# Role of Phosphorus and FGF 23 in Patients with Dent Disease

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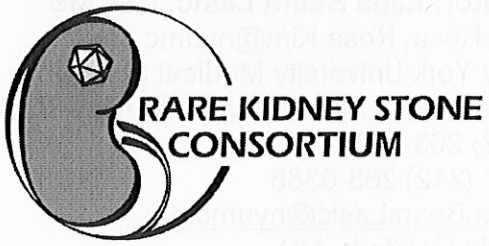


# "ROLE OF PHOSPHORUS AND FGF 23 IN PATIENTS WITH DENT DISEASE"

## Rare Diseases Clinical Research Network

**Protocol Version 5**
**Dated: 12/15/16**



**This protocol is for research purposes only, and should not be copied, redistributed or used for any other purpose. The procedures in this protocol are intended only for use by Consortium investigators in carefully controlled settings. The Chair of this study should be consulted before using or attempting any procedure in this protocol.**

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## 1. Protocol Synopsis

Interventional Synopsis

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|---|---|
| **Protocol Number:** | 6414 |
| **Protocol Title:** | Role of phosphorus and FGF23 in patients with Dent disease |
| **Study Chair:** | Lada Beara Lasic, MD |
| **Statistician:** | Enders, Felicity T., Ph.D. [Enders.Felicity@mayo.edu] |
| **Consortium:** | RKSC |
| **Participating Sites:** | Mayo Clinic, Rochester; Mayo Clinic, Jacksonville, FL; NYU MC, Department of Veterans Affairs New York Harbor Healthcare System (NYHHS), The Children's Hospital of Philadelphia (CHOPP) |
| **Activation Date:** | 10-15-13 |
| **Current Status:** | Active |
| **Sample Size:** | 40 participants total:<br>10 with DENT to provide specimens AND receive intervention (interventional cohort)<br>10 with DENT disease to provide specimens (observational cohort)<br>10 with kidney stones without phosphate leak to provide specimens AND receive intervention<br>10 with kidney stones with phosphate leak to provide specimens AND receive intervention |
| **Target Enrollment Period:** | 4 years |
| **Study Design:** | Allocation: Non-Randomized<br>Endpoint Classification: Efficacy Study<br>Masking: Open Label<br>Primary Purpose: treatment |
| **Primary Study Objective:** | Change in 24 hour urine calcium excretion after 2 weeks of phosphorus supplementation. |
| **Secondary Study Objective(s):** | • Baseline and change in serum FGF 23.<br>• Change in 24 hr urine supersaturation.<br>• Baseline and change in serum 1,25(OH)2-vitamin D3<br>• Correlation of previous numbers of stone episodes within 4 years with level of FGF 23 suppression, phosphate intake, hypercalciuria. |
| **Study Population and Main Eligibility/ Exclusion Criteria:** | 1. Dent patients (n=20) will be recruited from the RKSC Dent Disease Registry. Dent patients will have 2 cohorts:<br><br>I. Interventional cohort (n=10), age≥18. These patients will get 2 week supplementation with phosphorus.<br><br><u>Inclusion criteria</u>: At least two of following:<br>A. LMWP (at least 5 times above the upper limit of normal)<br>B. One of the following criteria: 1. Hypercalciuria, 2. Kidney stones, 3. Nephrocalcinosis, 4. Hypophosphatemia, 5. Renal phosphate leak, 6. Aminoaciduria, 7. Glucosuria without diabetes mellitus, 8. Hematuria, 9. Renal insufficiency, 10. Family history with X-linked inheritance.<br>C. Confirmed genetic mutation of CLCN5 or OCRL1.<br><br><u>Exclusion criteria</u>: |

A. primary or secondary hyperparathyroidism;
B. hyperthyroidism
C. estimated GFR < 40 ml/min/1.73 m²
D. chronic diarrhea states;
E. intake of thiazide diuretics, glucocorticoids, or estrogens within one month of the study

II. Observational cohort (n=10), Dent patients <18 years old. These patients will NOT get phosphorus supplementation. They will only get baseline blood and urine measurements.

Inclusion criteria: At least two of the following:
A. LMWP (at least 5 times above the upper limit of normal)
B. One of the following criteria: 1. Hypercalciuria, 2. Kidney stones, 3. Nephrocalcinosis, 4. Hypophosphatemia, 5. Renal phosphate leak, 6. Aminoaciduria, 7. Glucosuria without diabetes mellitus, 8. Hematuria, 9. Renal insufficiency, 10. Family history with X-linked inheritance.
C. Confirmed genetic mutation of CLCN5 or OCRL1.

