STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

Official title: Pharmacological Therapy for Calcium Phosphate Urolithiasis

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Title of Project: Pharmacological Therapy for Calcium Phosphate Urolithiasis

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Background & Significance

The incidence of calcium phosphate (CaP) kidney stone disease has increased significantly over the last three decades. *Patients suffering from CaP urolithiasis often experience stone recurrence* despite pharmacological interventions, an indication to the suboptimal nature of the current medical regimen.

The major metabolic risk factors predisposing to CaP stone formation are hypercalciuria (60-80% of CaP stone formers), high urine pH (50-60%), and hypocitraturia (30-50%). While both CaP and calcium oxalate stone formers frequently exhibit hypercalciuria and hypocitraturia, a notable distinction between these two groups is the significantly higher urine pH among CaP stone formers. This is pathogenetically important because *urine pH above 6.0 is essential for crystallization of CaP* driven by the higher concentration of divalent phosphate ion.

Currently, there is *no proven countermeasure for treatment and prevention* of recurrent CaP stone disease. Raising fluid intake, protein and sodium restriction, and thiazide are all likely to reduce stone recurrence in CaP stone formers by decreasing urine calcium concentration and CaP supersaturation. However, many CaP stone formers often experience stone recurrence despite compliance with these measures, suggesting the need to evaluate additional therapies.

One frequently prescribed medication for calcium stone formers is potassium citrate, which has proven efficacy against calcium oxalate stones. Potassium citrate increases urine citrate and lowers urine calcium, which in turn reduce CaP crystallization. However, a concern is that, in CaP stone formers, these beneficial effects may be negated by a further rise in urine pH induced by potassium citrate, thus promoting CaP crystallization. *No study has directly assessed the role of potassium citrate as a countermeasure to stone recurrence in CaP stone formers.* An alternative strategy that is physiologically-based but not clinically-tested is *citric acid administration that can potentially increase urine citrate without raising urine pH.*

Effects of potassium citrate and citric acid in vitro and in vivo: We conducted *in vitro* experiments in which KCit and CitA were added in increasing concentration to filtered aliquots of urines from healthy individuals. CaP (brushite) crystals were added, and urines incubated for 3 hours at 37°C then filtered to remove any crystals formed. [Ca][Phos] in filtrate was compared to that in original urine.

We also tested the effects of KCit and CitA administration to a small number of CaP stone formers: In 4 CaP stone formers, administration of KCit 20 mEq BID increased urine citrate and pH in all patients, and lowered urine calcium and saturation of CaP as brushite. The decline in brushite saturation is likely due to the combined effect of a rise in urine citrate, slight reduction in calciuria, and formation of pH-dependent calcium citrate-phosphate soluble complexes[1, 2]. This encouraging result was obtained while patients were in an outpatient setting in which environmental factors may confound/attenuate some of the findings. We feel that KCit needs to be studied further and in a more controlled setting, especially in view of it reducing stone recurrence in patients with dRTA[3, 4] or MSK[5], conditions that present with CaP stones.

Specific Aims

Based on the knowledge and rationale stated above and our preliminary results, we submit the following *hypothesis:*

Potassium citrate and/or citric acid are potential countermeasures that attenuate the risk of recurrent stone formation in CaP stone formers.

To test this hypothesis, we will pursue the following *objectives:*

We will examine in two short-term placebo-controlled cross-over metabolic studies whether citric acid or potassium citrate can reduce calcium phosphate saturation in urine of CaP stone formers. In the first study (Aims 1 &1a) that was recently conducted in hypocitraturic *CaP stone formers without hypercalciuria*, and we compared the effects of potassium citrate, citric acid and placebo. The results of the study showed that the rise in urinary citrate (an inhibitor of CaP crystallization) with potassium citrate supplementation was negated with a significant elevation in urinary pH resulting in increased urinary supersaturation with CaP salts. *(In this revised version of the protocol we are adding a pilot project as another aim to the first study (Aim 1c), in which* we are proposing a lower dose of potassium citrate sufficient enough to raise the urinary citrate modestly, without altering the urinary pH to negate the protective inhibitory effect of urinary citrate. Aim 1c will recruit up to five patients with calcium phosphate stones CaP regardless of being hypercalciuric or not, and five normal healthy subjects without kidney stones.)

