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Role of Bicarbonate Supplementation on Urine Uric Acid Crystals and Diabetic Tubulopathy in Adults with Type 1 Diabetes: A Brief Report

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Abstract

Uricosuria and crystallization are increasingly recognized risk factors for diabetic tubulopathy. This pilot clinical trial aimed to determine the acute effect of urinary alkalinization using oral sodium bicarbonate [$NaHCO_3$] on UA crystals in adults with type 1 diabetes (T1D). Adults with T1D ages 18–65 years (n=45, 60% female, HbA1c 7.5±1.2%, 20.2±9.3 years duration) without chronic kidney disease (eGFR ≥60ml/min/1.73m^2 and albumin-to-creatinine ratio <30mg/g) received two doses of 1950 mg oral $NaHCO_3$ over 24 hours. Fasting urine and serum were collected pre- and post-intervention. UA crystals were identified under polarized microscopy. Urine measurements included: osmolality, pH, UA, creatinine, and kidney injury molecule-1 [KIM-1].

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$NaHCO_3$ therapy increased mean±SD urine pH from 6.1±0.7 to 6.5±0.7 (p<0.0001). Pre-therapy, 31.0% of participants had UA crystals vs. 6.7% post-therapy (p=0.005). Change in urine pH inversely correlated with change in urine KIM-1 (r:−0.51, p=0.0003). In addition, change in urine UA over 24 hours correlated with change in urine KIM-1 (r:0.37, p=0.01). In conclusion, oral $NaHCO_3$ normalized urine pH and decreased UA crystals, and may hold promise as an inexpensive and safe tubulo-protective intervention in people with T1D.

Keywords

Uric acid; urine uric acid crystals; sodium bicarbonate; type 1 diabetes

Introduction:

Diabetic kidney disease (DKD) remains the leading cause of dialysis in the developed world (1). While diabetic glomerulopathy has received significant attention from researchers, determinants of diabetic tubulopathy are less well examined. Compared to glomerular injury, tubular injury is more strongly associated with renal function (2). Whereas the mechanisms underlying diabetic tubulopathy are still incompletely understood, there is growing evidence that a glucosuria mediated increase in urine uric acid (UA) is a major determinant (3, 4).

Glucosuria is associated with activation of the polyol pathway and consequent increased fructose concentration (3). Intracellular fructose is further metabolized, generating UA as a byproduct (3). People with type 1 diabetes (T1D) have more acidic urine than their non-diabetic peers (4), which may predispose to UA crystallization and UA-mediated tubulopathy by inflammation and apoptosis of tubular cells (5–7). In animal studies, inhibition of UA production protects the kidney from tubular injury, suggesting a causal role for UA in the development of diabetic tubulopathy (8, 9).

Despite the compelling evidence implicating UA in the pathogenesis of vascular disease (10) and diabetic tubulopathy, it is unknown whether urinary alkalinization can attenuate UA crystals and tubular injury in the setting of T1D. Accordingly, the goal of this pilot study was to determine the effect of urinary alkalinization with oral sodium bicarbonate ($NaHCO_3$) on UA crystals and markers of tubular injury in adults with T1D. We hypothesized that $NaHCO_3$ supplementation would raise urine pH and reduce UA crystals in adults with T1D.

Materials and Methods

Study design

Participants (n=45, 60% females, mean age 33.6±8.5 years and duration 20.2±9.3 years) in the non-randomized non-controlled *Effect of Urinary Alkalinization on Urine Uric Acid Precipitation and Crystallization in Adults with Type 1 Diabetes (Alk-UA Study)* pilot trial (NCT02502071) received 2 doses of 1950 mg oral $NaHCO_3$ over 24 hours, and were examined with fasting urine and blood collected over two consecutive days (day 1: pre-therapy, and day 2: post-therapy). Inclusion criteria included age 18–50 years, T1D and ability to fast and provide informed consent. Exclusion criteria included history of estimated

GFR (eGFR) <60 ml/min/1.73m^2 or albumin-to-creatinine ratio (ACR) ≥30mg/g, history of hypocalcemia, taking allopurinol or other UA altering medications, phosphorus binders, SGLT2 inhibitors, blood pressure medications, or medications which may interact with sodium bicarbonate (phentermine, pseudoephedrine, antifungal medication, cephalosporin antibiotics [e.g. Keflex], tetracycline antibiotics [e.g. doxycycline], steroids or lithium). The study was approved by the Colorado Multiple Institutional Review Board (protocol #: 15–0541) and all participants provided informed consent. All clinical experimentation adheres to the Declaration of Helsinki.