Exclusion criteria:
A. primary or secondary hyperparathyroidism;
B. hyperthyroidism
C. chronic diarrhea states
D. intake of thiazide diuretics, glucocorticoids, or estrogens within one month of the study

2. Kidney Stone patients (n=20) will be recruited from the stone clinics at Mayo Clinic and NY Harbor VA Medical Center. Kidney stone patients will have 2 cohorts.

I. Kidney stone patients without phosphate leak ≥18 years old males (n=10) recruited from the stone clinics at Mayo Clinic and NY Harbor VA Medical Center.

Inclusion criteria: All required
A. History of a symptomatic calcium oxalate or calcium phosphate stone;
B. hypercalciuria (> 250 mg/ 24 hrs);
C. TMP/GFR >2.07 mg/dl);

Exclusion criteria:
A. primary or secondary hyperparathyroidism;
B. hyperthyroidism
C. estimated GFR < 40 ml/min/1.73 m²,
D. chronic diarrhea states;
E. intake of thiazide diuretics, glucocorticoids, or estrogens within one month of the study.

| | |
|---|---|
| | II. Kidney stone patients with phosphate leak ≥18 years old males (n=10) recruited from the stone clinics at Mayo Clinic and NY Harbor VA Medical Center.<br><br>Inclusion criteria: all required<br>A. History of a symptomatic calcium oxalate or calcium phosphate stone;<br>B. hypercalciuria (> 250 mg/ 24 hrs);<br>C. TMP/GFR <2.07 mg/dl);<br><br>Exclusion criteria:<br>A. primary or secondary hyperparathyroidism;<br>B. hyperthyroidism,<br>C. estimated GFR < 40 ml/min/1.73 m$^2$,<br>D. chronic diarrhea states;<br>E. intake of thiazide diuretics, glucocorticoids, or estrogens within one month of the study. |
| **Treatment** | |
| **Agent:** | K-phos neutral |
| **Dosage, schedule, route of administration:** | 250 mg po qid |
| **Safety Issues:** | This study does not pose additional risk to the patient beyond the risks for standard diagnosis and treatment of nephrolithiasis and kidney disease. There are no real risks to 24-hour urine collection, random urine collection and/or risks for venipuncture are minor. Supplementation with K-phos neutral may cause gastrointestinal upset (diarrhea, nausea, stomach pain, and vomiting) in the first several days of treatment, bone and joint pain (due to possible phosphate-induced osteomalacia) and hypernatremia and hyperkalemia. Risk for hypernatremia and hyperkalemia will be evaluated before starting therapy by Study Chair and patients with high risk will be excluded. Levels of sodium and potassium will be followed up in 2 weeks when phosphate therapy will be stopped. |
| **Primary Outcome Measures:** | Change in 24 hour urine calcium excretion after 2 weeks of phosphorus supplementation. |
| **Secondary Outcome Measures:** | 1. Baseline and change in serum FGF 23.<br>2. Change in 24 hr urine supersaturation.<br>3. Baseline and change in serum 1,25(OH)2-vitamin D3<br>4. Correlation of previous numbers of stone episodes within 4 years with level of FGF 23 suppression, phosphate intake, hypercalciuria. |
| **Statistical Considerations (sample size and analysis plan):** | With n=10, in a paired analysis of 24h urine calcium (pre-post treatment) p=0.05; 80% power, we can detect a 1 SD difference or difference of 100 mg of urine calcium per 24 hour. |
| **Sponsors (federal, state, foundation and industry support):** | National Institutes of Health (NIH) through the National Institutes of Diabetes and Digestive and Kidney Diseases (NIDDK) and Office of Rare Diseases Research (ORDR). Rare Kidney Stone Consortium (RKSC) is a member of Rare Diseases Clinical Research Network. |

## 1.1 Overview

### Brief Summary

Metabolism of calcium and phosphorus are closely connected. Most of the patients with Dent disease have increased calcium in the urine and may also have increased urinary phosphate loss. In that way, they are similar to some patients with calcium stones. The purpose of this study is to evaluate the role of the fibroblast growth factor 23 (FGF 23), a major factor controlling urinary phosphorus excretion and phosphorus supplementation in both patients with Dent disease and calcium stone formers with urinary phosphorus leak. Phosphorus supplementation could be a safer treatment for increased calcium in urine, kidney stones and kidney calcifications commonly found in patients with Dent disease.