The second study will be conducted in *hypercalciuric CaP stone formers* on a thiazide diuretic who require potassium supplementation, and will compare the effects of potassium chloride alone, potassium chloride + citric acid, and potassium citrate alone. Physicochemical assays will be applied in addition to computer-based stone risk prediction programs to assess risk of stone recurrence.

The proposed small scale clinical pilot studies will use surrogate measures to test two simple interventions. They address a clinical question of utmost importance as we are in dire need of an effective therapy for patients with recurrent CaP stones, a group of stone formers that have not been specifically evaluated in past clinical trials. Results from these studies are likely to lead to full-scale randomized clinical trials with clinical outcomes for the prevention and treatment of recurrent CaP urolithiasis, an increasingly encountered condition in clinical practice.

Rationale and overall strategy: We will examine whether CitA and/or KCit can reduce the risk of recurrent nephrolithiasis in CaP stone formers. Subjects will be equilibrated on a fixed metabolic diet prior to urine collection for measurement of outcomes. Use of metabolic diet in this pilot study is essential to eliminate potential confounders from differences in dietary intake across phases. Physicochemical assays will be used in addition to computer-based stone risk prediction programs to determine stone risk. Once a regimen is identified, a trial with clinical outcomes can be designed in the future. Inclusion of patients without hypercalciuria will provide a cleaner sample to examine urine pH and citrate. However, since a large portion of CaP formers are hypercalciuric, we need to include these subjects to build a foundation for future trials. Based on the presence or absence of hypercalciuria, CaP stone formers will be included into 2 separate Aims.

Study Protocol:

Study Design & Methods:

Aim 1: Calcium phosphate stone formers without hypercalciuria

Subjects: 25 hypocitraturic stone formers without hypercalciuria will participate in this 3-phase cross-over metabolic study. Subjects will be recruited from the UTSW Mineral Metabolism and Urology clinics.

Inclusion criteria: Hypocitraturic CaP stone formers with elevated urine pH will be >21 years, of either gender, any race and ethnicity. Hypocitraturia will be defined as 24-hr urine citrate < 320 mg/d and elevated pH as 24-hr urine pH above 6.40[6, 7] in the absence of urinary tract infection. CaP stone disease will be defined based on most recent available stone composition with CaP constituting over 70% of overall stone components.

Exclusion criteria: History of recurrent urinary tract infections, conditions that predispose to acid-base disorders such as chronic diarrhea, estimated GFR<60 ml/min, chronic use of non-steroidal anti-inflammatory drugs, angiotensin 2 receptor blockers, ACE-inhibitors, diuretics, antacids or alkali treatment, and carbonic anhydrase inhibitors. Patients with hypercalciuria (24-hr urine calcium > 250 mg/day) will be allocated to Aim 2.

Study protocol: In this double-blind, placebo-controlled, crossover study, each subject will undergo 3 phases, the order of which will be randomized by a simple randomization scheme. The 3 phases will be Placebo (PBO), Citric Acid (CitA), and Potassium Citrate (KCit). Each phase will be 1 week in duration, during which subjects will take assigned study medications. A 1-week washout period is imposed between phases (Figure 1). During the first 2 days of each phase, subjects will be instructed to adhere to a diet at home with a daily composition of 800 mg calcium, 100 mEq sodium, 800 mg phosphorus, 50 mEq potassium and 2 liters of total fluids daily. On the last 5 days of each phase, subjects will be kept on a constant metabolic diet of the same composition provided by the Clinical Research Unit (CRU). During the final two study days (days 6-7), subjects will be admitted to the CRU where a 22-hr urine and 2-hr fasting urine will be collected on day 6 under mineral oil to measure urine chemistries (stone risk factors) and acid-base parameters, and on day 7 for crystallization studies. Fasting blood will be obtained at the end of each urine collection.