Pre-study diet, fasting instructions and intervention

Participants were asked to maintain a moderate protein (1.5g/kg of weight), and high sodium diet (3,450 mg of sodium per day) for one week prior to the first study visit, and between study visits 1 and 2. They were also instructed to fast for 8 hours prior to each study visit. Fasting and insulin dosing instructions were provided for the participants to reduce risk of hypoglycemia. After completion of day 1 assessment, all participants received 2 doses of 1950 mg of oral $NaHCO_3$ (three tablets of 650 mg $NaHCO_3$). The first dose was administered in the Clinical & Translational Research Center (CTRC) outpatient clinic, and the participants were instructed to take the second dose at home 12 hours later. All participants returned empty pill containers on day 2.

Clinical and Laboratory Measurements

Physical examination measurements including height, weight, body mass index (BMI), systolic (SBP) and diastolic blood pressure (DBP) were performed at both study visits. All subjects were given standardized questionnaires to obtain demographics, medical history and medication use. After an 8 hour fast, blood and urine were collected, centrifuged, and separated. Urine samples were centrifuged at 3900 rpm for 10 minutes at 4^o C and the urine pH was measured from supernatant by Accumet basic AB 15 plus pH meter (Fisher Scientific, New Hampshire, USA). Urine osmolality was measured using freezing point method with Micro-Osmometer Model 3300 (Advanced Instruments, Massachusetts, USA). Urine and serum UA were evaluated using a QuantiChrom UA kit assay (DIUA-250) with quantitative colorimetric UA determination at 590 nm (BioAssay System, California, USA). Urine and serum creatinine were analyzed by high-performance liquid chromatography–tandem mass spectrometry (Prominence Liquid Chromatograph LC 20 AD Shimadzu 3200 Q-TRAP, Applied Biosystem, California, USA). Serum glucose was measured by Hexokinase, UV methodology (Brea, California, USA). Serum cystatin C was measured using the commercially available Dade-Behring assay following package insert instructions on a BNII instrument. Urine NGAL was measured with Human Lipocalin 2/NGAL ELISA Kit and KIM-1 measured with Human KIM-1 ELISA Kit (R&D System, Minnesota, USA). Urine NGAL and KIM-1 was normalized for urine creatinine. Estimated GFR (eGFR) were calculated by CKD-EPI creatinine and CKD-EPI cystatin C. UA crystals were identified by polarized microscopy (Polarized light imaging Zeiss Axiovert 135; 0.3NA objective), and pictures were captured from each urine sample. UA crystals were defined dichotomously as being present or absent.

Statistical analysis

Per our power analyses, a sample size of 45 would provide greater than 80% power to detect a change in urine pH of 0.50 following 24 hours of $NaHCO_3$ assuming a SD of change of 0.42 and a correlation of pre- and post- urine pH greater than 0.5 (4). Variables were checked for the distributional assumption of normality using normal plots. Variables that were positively skewed were natural log-transformed for the analyses. Paired *t*-test were used for normally distributed continuous parameters, and McNemar's test for categorical variables. Pearson and Spearman correlation employed to evaluate the relationships between continuous variables. A two-sided $p<0.05$ was considered statistically significant. Data are presented as mean ± SD for normally distributed variables, and median (p25, p75) for positively skewed variables. Analyses were performed in SAS (version 9.4 for Windows; SAS Institute, Cary, NC).

Results:

Clinical characteristics of the study cohort are shown in Table 1. Thirty-one percent of participants had evidence of UA crystals pre-therapy. Supplementary Table 2 shows the characteristics stratified by the presence of UA crystals at baseline.

Oral $NaHCO_3$ therapy increased urine pH (6.1±0.7 vs. 6.5±0.7, $p<0.0001$, Figure 1) and decreased UA crystals (31.0% vs. 6.7%, $p=0.0045$, Figure 1). There was also a modest increase in SBP in response to oral $NaHCO_3$, but we observed no significant effects on DBP, HR, eGFR, serum glucose and UA (Supplementary Table 3). As expected, there were no significant differences in serum and urine UA, urine osmolality or eGFR pre- and post-$NaHCO_3$ (Supplementary Table 3).

