An Update on FGF23: Bone and beyond

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National Institutes of Health
Disclosures

• NIDCR receives funding from Shire to study a preclinical model of FTC
• Off label uses will be mentioned
Case Presentation

• 49 y.o. woman
• 1/2010: several years progressive fatigue, ↓ hip strength, unsteady gate, bone pain
• Rheumatologic evaluation negative; isolated ↑ alk. phos., normal LFTs
• 8/2010 fell fx both patellae
• DXA:T=-0.9 L/S, -1.9 hip; Rx: risedronate
• Bone scan
Case Presentation

• Oncological evaluation negative
• 2/2011 hypophosphatemia first noted
• 1.9 mg/dl (2.7-4.5); PTH 126 (15-65)
• Endocrine evaluation of ↑PTH
• Pi 1.8, PTH 87, 25-OH vit-D 25 ng/ml (>20), 1,25 (OH)₂ vit-D < 8
• FGF23 660 RU/ml (<180)
FGF23 biology, physiology, diseases and treatment

- Background physiology
- Evolution of our current understanding
- FGF23 biology and physiology
- FGF23 in rare disorders
- Implications for common disorders
Renal Mineral Physiology

Serum\(_{\text{PO}_4}\) filtered

\(\text{PO}_4\) reabsorbed

Urine\(_{\text{PO}_4}\) excreted
Renal Mineral Physiology

- **Serum**$_{PO_4}$ filtered
- **PO$_4$** reabsorbed
- **PTH**
- **Urine**$_{PO_4}$ cAMP excreted
Renal Mineral Physiology

PTH

25-vitamin D

1-α hydroxylase

1,25(OH)₂-D

GI calcium and phosphate absorption
Why do we care about Phosphate?

hydroxyapatite

\[
\text{Ca}^{2+}, \quad \text{PO}_4^{2-}, \quad \text{OH}^-, \quad \text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2
\]

Phosphate and Cell Biology

- signaling
- energy (ATP)
- phosphorylation

- cofactors
- macromolecules
- neurotransmission

mineralization
Evolution of our current understanding of FGF23

Calcium 10.0 mg/dl
(8.5 – 10.5)

Phosphorus 1.6 mg/dl
(3.2 – 6.3)
## Vitamin D-Resistant Rickets

**Table 3.** Metabolic Data Showing That Extreme Doses of Vitamin D Administered Orally as Viosterol Were Followed by Marked Changes in the Calcium and Phosphorus Metabolism

<table>
<thead>
<tr>
<th>Period</th>
<th>Calcium, Gm. per Day</th>
<th>Phosphorus, Gm. per Day</th>
<th>Serum, Mg. per 100 Cc.</th>
<th>Plasma Phosphatase Units*</th>
<th>Vitamin D, U. S. P. Units</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Urine</td>
<td>Feces</td>
<td>Intake</td>
<td>Balance</td>
<td>Urine</td>
</tr>
<tr>
<td>I</td>
<td>0.01</td>
<td>0.65</td>
<td>0.76</td>
<td>+0.10</td>
<td>0.53</td>
</tr>
<tr>
<td>II</td>
<td>0.01</td>
<td>0.61</td>
<td>0.67</td>
<td>+0.05</td>
<td>0.51</td>
</tr>
<tr>
<td>III</td>
<td>0.01</td>
<td>0.74</td>
<td>0.76</td>
<td>+0.01</td>
<td>0.44</td>
</tr>
<tr>
<td>IV</td>
<td>0.01</td>
<td>0.60</td>
<td>0.76</td>
<td>+0.15</td>
<td>0.55</td>
</tr>
<tr>
<td>V</td>
<td>0.01</td>
<td>0.78</td>
<td>0.76</td>
<td>-0.03</td>
<td>0.53</td>
</tr>
<tr>
<td>VI</td>
<td>0.02</td>
<td>0.59</td>
<td>0.76</td>
<td>+0.15</td>
<td>0.56</td>
</tr>
<tr>
<td>VII</td>
<td>0.01</td>
<td>0.56</td>
<td>0.76</td>
<td>+0.19</td>
<td>0.56</td>
</tr>
<tr>
<td>VIII</td>
<td>0.01</td>
<td>0.56</td>
<td>0.76</td>
<td>+0.19</td>
<td>0.49</td>
</tr>
<tr>
<td>IX</td>
<td>0.01</td>
<td>0.38</td>
<td>0.76</td>
<td>+0.37</td>
<td>0.43</td>
</tr>
<tr>
<td>X</td>
<td>0.04</td>
<td>0.17</td>
<td>0.76</td>
<td>+0.55</td>
<td>0.43</td>
</tr>
<tr>
<td>XI</td>
<td>0.04</td>
<td>0.21</td>
<td>0.76</td>
<td>+0.51</td>
<td>0.56</td>
</tr>
<tr>
<td>XII</td>
<td>0.03</td>
<td>0.28</td>
<td>0.76</td>
<td>+0.45</td>
<td>0.57</td>
</tr>
</tbody>
</table>

* Modified Bodansky units.²

† The Roman numeral indicates on which day of the period the determination was made.
Vitamin D-Resistant Rickets = X-linked Hypophosphatemic Rickets

None of the sons of affected fathers were affected
All of the daughters of the affected males were affected
X-linked dominant
The *Hyp* Mouse, an Animal Model for X-linked Hypophosphatemic Rickets

*Proc. Natl. Acad. Sci. USA*
Vol. 73, No. 12, pp. 4667–4671, December 1976
Medical Sciences