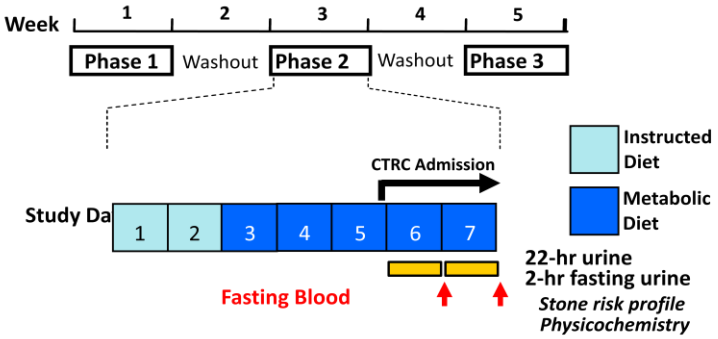

Figure 1. Experimental design

Study Medications: Subjects will receive three 10 mEq tablets of CitA twice a day during the CitA phase (60 mEq/day), two 10 mEq KCit tablets and one placebo tablet twice a day during the KCit phase (40 mEq/day), and 3 tablets twice daily of matching placebo during the PBO phase. Study tablets are prepared by a compounding pharmacy, with placebo tablets similar in appearance and size to the active medication tablets.

Sample size: This was calculated based on our preliminary studies. 20 subjects will provide a power of 0.80 at the 0.015 level of significance (to adjust for multiple comparisons of the three phases) to detect a difference of 0.3 units in CPR brushite, between treatment and placebo phases (within subject standard deviation of 0.38). Assuming 20% withdrawal, 25 subjects will be enrolled with the expectation that 20 subjects will complete the entire study.

Serum: Blood will be collected for measurement of serum sodium, potassium, chloride, CO_2, glucose, BUN, creatinine, calcium, albumin, magnesium, phosphorus, and uric acid. These will be measured primarily to assure subject safety (e.g. hyperkalemia, renal insufficiency, metabolic acidosis/alkalosis).

24-hr urine stone risk factors: These are well established at the UT Southwestern Mineral Metabolism Laboratories:[8] urine pH, citrate, calcium, phosphorus, oxalate, uric acid, ammonium, sulfate, chloride, sodium, potassium, magnesium, total volume, creatinine, TA, HCO_3^-. These parameters will be combined to calculate saturation by JESS and compared individually across phases.

Saturation: Urine saturation will be directly measured by CPR as previously described[9], and will be calculated from the measured urinary parameters by JESS as Saturation Index[1, 2, 10].

Additional physicochemical measures: In addition to CPR, we will assess *crystal growth (CG)* of brushite after seeding urine with a small amount of brushite (0.25 mg/ml urine) as previously described[11]. We will also measure overall activity of urinary promoters and inhibitors to brushite crystallization as *formation product (FP).* This will be based on an established method to assess the limit of metastability of brushite[12]. FP is obtained by adding increasing amount of Ca to a series of aliquots of urine at constant pH for 2hrs, and is identified by the point at which visible brushite precipitation is elicited. Calculated SI using [Ca] and [P] at that point represents FP brushite. Measurement of CG and FP brushite will provide additional insights on the effects of KCit and CitA on CaP stone formation beside their effect on saturation, since the process of kidney stone formation depends on the complex interplay between these three factors.

Statistical Analysis: For each phase, descriptive statistics will be computed for continuous variables. Data transformation or nonparametric tests will be utilized as needed to meet analysis assumptions. For this crossover design, repeated measures analysis will be implemented to assess treatment effects for biochemical parameters[13]. A Bonferroni-Hochberg adjustment will be used to adjust for multiple testing[14]. A mixed model approach will be used so that the covariance structure can be specified. If necessary,

Table 1: Experimental groups and **expected** findings

	Urine			Brushite		
	Cit	pH	Ca	CPR / SI	CG	FP
CitA	↑	↔	↔	↓	↓	↑
KCit	↑	↑	↓	↔/↓	↓	↑

Expected changes (↔, ↑, or ↓) compared with placebo

pairwise multiple comparisons will be made with with contrasts derived from the repeated measures models.