### Detailed Description

Dent disease is a heterogeneous group of hereditary X-linked recessive renal tubular disorders with wide phenotypic heterogeneity most consistently characterized by low molecular weight proteinuria (LMWP) and frequently accompanied by hypercalciuria. Patients often develop stone disease or nephrocalcinosis. Pathogenetic mechanisms involved in increased urinary calcium (Ca) excretion are not fully elucidated but are thought to be, at least in part, due to elevated $1,25(OH)_2$-vitamin $D_3$. Fibroblast growth factor 23 (FGF 23) plays an important role in regulating serum phosphorus (Pi) by inhibiting proximal tubular phosphate reabsorption and decreasing levels of $1,25(OH)_2$-vitamin $D_3$. FGF 23 levels are shown to be suppressed in a group of patients with Fanconi syndrome and other causes of tubular phosphaturia. We propose that the FGF 23 levels may be suppressed in Dent disease, even in Dent patients with normal urine $P_i$, as suppressed FGF 23 could compensate for decreased proximal tubule $P_i$ reabsorption caused by loss of NPT2a and NPT2c transporters in impaired endocytosis and decreased endosomal trafficking. By supplementing $P_i$, this compensatory mechanism could potentially be "turned off" or reduced, leading to amelioration of hypercalciuria and protection of kidney function thus avoiding the potentially harmful thiazide diuretics, a current standard treatment. We will take a two-staged approach for studying this relationship: measure serum FGF 23, $1,25(OH)_2$-vitamin $D_3$, 25(OH) vitamin $D_3$, intact parathyroid hormone (PTHi), urine and serum Ca, Pi, creatinine (Cr) and uric acid, and in the second stage supplement phosphorus and re-measure these parameters.

The populations we plan to study are:

a) Dent patients will have 2 cohorts:

I. Interventional cohort, age≥18. These patients will get 2 week supplementation with phosphorus.
II. Observational cohort, Dent patients <18 years old. These patients will NOT get phosphorus supplementation. They will only get baseline blood and urine measurements.

b) Patients with Kidney stones will have 2 cohorts (both will receive phosphorus):

I. Male patients with calcium oxalate nephrolithiasis, hypercalciuria and renal phosphate leak (TMP/GFR <2.07 mg/dl).
II. Male patients with calcium oxalate nephrolithiasis, hypercalciuria and TMP/GFR >2.07 mg/dl without renal phosphate leak.

**Study Hypothesis**: Patients with Dent disease have suppressed levels of fibroblast growth factor 23 (FGF 23) due to renal $P_i$ wasting which causes elevated 1,25 vitamin D and contribute to hypercalciuria, kidney stones, nephrocalcinosis and renal failure. Supplementation with phosphorus may reduce hypercalciuria.

**Comparison(s):** Phosphorus supplementation has been proposed for a subgroup of patients with calcium oxalate nephrolithiasis, hypercalciuria, and renal phosphate leak, but this has not been extensively studied or definitively proven as effective therapy. We propose that this subgroup of patients is a good comparison group for the Dent disease population. We have taken 2.07 mg/dl for the TMP/GFR threshold, as in the recent observational case-control study of Mayo clinic stone patients, 95% of control population has the TMP/GFR higher than this value (unpublished data). We will also study the effect of phosphorus supplement on patients with calcium oxalate nephrolithiasis, hypercalciuria without renal phosphate leak.

## 2. Specific Aims (Hypothesis and Objectives)

**Specific Aim #1:** Measure serum sodium (Na), potassium (K), Ca, $P_i$, Cr, uric acid, FGF 23, PTHi, 1,25$(OH)_2$-vitamin $D_3$, 25(OH) vitamin $D_3$ and 24 hour urine Ca, $P_i$, Cr, Na, uric acid, oxalate, citrate and TMP/GFR in:

a) Male patients with Dent disease (identified from the Dent disease registry), interventional cohort (n=10) and observational cohort (n=10).
b) Male patients with calcium oxalate nephrolithiasis, hypercalciuria (> 250 mg/24 hrs) and renal phosphate leak (TMP/GFR<2.07 mg/dl; n=10).
c) Male patients with calcium oxalate nephrolithiasis, hypercalciuria (> 250 mg/24 hrs) and TMP/GFR >2.07 mg/dl (n=10) without renal phosphate leak.

**Specific Aim #2**: After completing Aim #1, the Dent interventional cohort and male patients with calcium oxalate nephrolithiasis will be started on K-phos neutral 250 mg QID for 2 weeks. All baseline blood and 24 hour urinary tests will be repeated. Patients will be asked to maintain similar dietary intake during phosphate supplementation as they did in the week prior to baseline urine collections. Patients will be asked to record dietary intake for the 7 days before both measurements, which will be evaluated by dietician to estimate dietary phosphate intake.