The change in urine UA over 24 hours correlated with the change in urine KIM-1 (r: 0.37, $p=0.01$). Participants who experienced an increase in urine UA over 24 hours therefore demonstrated an increase in urine KIM-1 excretion. Furthermore, there was an inverse correlation between change in urine pH over 24 hours and change in urine KIM-1 (r: −0.51, $p=0.0003$). Participants who experienced a decrease in their urine pH over 24 hours exhibited an increase in urine KIM-1 excretion. These relationships were not evident with urine NGAL (Supplementary Table 4). Conversely, participants who experienced resolution of UA crystals in response to $NaHCO_3$ experienced a greater decrease in urine NGAL over 24 hours compared to those who had no UA crystals present before or after intervention (Supplementary Table 5).

Discussion:

In this pilot study, almost a third of adults with T1D without CKD had evidence of UA crystals. Oral $NaHCO_3$ therapy normalized urine pH and decreased the prevalence of UA crystals. Furthermore, an increase in urine pH and decrease in UA in response to $NaHCO_3$ were associated with a reduction in KIM-1 excretion, a marker of tubular injury. While this pilot study cannot imply causality between UA crystals and tubular injury, these observations support the hypothesis that urinary alkalinization dissolves UA crystals.

$NaHCO_3$ therefore holds promise as an inexpensive and safe tubule-protective intervention in T1D.

The positive effects of $NaHCO_3$ supplementation were observed in the absence of any acute effect on serum UA, urine UA or eGFR, suggestive of an independent effect on UA solubility and crystallization. We decided on a total dose of 3900 mg of oral $NaHCO_3$ *a priori* for the following reasons: usual adult daily doses range between 1,200–8,000mg, doses for urinary alkalinization with a goal urine pH of 8.0 tend to be up to 12,000 mg daily (11). We did not aim to raise the urine pH above 8.0, but rather normalize the relatively acidic urine found in participants with T1D, by increasing the urine pH by 0.5–1.0.

$NaHCO_3$ supplementation has been shown to preserve renal function in patients with CKD (12). Experimental data suggest that the benefit of $NaHCO_3$ may relate to prevention of tubular injury by decreasing cellular β2-microglobulin generation and renal ammoniogenesis (13, 14). While these data may support our findings, the findings may not be generalizable to our cohort of adults with T1D without CKD. To our knowledge there are no large interventional trials of alkali therapy in adults with early kidney disease.

Diabetic tubulopathy may precede glomerulopathy. For example, tubular proteinuria has been shown to precede elevated albumin excretion in children with T1D (2). Exactly how UA contributes to the development of DKD remains incompletely understood. What is known is that glucosuria results in elevated UA load in T1D by the uricosuric effect (15), and that elevated UA may precipitate and crystalize in the setting of urinary acidification. We have previously demonstrated that youth with T1D have more acidic urine than their normoglycemic peers (4). The UA crystals activate tubular cells via both crystalline and non-crystalline effects, resulting in inflammation, oxidative stress, epithelial-mesenchymal cell transformation and apoptosis with resultant tubulopathy (5–7).

Limitations to the present study include the small sample size and the non-randomized non-controlled study design. We are also unable to determine whether urinary alkalinization resulted in decreased UA crystals through decreased crystal formation, crystal dissolution or both. Furthermore, we are unable to determine whether the relationships between change in urine UA, KIM-1 and NGAL are independent of urine pH, as urine UA and urine pH are collinear. For these reasons, the data should be viewed as hypothesis generating, and needs to be validated in longer and larger clinical trials. Strengths of the study include strict eligibility criteria and a pre-study diet to control for medication and dietary effects on uricosuria and urine pH. Furthermore, we also directly quantified urine osmolality pre- and post-intervention to control for the differences in hydration status.