Expected Findings, Data Interpretation: Table 1 shows the expected urinary and physicochemical findings based on published and preliminary studies[15-18]. We expect CitA to raise urine citrate without changing pH or Ca, and KCit to raise both urine pH and citrate while lowering urine Ca.

Aim 1a Optional Outpatient Study:

Subjects: Patients being enrolled into Aim 1 will be given the option to participate in the study as an outpatient if it is more convenient.

Inclusion criteria: Same as above.

Exclusion criteria: Same as above.

Study protocol: In this double-blind, placebo-controlled, crossover study, each subject will undergo 3 phases, the order of which will be randomized by a simple randomization scheme. The 3 phases will be Placebo (PBO), Citric Acid (CitA), and Potassium Citrate (KCit). Each phase will be 1 week in duration, during which subjects will take assigned study medications. A 1-week washout period is imposed between phases (Figure 1). During the first 4 days of each phase, subjects will be instructed to adhere to a diet at home with a daily composition of 800 mg calcium, 100 mEq sodium, 800 mg phosphorus, 50 mEq potassium and 2 liters of total fluids daily. On the last 3 days of each phase, subjects will be kept on a constant metabolic diet of the same composition provided by the Clinical Research Unit (CRU). During the final two study days (days 6-7), subjects will collect a 24 hour urine at home on day 6 for crystallization studies, and also under mineral oil on day 7 to measure urine chemistries (stone risk factors) and acid-base parameters. The subjects will bring the urine to the Mineral Metabolism Clinic at Aston on the morning of day 8. Fasting blood will be obtained in the Mineral Metabolism Clinic on day 8 during this visit.

Aim 1b Outpatient Study:

Aim 1b of this protocol represents an extension of Aim 1. Aim 1b will also be conducted in the same patient population as Aim 1, but will entail a change in the medication dose/frequency of citric acid and placebo.

Subjects: - Hypocitraturic CaP stone formers without hypercalciuria.

Inclusion criteria: Same as above.

Exclusion criteria: Same as above.

Study protocol: In this double-blind, placebo-controlled, crossover study, each subject will undergo 3 phases, the order of which will be randomized by a simple randomization scheme. In this aim we will utilize the following medications during the 3 phases:

a. Placebo, 3 pills 3 times a day
b. Citric Acid 10 mEq 2 pills + Placebo 1 pill, 3 times a day
c. Citric Acid 10 mEq, 3 pills 3 times a day

A 1-week washout period is imposed between phases (Figure 1). During the first 4 days of each phase, subjects will be instructed to adhere to a diet at home with a daily composition of 800 mg calcium, 100 mEq sodium, 800 mg phosphorus, 50 mEq potassium and 2 liters of total fluids daily. On the last 3 days of each phase, subjects will be kept on a constant metabolic diet of the same composition provided by the Clinical Research Unit (CRU). During the final two study days (days 6-7), subjects will collect a 24 hour urine at home on day 6 for crystallization studies, and also under mineral oil on day 7 to measure urine chemistries (stone risk factors) and acid-base parameters. The subjects will bring the urine to the Mineral Metabolism Clinic at Aston on the morning of day 8. Fasting blood will be obtained in the Mineral Metabolism Clinic on day 8 during this visit.

The rationale for the adjustment in medication dose/frequency is that the data we have so far collected in the pilot study seems to suggest that the dose of citric acid used previously in Aim 1 does not significantly raise urine citrate as we had hypothesized. Some of the possibilities are: 1. medication doses given twice a day are not frequent enough (hence looking at the scheme in b. above) or, 2. the total dose given was not sufficient (hence the scheme c above), or that patients with Calcium Phosphate stones do not respond to Citric Acid the same way that healthy individuals without stones respond.

Aim 1c Outpatient Study:

Aim 1c of this protocol also represents an extension of Aim 1. Aim 1c is a pilot project which proposes a lower dose of potassium citrate over the three phases of the study.

Subjects: - Aim 1c will recruit up to five patients with calcium phosphate stones CaP with or without hypercalciuria, and five normal healthy subjects without kidney stones.

Inclusion criteria: CaP Stone Former with elevated urinary pH will be >25 years, of either gender and any race and ethnicity. CaP stone disease will be defined based on the most recent available stone composition with CaP constituting over 70% of overall stone components.

Exclusion criteria: History of recurrent urinary tract infections, chronic diarrhea, estimated eGFR <60 ml/min and chronic use of non-steroidal anti-inflammatory drugs, angiotensin 2 receptor blocker, ACE-inhibitors, diuretics, antacids, alkali treatment and carbonic anhydrase inhibitors.

Study protocol: In this double-blind, placebo-controlled, crossover study, each subject will undergo 3 phases, the order of which will be randomized by a simple randomization scheme. In this aim, we will utilize the following medications during the 3 phases:

a. Control, no medication
b. Potassium Citrate 5mEq 1 pill, 2 times a day
c. Potassium Citrate 10mEq, 1 pill, 2 times a day

In each phase, the subjects will be instructed to adhere to a diet on a instructed diet consisting of 800 mg calcium, 800 mg phosphorus, 100 mEq of sodium, 50 mEq of potassium and 2 liters of fluids daily at home. On the third day of the study, while on the instructed diet the subjects will collect 24-hour urine at home for the kidney stone risk profiles. The subjects will bring the urine to the Mineral Metabolism Clinic at Aston, 9th floor on the morning of day 4.

The rationale for the adjustment in medication dose/frequency of the Potassium Citrate is evidenced in the recently completed three phases of the study control, potassium citrate and citric acid in calcium phosphate stone formers. The results of the study showed that the rise in urinary citrate (an inhibitor of CaP crystallization) with potassium citrate supplementation was negated with a significant elevation in urinary pH resulting in increased urinary supersaturation with CaP salts. In this aim, we are proposing a lower dose of potassium citrate sufficient enough to raise the urinary citrate modestly, while does not alter the urinary pH to negate the protective inhibitory effect of urinary citrate.

Aim 2: Calcium phosphate stone formers with hypercalciuria

Rationale: Since the majority of CaP stone formers are hypercalciuric (60-80%), we will separately study this group with a similar 3-phase design. In our practice, these patients are all prescribed a thiazide diuretic (generally indapamide due to its long half-life, allowing once a day dosing) to reduce hypercalciuria along with a potassium supplement to avert thiazide-induced hypokalemia[19]. However, it is unclear whether KCl or KCit is the optimal K supplement for CaP stone formers on a thiazide diuretic.

Study protocol: In this double-blind, placebo-controlled crossover study, each hypercalciuric CaP stone former will undergo 3 phases, the order of which will be randomized by a simple randomization scheme.

Phase	Ind+KCl+PBO	Ind+KCl+CitA	Ind+KCit+PBO
Potassium dose	20 mEq BID KCl	20 mEq BID KCl	20 mEq BID KCit
Citrate dose	None	20 mEq BID CitA	
Expected effect on urine pH	↔	↔	↑
Expected effect on urine citrate	↔	↑	↑
Expected effect on urine calcium	↔	↔	↓
Expected effect on CPR$_{(brushite)}$	↔	↓	↓

Table 2. Experimental design and expected findings in Aim 2. Ind: Indapamide; PBO: Placebo. Note that "Expected effects" in this table represent the expected effects of KCl vs. KCl+CitA vs KCit beyond effect of indapamide which will be fixed throughout the study

Study medications: The 3 phases will be Indapamide+KCl+PBO, Indapamide+KCl+CitA, and Indapamide+KCit+PBO. The dose of indapamide will be fixed at 1.25 mg/day in each subject, the amount of potassium provided as KCit or KCl will be kept constant at 20 mEq BID, and the amount of Citrate provided either

as KCit or CitA will be 20 mEq BID (Table 2). This will allow for direct assessment of effects of KCl vs. KCl+CitA vs. KCit. Subjects will be studied in the same experimental protocol described in Figure 1.

Inclusion criteria: Hypercalciuric CaP stone formers with elevated urine pH will be >21 years, of either gender, any race and ethnicity. Hypercalciuria will be defined as 24-hr urine calc ium > 250 mg/d in women and > 300 mg/d in men prior to indapamide use, and high pH as >6.40 in the absence of urinary tract infection. CaP stone disease will be defined based on most recent available stone composition with CaP constituting over 70% of overall stone components. Subjects will be included irrespective of urinary citrate

Exclusion criteria: Same as in Aim 1 except for hypercalciuria.

Analyses: Analyses will be conducted in a similar fashion to those described under Aim 1.

Aim 2a Optional Outpatient Study:

Subjects: Patients being enrolled into Aim 2 will be given the option to participate in the study as an outpatient if it is more convenient.

Inclusion criteria: Same as above.

Exclusion criteria: Same as above.

Study protocol: In this double-blind, placebo-controlled crossover study, each hypercalciuric CaP stone former will undergo 3 phases, the order of which will be randomized by a simple randomization scheme. The 3 phases will be Indapamide+KCl+PBO, Indapamide+KCl+CitA, and Indapamide+KCit+PBO. The dose of indapamide will be fixed at 1.25 mg/day in each subject, the amount of potassium provided as KCit or KCl will be kept constant at 20 mEq BID, and the amount of Citrate provided either as KCit or CitA will be 20 mEq BID (Table 2). This will allow for direct assessment of effects of KCl vs. KCl+CitA vs. KCit. During the first 4 days of each phase, subjects will be instructed to adhere to a diet at home with a daily composition of 800 mg calcium, 100 mEq sodium, 800 mg phosphorus, 50 mEq potassium and 2 liters of total fluids daily. On the last 3 days of each phase, subjects will be kept on a constant metabolic diet of the same composition provided by the Clinical Research Unit (CRU). During the final two study days (days 6-7), subjects will collect a 24 hour urine at home on day 6 for crystallization studies, and also under mineral oil on day 7 to measure urine chemistries (stone risk factors) and acid-base parameters. The subjects will bring the urine to the Mineral Metabolism Clinic at Aston on the morning of day 8. Fasting blood will be obtained in the Mineral Metabolism Clinic on day 8 during this visit.

Protection of Human Subjects

1. 1. Risks to the Subjects

Human Subjects Involvement and Characteristics

Aim 1

3-phase, double-blind, cross-over metabolic study examining the effects of potassium citrate and citric acid on urinary predictors of stone formation in calcium phosphate stone formers *without* hypercalciuria

Disease State	Subject Number	Inclusion Criteria	Exclusion Criteria
Calcium phosphate stone formers without hypercalciuria	25	• ≥ 21 years of age for all subjects • Stone analysis showing calcium phosphate as major component of stone (>70%) • Hypocitraturia (urine citrate < 320 mg/d) • 24hr urine pH>6.40	• Hypercalciuria (24h urine calcium > 250 mg/day) • Recurrent urinary tract infections • Chronic diarrhea • Endogenous creatinine clearance < 70ml/minute by eGFR • Chronic use of non-steroidal anti-inflammatory drugs, angiotensin 2 receptor blockers, ACE inhibitors, diuretics, antacids/alkali treatment, or carbonic anhydrase inhibitors

Aim 2
3-phase, double-blind, cross-over metabolic study examining the effects of potassium citrate and citric acid on urinary predictors of stone formation in calcium phosphate stone formers *with* hypercalciuria

Disease State	Subject Number	Inclusion Criteria	Exclusion Criteria
Calcium phosphate stone formers with hypercalciuria	25	• ≥ 21 years of age for all subjects • Stone analysis showing calcium phosphate as major component of stone (>70%) • Hypercalciuria (urine calcium > 250 mg/d in women and >300 mg/d in men) • 24hr urine pH>6.40	• Recurrent urinary tract infections • Chronic diarrhea • Endogenous creatinine clearance < 70ml/minute by eGFR • Chronic use of non-steroidal anti-inflammatory drugs, angiotensin 2 receptor blockers, ACE inhibitors, diuretics, antacids/alkali treatment, or carbonic anhydrase inhibitors

Prisoners, institutionalized individuals, children under the age of 21 and pregnant women will be excluded from all studies.

Sources of Materials: Results from medical, diet history, pregnancy tests, blood and urine tests, physical examinations, medication and dietary compliance, and demographics will be used in this study and accessed by the study investigators, research coordinator and study nurses and the biostatistician.

Research data recorded in this study will include:
- Medical History: medications, surgeries, allergies, use of alcohol and/or tobacco,
- Pregnancy test results
- Blood tests: Comprehensive metabolic panel (sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, total protein, albumin, bilirubin, alkaline phosphatase, AST, ALT), magnesium, phosphorus and uric acid.
- Urine tests: total volume, pH, creatinine, sodium, potassium, calcium, magnesium, phosphorus, oxalate, uric acid, sulfate, citrate, chloride and ammonium, spot urinalysis, pregnancy test, and physicochemical assays (concentration product ratio, crystal growth, formation product).
- Physical examinations: diet history, height and weight, blood pressure
- Assessments from clinic visits: adverse events, medication and dietary compliance
- Demographics: name, date of birth, gender, and race/ethnic background

Potential Risks: Risks are enumerated in the consent form associated with the study that is explained to and signed by the participants. Individual aims may include some or all of the risks listed below:
- *Blood Draws* - Some common risks from venipuncture include discomfort, bleeding and/or bruising, dizziness or feeling faint. On a rare occasion, an infection could develop at the site where blood was collected.
- *Potassium Citrate* may cause diarrhea, nausea and abdominal cramping and a high blood potassium level. Signs of high potassium levels include feeling weak, lightheaded, dizzy, or having numbness or tingling.
- *Citric Acid* is a weak organic acid found in a variety of citrus fruits and vegetables; it is commonly used as a natural preservative or to improve taste to foods and soft drinks.

Subjects will be advised beforehand of the nature of potential side effects. Those with an increased risk of injury or side effects will be excluded from the study. If adverse symptoms appear, patients will be asked to contact the investigators.

2. Adequacy of Protection Against Risks

Recruitment and Informed Consent: Recruitment of subjects will be attempted via referral from the UT Southwestern Medical Center Urology and Mineral Metabolism Clinics. Consent of patients will be obtained prior to their involvement in the study by one of the investigators and will be witnessed by personnel not involved in the study. The subjects will receive a copy of the IRB-approved consent and a copy will be maintained in their research chart. All efforts will be utilized to ensure subject privacy and all data will be held confidentially. HIPPA regulations will be discussed with all participants and HIPPA consent will be obtained concurrently with the study consent.

Protection Against Risk: Subjects will be screened for any diseases that would increase the likelihood of side effects. Subjects will be closely monitored for any adverse effects and investigators will be alerted immediately in the case of any untoward outcomes. Participation in the study will be terminated if the subjects encounter any serious adverse effects.

3. Potential Benefits of the Proposed Research to the Subjects and Others

The immediate benefits to participants of the study will be limited. Subjects will receive the results of their laboratory work and will receive financial reimbursement for their time. The risks are minimal and are acceptable when the potential benefits are considered. The benefits mainly include the knowledge that may be gained regarding risk of recurrent urinary stones, which in the long-term could impact the care of the subjects themselves.

4. Importance of the Knowledge to be Gained

Calcium phosphate kidney stones are increasingly encountered in clinical practice, and are highly recurrent and difficult to treat. Currently, there is no proven measure for the prevention and treatment of recurrent calcium phosphate stones. This proposal will test whether pharmacological therapy with potassium citrate or citric acid reduces the risk of recurrent stone formation in calcium phosphate stone formers. Results from this pilot study will help identify options for the prevention and treatment of recurrent stones in this group of patients.

Inclusion of Women, Minorities, and Pediatric Populations

Inclusion of Women: The targeted/planned distribution of subjects by sex/gender and racial/ethnic groups is included. The study will include both men and women. There is no reason why either gender should be excluded from the investigation. The recruitment process will focus equally on obtaining both male and female participants.

Inclusion of Minorities: All minorities will be included as there is no reason to exclude any individual based on ethnicity. Recruitment will be extended to all racial/ethnic groups. All subjects who meet inclusion/exclusion criteria to the target enrollment will be included.

Inclusion of Children: The subject selection criteria include subjects age 21 years and above. Children will be excluded from this study because the investigative team does not include pediatricians with experience treating children.

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