## 1) Background

*Mechanisms of hypercalciuria in Dent disease.*

Dent disease is a group of hereditary renal tubular disorders caused by mutations in at least two genes (*CLCN5* and *OCRL1*) while 20% of patients still lack genetic characterization [1]. The disease is characterized by wide phenotypic heterogeneity between families and between individuals of the same family. The most consistent finding is low molecular weight proteinuria (LMWP), which is frequently accompanied by hypercalciuria, and patients may develop stone disease or nephrocalcinosis [2]. In a review by Bokenkamp et al., hypercalciuria has been reported in 90% of patients with Dent 1 and 86% of patients with Dent 2[3].

In ClC-5 KO mice and patients with Dent disease, PTH levels are increased in the urine, generating the hypothesis that elevated PTH in the distal part of proximal tubule stimulates PTH receptors leading to increased 1-α hydroxylation of Vitamin D as well as increased internalization and degradation of NPT2a transporters, thus increasing urinary $P_i$ concentration and increasing Ca excretion in the urine [4]. Dent disease patients are, in fact, commonly found to have high 1,25$(OH)_2$-vitamin $D_3$ and low levels of serum PTH [5]. However, the role of FGF 23, a widely accepted key regulator of $P_i$ homeostasis has not yet been investigated in Dent disease. FGF 23 acts mainly by reducing expression of NPT2a and NPT2c transporters in the brush border membrane of proximal tubules, as well as NPT2b transporters in the intestines mediated by decreased levels of 1,25$(OH)_2$-vitamin $D_3$[6, 7]. The FGF 23 concentration is modulated by serum $P_i$ and dietary $P_i$ intake [8-10]. FGF 23 levels have been found to be suppressed in patients with Fanconi syndrome [11], [12].

The pathogenetic mechanism of hypercalciuria in Dent disease has yet to be elucidated. It may result from increased 1,25$(OH)_2$-vitamin $D_3$ synthesis or the functional loss of CLC-5 in the thick ascending limb, a key site of Ca reabsorption [13]. One experimental study failed to show increased intestinal absorption of Ca and hypercalciuria was thought to be result of the primary renal loss and increased bone turnover [14]. There is no phenotype-genotype correlation with hypercalciuria as the same mutations can be observed with and without hypercalciuria even with the same family [15]. It is possible that hypercalciuria is, in part, controlled by $P_i$ intake. Stones found in Dent disease are composed of Ca oxalate or Ca phosphate or a combination of both. Hypercalciuria together with impaired handling of Ca phosphate and Ca oxalate crystals that form in the collecting duct are likely contributing factors [4]. It has been suggested that hypercalciuria, nephrocalcinosis and kidney stones contribute to the development of ESRD, a major consequence of Dent disease.

Current treatment of Dent disease aims to reduce nephrolithiasis and nephrocalcinosis by reducing urinary Ca concentration. Patients are given instructions to increase oral fluid intake and in some cases, thiazide diuretics to reduce urinary Ca levels through inhibition of $Na^+$-$Cl^-$ cotransporter in the distal convoluted tubular cells, and secondarily increased passive calcium reabsorption in the proximal tubule [16]. In children and young adults with Dent disease, thiazides are often poorly tolerated and have been associated with significant hypokalemia and volume depletion [17].

***Mechanisms of hypercalciuria in idiopathic calcium nephrolithiasis: role of phosphate leak***

Up to 40-60% of hypercalciuric stone formers have elevated 1,25(OH)$_2$-vitamin D$_3$, which at high levels increases bone resorption [18]. Elevated 1,25(OH)$_2$-vitamin D$_3$ levels, in the context of normal PTH, are thought to be caused by altered $P_i$ metabolism [19]. Indeed, approximately 20% of Ca stone formers with normal PTH function have hypophosphatemia and $P_i$ leak [7]. In a study by Rendina et al., 22 Ca stone formers with normal PTH function and renal $P_i$ leak had surprising and significantly increased FGF 23 levels, compared to 88 stone formers without $P_i$ leak and healthy controls. None of the Ca stone formers with hypophosphatemia and renal $P_i$ leak had FGF 23 levels suppressed below normal range, however these patients had no measurements of 1,25(OH)$_2$-vitamin D$_3$ levels [9]. This is currently the only published study that measured FGF 23 levels in hypercalciuric stone forms with renal phosphate leak. In a small previous pilot study, Van Den Berg et al. supplemented a group of 11 hypercalciuric patients who had elevated 1,25(OH)$_2$-vitamin D$_3$ levels, with 2 grams of neutral orthophosphate. Urine Ca levels and 1,25(OH)$_2$-vitamin D$_3$ levels both decreased [20].

**2) Study Design and Methods**

This is a non-randomized, open-label study of human subjects. Three groups of patients will be given intervention: patients with Dent disease, patients with idiopathic hypercalciuria with and without urinary phosphate leak. Patients will be recruited from the RKSC Registry of Dent disease, stone clinics of Mayo clinic and Department of Veterans Affairs New York Harbor Medical Center.

At baseline, eligible patients will collect a 24 hour urine for urinary supersaturation including urine Ca, $P_i$, Cr, Na, uric acid, oxalate, citrate and will have a blood drawn for serum K, Na, Ca, $P_i$, Cr, uric acid, FGF 23, PTHi, 1,25(OH)$_2$-vitamin D$_3$, 25(OH) vitamin D$_3$. Tubular maximum for phosphate reabsorption expressed per unit glomerular filtration rate (TMP/GFR) will be calculated from these values. Patients will be asked to record dietary intake for the 7 days before both measurements, which will be evaluated by dietician to estimate dietary phosphate intake. Patients will be asked to maintain similar dietary intake during phosphate supplementation in Aim #2. A total of 20 ml blood will be needed for this study.

K-phos neutral will be discontinued in case of persistent gastrointestinal complaints and /or bone pains at the discretion of the PI's. The necessary treatment period for the subject to receive an adequate trial is two weeks and subjects will be evaluable for assessing the end point, off study criteria (in light of adverse events or lack of compliance).

**4.1 Inclusion and Exclusion Criteria**

1. Dent patients (n=20) will be recruited from the RKSC Dent Disease Registry. Dent patients will have 2 cohorts:

    I. Interventional cohort (n=10), age≥18. These patients will get 2 week supplementation with phosphorus.

    Inclusion criteria: At least two of following:
    A. LMWP (at least 5 times above the upper limit of normal)

B. One of the following criteria: 1. Hypercalciuria, 2. Kidney stones, 3. Nephrocalcinosis, 4. Hypophosphatemia, 5. Renal phosphate leak, 6. Aminoaciduria, 7. Glucosuria without diabetes mellitus, 8. Hematuria, 9. Renal insufficiency, 10. Family history with X-linked inheritance.
C. Confirmed genetic mutation of CLCN5 or OCRL1.

Exclusion criteria:
A. primary or secondary hyperparathyroidism;
B. hyperthyroidism
C. estimated GFR < 40 ml/min/1.73 $m^2$
D. chronic diarrhea states;
E. intake of thiazide diuretics, glucocorticoids, or estrogens within one month of the study

II. Observational cohort (n=10), Dent patients <18 years old. These patients will NOT get phosphorus supplementation. They will only get baseline blood and urine measurements.

Inclusion criteria: At least two of the following:
A. LMWP (at least 5 times above the upper limit of normal)
B. One of the following criteria: 1. Hypercalciuria, 2. Kidney stones, 3. Nephrocalcinosis, 4. Hypophosphatemia, 5. Renal phosphate leak, 6. Aminoaciduria, 7. Glucosuria without diabetes mellitus, 8. Hematuria, 9. Renal insufficiency, 10. Family history with X-linked inheritance.
C. Confirmed genetic mutation of CLCN5 or OCRL1.

Exclusion criteria:
A. primary or secondary hyperparathyroidism;
B. hyperthyroidism
C. chronic diarrhea states
D. intake of thiazide diuretics, glucocorticoids, or estrogens within one month of the study



2. Kidney Stone patients (n=20) will be recruited from the stone clinics at Mayo Clinic and NY Harbor VA Medical Center. Kidney stone patients will have 2 cohorts.

I. Kidney stone patients without phosphate leak ≥18 years old males (n=10) recruited from the stone clinics at Mayo Clinic and NY Harbor VA Medical Center.

Inclusion criteria: All required
A. History of a symptomatic calcium oxalate or calcium phosphate stone;
B. hypercalciuria (> 250 mg/ 24 hrs);

C. TMP/GFR >2.07 mg/dl);

Exclusion criteria:
A. primary or secondary hyperparathyroidism;
B. hyperthyroidism
C. estimated GFR < 40 ml/min/1.73 $m^2$,
D. chronic diarrhea states;
E. intake of thiazide diuretics, glucocorticoids, or estrogens within one month of the study.

II. Kidney stone patients with phosphate leak ≥18 years old males (n=10) recruited from the stone clinics at Mayo Clinic and NY Harbor VA Medical Center.