In summary, UA crystals were common in adults with T1D without CKD, which may predispose them to diabetic tubulopathy. $NaHCO_3$ supplementation over 24 hours normalized urine pH and decreased the prevalence of UA crystals. Finally, an increase in urine pH over 24 hours was associated with lower urine KIM-1, a tubular injury marker. Further research is needed to define the effect of long term bicarbonate therapy in people with T1D, and also whether such supplementation can delay or prevent the development of renal function impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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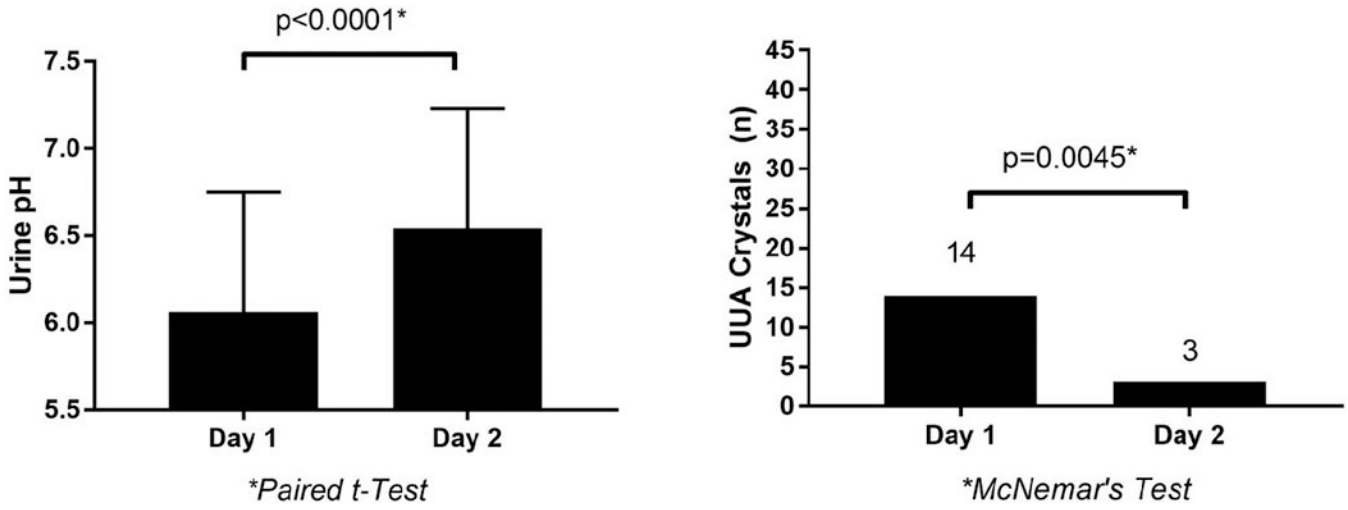

Figure 1. Effect of $NaHCO_3$ on Urine pH and UA Crystals in Adults with Type 1 Diabetes

UUA = urine uric acid

Table 1

Baseline Characteristics

	Adults with Type 1 Diabetes (n=45)
Age (years)	33.6±8.5
Type 1 Diabetes duration (years)	20.2±9.3
Sex (% female)	60%
Weight (kg)	77.5±15.6
BMI (kg/m^2)	25.9±3.5
Serum glucose (mg/dl)	151±60
Point of care glucose (mg/dl)	146±54
HbA1c (%)	7.5±1.2
HbA1c (mmol/mol)	58±13
Total Daily Insulin (units)	40.8±16.3
Total Daily Insulin per weight (units/kg)	0.5±0.2
MDI (%)	29%
CSII or HCL (%)	71%
SBP (mm Hg)	120±9
DBP (mm Hg)	74±8
HR (min^{-1})	70±12
Serum uric acid (mg/dl)	4.1±0.9
Albumin-to-creatinine ratio (mg/g)[a]	4.1 (3.0–9.0)
CKD-EPI Creatinine (ml/min/1.73m^2)	98±16
CKD-EPI Cystatin C (ml/min/1.73m^2)	113±15
Urine pH	6.1±0.7
Compliance[b]	100%

[a] Median, p25–75

[b] Based on returning empty pill containers

BMI = body mass index; HbA1c = hemoglobin A1c; MDI = multiple daily injections; CSII = continuous subcutaneous insulin infusion; HCL = hybrid-closed loop; SBP = systolic blood pressure; DBP = diastolic blood pressure; HR = heart rate; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration