 months to the randomized treatment groups while controlling for the baseline value of TGF-β1. This analysis will have the structure of an analysis of covariance (ANCOVA) in which the effect of the sodium bicarbonate intervention on TGF-β1 will be estimated after controlling for the baseline TGF-β1 value in order to increase statistical power. The primary analysis will estimate the average of the treatment effects across the 3-month and 6-month assessments. We have selected the average of the treatment effects at months 3 and 6 as the contrast for our primary analysis because this contrast maximizes statistical power among all possible linear contrasts under our hypothesis that the treatment effect will occur by 3 months and persist to 6 months. Further secondary contrasts will be constructed to compare the change in TGF-β1 between months 3 and 6 between the treatment groups to evaluate the persistence in any treatment effects after 3 months, and to estimate the treatment effect at both individual follow-up assessments. In the event of a linear pattern of change in log-transformed TGF-β1 over the follow-up period, an additional secondary contrast will be constructed to compare slopes from baseline to 6 months. An unstructured covariance matrix (13) will be used to account for correlations in the baseline and two follow-up outcome measurements within the same participants. The same analytic approach will be used to estimate effects of the secondary outcomes of log-transformed urinary Bb/Cr and log-transformed urinary MAC/Cr. Secondary analyses will be performed on a comparison-wise basis without formal adjustment for multiple comparisons.

C. Sensitivity analyses to address missing data: Under the intent-to-treat analysis plan, all efforts will be made to continue to obtain planned follow-up measurements for any patients who cease taking study medications. Although it is highly unlikely that a participant with stage 3 CKD will develop ESRD requiring dialysis or transplantation during the 6-month follow-up period, if this occurs, the participant will be censored at that time because of the complex nature of acid-base balance with dialysis or immunosuppressive therapy. The mixed-effect model results of the primary analysis will remain valid in the presence of missing data if data are missing at random, i.e., if values of missing responses are independent of the missing data mechanism after taking into account non-missing measurements. Informative-censoring models or multiple-imputation procedures may be used to further address the sensitivity of the results to missing data (14, 15). In the event that sensitivity analyses indicate that the conclusions are heavily influenced by the missing observations, the pre-specified mixed effects analyses will be retained for the primary presentation of results, but the results of sensitivity analyses will also be presented, and the conclusions will be appropriately tempered in the discussion section of the manuscript.

D. **Other analytic issues:** Intent-to-treat strategy where all patients are analyzed according to their randomized assignment, regardless of whether they continue to take the study medication will be the primary methodology used to examine the effects of sodium bicarbonate. Percent pill count compliance will be summarized to characterize adherence to the intervention.