Inclusion criteria: all required
A. History of a symptomatic calcium oxalate or calcium phosphate stone;
B. hypercalciuria (> 250 mg/ 24 hrs);
C. TMP/GFR <2.07 mg/dl);

Exclusion criteria:
A. primary or secondary hyperparathyroidism;
B. hyperthyroidism,
C. estimated GFR < 40 ml/min/1.73 $m^2$,
D. chronic diarrhea states;
E. intake of thiazide diuretics, glucocorticoids, or estrogens within one month of the study.



**4.2 Recruitment of Participants**
Patients will be recruited from the RKSC Dent disease registry and stone clinics at Mayo Clinic and NY Harbor VA Medical Center. Patients from the Dent disease Registry will be approached by telephone. Patients from stone clinics and healthy controls will be approached by the PI's.

**4.3 Retention Strategies**
Patients will be contacted weekly by PI's or study coordinators to assure compliance with dietary log and reinforce compliance with therapy.

**4.4 Data Elements**
24 hour urine Ca, $P_i$, Cr, Na, uric acid, oxalate, citrate and will have a blood drawn for serum Na, K, Ca, , $P_i$, Cr, uric acid, FGF 23, PTHi, 1,25$(OH)_2$-vitamin $D_3$, 25(OH) vitamin $D_3$.

**4.5 Schedule of Events**

| TESTS | TIME POINT Screening | TIME POINT Day 1 | TIME POINT Day 8 | TIME POINT Day 14 | TIME POINT Day 22 |
|---|---|---|---|---|---|
| Evaluation of inclusion and exclusion criteria (blood test for screening within last 3 months) | x | | | | |
| Food diary x 7 days | | x | | x | |
| 24h urine Ca | | | x | | x |
| 24h urinePi | | | x | | x |
| 24h urine Cr | | | x | | x |
| 24h urine Na | | | x | | x |
| 24h urine uric acid | | | x | | x |
| 24h urine oxalate | | | x | | x |
| 24h urine citrate | | | x | | x |
| Serum Na | | | x | | x |
| Serum K | | | x | | x |
| Serum Ca | | | x | | x |
| Serum Pi | | | x | | x |
| Serum Cr | | | x | | x |
| Serum uric acid | | | x | | x |
| Serum FGF 23 | | | x | | x |
| Serum PTHi | | | x | | x |
| Serum $1,25(OH)_2 D_3$ | | | x | | x |
| Serum 25(OH) $D_3$ | | | x | | x |



**5.0 Data and Safety Monitoring Plan**

The study protocol will be reviewed and approved by the National Institutes of Health (NIH) before submission to individual center IRBs for approval. Participant enrollment may only begin with IRB approved consent forms.

This is an interventional pilot study that meets the federal definition of low risk.

The adverse events are to be reported by the Study Chair who will be monitoring the study. Moderate dose of phosphate supplementation is chosen for the short period of time which is not likely to cause serious side effects, thus early termination is not expected.

### 5.1 Study Oversight

The Study Chair has primary oversight responsibility of this clinical trial. The NIH appointed Data Safety Monitoring Board (D/OSMB) has oversight responsibility of the Data Safety Monitoring Plan (DSMP) for this clinical trial. The D/OSMB will review accrual, patterns and frequencies of all adverse events, and protocol compliance every 6 months. The D/OSMB makes recommendations to the NIH regarding the continuation status of the protocol. The RDCRN NIDDK Data and Safety Monitoring Board/Observational Study Monitoring Board (DSMB/OSMB) will be provided with the preliminary data after 3 patients have been enrolled.

Each site's Principal Investigator and their research team (co-Investigators, research nurses, clinical trial coordinators, and data managers) are responsible for identifying adverse events. Aggregate report- detailed by severity, attribution (expected or unexpected), and relationship to the study drug/study procedures – will be available from the DMCC for site review. Adverse events will be reviewed every two weeks by the research team. A separate report detailing protocol compliance will also be available from the DMCC for site review on a monthly basis. The research team will then evaluate whether the protocol or informed consent document requires revision based on the reports.

### 5.2 Definitions and Standards

The Rare Diseases Clinical Research Network defines an adverse event as: "…an unfavorable and unintended sign, symptom or disease associated with a participant's participation in a Rare Diseases Clinical Research Network study."

Serious adverse events include those events that: "result in death; are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; create persistent or significant disability/incapacity, or a congenital anomaly/birth defects."

An unexpected adverse event is defined as any adverse experience…the specificity or severity of which is not consistent with the risks of information described in the protocol.

Expected adverse events are those that are identified in the research protocol as having been previously associated with or having the potential to arise as a consequence of participation in the study

All reported adverse events will be classified using the current version of the Common Terminology Criteria for Adverse Events (CTCAE) developed and maintained by CTEP at National Cancer Institute.

### 5.3 Expected/Known Risks/Discomforts/Adverse Events Associated with Study Intervention and Procedures: Definition of Expected Adverse Events

Study Drug/Intervention:
Drug Information for neutral K-phos.
Human Toxicity/ Adverse Events (adapted from package insert)
The following toxicities have been listed: gastrointestinal upset (diarrhea, nausea, stomach pain, and vomiting). Bone and joint pain (possible phosphate-induced osteomalacia) could occur. The following adverse effects may be observed (primarily from sodium or potassium): headaches; dizziness; mental confusion; seizures; weakness or heaviness of legs; unusual tiredness or weakness; muscle cramps; numbness, tingling, pain, or weakness of hands or feet; numbness or tingling around lips; fast or irregular heartbeat; shortness of breath or troubled breathing; swelling of feet or lower legs; unusual weight gain; low urine output; unusual thirst.

Study Procedures:
Venipuncture: The vein in which the needle has been inserted to draw blood may become sore and red. A temporary "black and blue mark" may develop, and rarely fainting may occur.
There is no real risk to 24 hour urine collection.



### 5.4 Reporting Timeline

- Within **24 hours** (of learning of the event), investigators must report any reportable Serious Adverse Event (SAE) that:
  - Is considered life-threatening/disabling or results in death of subject
  -OR-
  - Is Unexpected/Unanticipated
- Investigators must report all other reportable SAEs within **5 working days** (of learning of the event).
- All other (suspected) reportable AEs must be reported to the RDCRN within **20 working days** of the notification of the event or of the site becoming aware of the event.

Local institutional reporting requirements to IRBs, any GCRC oversight committee and the FDA, if appropriate, remain the responsibility of the treating physician and the Study Chair.

### 5.5 RDCRN Adverse Event Data Management System (AEDAMS)

Upon entry of a serious adverse event, the DMCC created Adverse Event Data Management System (AEDAMS) will immediately notify the Study Chair, site PIs, the Medical Review Officer, and any additional agencies (if applicable- industry sponsor, CTEP, etc) of any reported adverse events via email.

Serious adverse events: The NIH appointed Medical Review Officer (MRO) determines causality (definitely not related, probably not related, possibly related, probably related, definitely related) of the adverse event. The MRO [may request further information if necessary and possibly request changes to the protocol or consent form as a

consequence of the adverse event. A back-up notification system is in place so that any delays in review by the MRO beyond a specified period of time are forwarded to a secondary reviewer. The Adverse Event Data Management System (AEDAMS) maintains audit trails and stores data (and data updated) and communication related to any adverse event in the study.

Non-serious expected adverse events: Except those listed above as immediately reportable, non-serious expected adverse events that are reported to or observed by the investigator or a member of his/her research team will be submitted to the DMCC in a timely fashion (within 20 working days). The events will be presented in tabular form and given to the MRO and RDCRN DSMB on an interventional "bi-annual" basis. Local site investigators are also required to fulfill all reporting requirements of their local institutions.

The DMCC will post aggregate reports of all reported adverse events for site investigators and IRBs.

### 5.6 Study Discontinuation (Interventional)

The NIH, RDCRN DSMB and local IRBs (at their local site) have the authority to stop or suspend this trial at any time. This study may be suspended or closed if:

- Accrual has been met
- The study objectives have been met
- The Study Chair / Study Investigators believe it is not safe for the study to continue
- The RDCRN DSMB suspends or closes the trial
- The NIH suspends or closes the trial
- The FDA suspends or closes the trial

### 5.7 Subject Discontinuation

An intent to treat approach will be used. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless patient withdraws consent. Every effort will be made to conduct a final study visit with the participant and participants will be followed clinically until, if applicable, all adverse events resolve.

- Withdrawal of consent
- Withdrawal by the participant
- Withdrawal by the investigator
- Intercurrent illness or event that precludes further visits to the study site or ability to evaluate disease (e.g.-mental status change, large pleural effusion).

### 5.8 Data Quality and Monitoring Measures

As much as possible data quality is assessed at the data entry point using intelligent on-line data entry via visual basic designed screen forms. Data element constraints, whether independent range and/or format limitations or 'relative' referential integrity limitations, can be enforced by all methods employed for data input. QA reports assess data quality post-data entry. As we note, data quality begins with the design of the data

collection forms and procedures and incorporates reasonable checks to minimize transcription and omission errors. Of the more important quality assurance measures are the internal validity checks for reasonableness and consistency.

**6. Statistical Considerations**

With n=10, in a paired analysis of 24h urine calcium (pre-post treatment; p=0.05; 80% power), we can detect a 1 SD difference or difference of 100 mg of urine calcium per 24 hour.

a. Feasibility and Time Frame – Estimated study completion is 12/1/2014 allowing time to identify, recruit, collect samples and perform analysis.

b. Strengths – no measurement of FGF 23 has been done for Dent disease patients and it will add in knowledge on pathogenesis of disease. Potential role of phosphate supplement will be evaluated in Dent patients to reduce hypercalciuria in these patients, which is an important presumed mechanism in formation of calcium oxalate kidney stones. Role of phosphate supplementation in calcium oxalate stone forming patients and phosphate leak, will also be evaluated.

c. Limitation – dietary recall is limited in evaluating phosphate intake. Role of phosphate supplementation will be evaluated in Dent patients, disregarding the level of phosphate leak. The effect of phosphorus supplementation might be higher in Dent patients with significant phosphate leak. Because Dent disease is a very rare disease, limited numbers of patients are available.

**7. Data Management**

Data will be collected from patient's food diaries that will be submitted by mail or online. Lab test results before and after K-phos supplementation will be measured in Mayo clinic research lab. All data and results will be maintained in a REDCap database. Data will be transmitted to the RDCRN in a deidentified summary format at the end of the study.



***7.1 Registration***

Registration of participants on this protocol will employ an interactive data system in which the clinical site will attest to the participant's eligibility as per protocol criteria and obtain appropriate informed consent. IRB approval for the protocol must be on file at the DMCC before accrual can occur from the clinical site.

The DMCC will use a system of coded identifiers to protect participant confidentiality and safety. Each participant enrolled will be assigned a local identifier by the enrollment site. This number can be a combination of the site identifier (location code) and a serial accession number. Only the registering site will have access to the linkage between this number and the personal identifier of the subject. When the participant is registered to participate in the study, using the DMCC provided web-based registration system, the system will assign a participant ID number. Thus each participant will have two codes:

the local one that can be used by the registering site to obtain personal identifiers and a second code assigned by the DMCC. For all data transfers to the DMCC both numbers will be required to uniquely identify the subject. In this fashion, it is possible to protect against data keying errors, digit transposition or other mistakes when identifying a participant for data entry since the numbers should match to properly identify the participant. No personal identifiers would be accessible to the DMCC.

### 7.2 Data Entry

All study data will be collected through REDCap and will comply with all applicable guidelines regarding patient confidentiality and data integrity. REDCap is a secure, web-based application for building and managing online databases. On-line forms will be developed that contain the requisite data fields.

## 8. Human Subjects

### 8.1. GCP Statement

This clinical trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and all applicable regulatory requirements.

### 8.2. Risks

The potential risks of this study are:

This study does not pose additional risk to the patient beyond the risks for standard diagnosis and treatment of nephrolithiasis and kidney disease. There are no real risks to 24-hour urine collection, random urine collection and/or risks for venipuncture are minor. Supplementation with K-phos neutral may cause gastrointestinal upset (diarrhea, nausea, stomach pain, and vomiting) in the first several days of treatment, bone and joint pain (due to possible phosphate-induced osteomalacia) and hypernatremia and hyperkalemia. Risk for hypernatremia and hyperkalemia will be evaluated before starting therapy by the PI's and patients with high risk will be excluded per judgment of the PI's. Levels of sodium and potassium will be followed up in 2 weeks when phosphate therapy will be stopped.

### 8.3. Benefits

The potential benefits of this study are:

Improvement of urine supersaturation and reduced hypercalciuria after phosphorus supplementation in Dent disease patients and patients with idiopathic hypercalciuria with urinary phosphate leak. This study could provide an insight in benefit and starting point for phosphate supplementation even in patients with normal phosphorus levels. Dietary phosphate will be considered when evaluating response to phosphorus supplementation.

### 8.4. Recruitment

Since Dent disease is an X-linked disorder, all study patients will be male. We will aggressively promote recruitment of all races and ethnic groups.

**8.5. Written Informed Consent:**
Written informed consent will be obtained from each participant before any study-specific procedures or assessments are done and after the aims, methods, anticipated benefits, and potential hazards are explained. The participant's willingness to participate in the study will be documented in writing in a consent form, which will be signed by the participant with the date of that signature indicated. The investigator will keep the original consent forms and signed copies will be given to the participants. It will also be explained to the participants that they are free to refuse entry into the study and free to withdraw from the study at any time without prejudice to future treatment. Written and/or oral information about the study in a language understandable by the participant will be given to all participants.

**8.6. Process of Consent:**
Patients will be mailed the informed consents which will be explained either in person or over the telephone. Patients will sign the consents and mail them to the research coordinators to be filed.

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