**Hypophosphatemia: Mouse model for human familial hypophosphatemic (vitamin D-resistant) rickets**

(X-linkage/phosphate transport/animal model)

EVA M. EICHER*, JANICE L. SOUTHARD*, CHARLES R. SCRIVER†, AND FRANCIS H. GLORIEUX‡
Parabiosis Suggests a Humoral Factor Is Involved in X-Linked Hypophosphatemia in Mice

RALPH A. MEYER, JR.,1 MARTHA H. MEYER,1 and RICHARD W. GRAY2

A

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 4, Number 4, 1989

Hyp due to mutations in PHEX (phosphate-regulating endopeptidase homolog, X-linked); HYP Consortium Nat Gen, 1995

a “factor” in the hyp mouse’s blood made the normal mouse hypophosphatemic – “phosphatonin”
Discovery of Long-Elusive “Phosphatonin”

Autosomal dominant hypophosphataemic rickets is associated with mutations in FGF23

The ADHR Consortium

nature genetics • volume 26 • November 2000

- Intact FGF23 is the active hormone
- Mutations at the consensus sequence allow the intact molecule to escape degradation to inactive N- and C-terminus clips
- In ADHD serum levels of full length FGF23 accumulate
FGF23: a new hormone!

- Tissue source, physiology, biology
- Implications for human diseases
- Drug targets for diseases of FGF23 excess and deficiency
Bone is the physiologic source of FGF23

FGF23 in fibrous dysplasia bone cells

FGF23 in situ hybridization

fibrous dysplasia of bone

FGF23 in normal bone cells

FGF23 in situ hybridization

normal bone

Collins et al J Bone and Miner Res 2001
Riminucci, Collins et al J Clin Invest 2003
Sitara et al, Matrix Biology, 2004
Mirams et al, Bone, 2004

▲ = osteocyte  ↑ = osteoblast  b = bone
FGF23 made by bone cells, acts at the kidney to regulate serum phosphorus and 1,25-D.

- ↓ NaPi2a expression
- ↓ 1-α-hydroxylase
  (Shimada et al PNAS 2001)

↓ serum phosphate

↓ serum 1,25-D
FGF23 – 1,25-Vit D – PTH Axis
FGF23 made by bone cells, acts at the kidney to regulate serum phosphorus and 1,25-D.

- Phosphorus
  - Ferrari JCEM 2005
  - Antonucci JCEM 2006
  - Burnett JBMR 2006
  - Dilorio CJASN 2012

- 1,25-vit. D:
  - Collins JBMR, 2005
  - Kolek A J Gastr Liver Phys 2005
  - Barthel J Ster Mol Bio 2006
FGF23 receptor and Signaling

Klotho converts canonical FGF receptor into a specific receptor for FGF23

Nature (144), 2006

Itaru Urakawa¹, Yuji Yamazaki¹, Takashi Shimada¹, Kousuke Iijima¹, Hisashi Hasegawa¹, Katsuya Okawa¹, Toshiro Fujita², Seiji Fukumoto² & Takeyoshi Yamashita¹

• FGFRs are widely expressed
• FGF23 action requires FGFR1 + Klotho
• Klotho lends tissue specificity
FGF23/PTH: renal phosphate/Vit-D regulation
Hierarchical relationship

FGF23

NaPi2 expression
1α/24-hydroxylase
proximal renal tubule cell

serum phosphate
serum 1,25-D₃
FGF23 phosphaturic action is PTH-dependent

Gupta, JCEM, 2004
FGF23 phosphaturic action is PTH-dependent

• Hypothesis: FGF23 action is PTH-dependent
• Decrease PTH (cinacalcet)

Tumor-Induced Osteomalacia - An FGF23 Excess Disease

mesenchymal tumors

FGF23 overproduction

↓ Pi, ↓ 1,25-D, osteomalacia, fractures

Serum FGF23 (pg/ml)

Normal     TIO

0  100  200  300  400  500  600
Decreasing PTH inhibits FGF23 action
- two subjects, intractable TIO, treated with cinacalcet
- interdependent relationship between FGF23 and PTH

(Geller et al. J Bone and Miner Res 2007)
<table>
<thead>
<tr>
<th>Name</th>
<th>Abbreviation</th>
<th>Gene(s)</th>
<th>FGF23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal recessive hypophosphatemic rickets</td>
<td>ARHR1</td>
<td>$DMP-1$</td>
<td>↑</td>
</tr>
<tr>
<td>Autosomal recessive hypophosphatemic rickets</td>
<td>ARHR2</td>
<td>$E-NPP1$</td>
<td>↑</td>
</tr>
<tr>
<td>X-linked hypophosphatemic rickets</td>
<td>XLH!</td>
<td>$PHEX$</td>
<td>↑</td>
</tr>
<tr>
<td>Autosomal dominant hypophosphatemic rickets</td>
<td>ADHR</td>
<td>$FGF23$</td>
<td>↑</td>
</tr>
<tr>
<td>McCune-Albright syndrome</td>
<td>MAS</td>
<td>$GNAS$ (mosaic)</td>
<td>↑</td>
</tr>
<tr>
<td>Cutaneous skeletal hypophosphatemia syndrome</td>
<td>CSHS</td>
<td>$RAS$ (mosaic)</td>
<td>↑</td>
</tr>
<tr>
<td>Jansen metaphyseal chondroplasia</td>
<td>JMC</td>
<td>$PTH/PTHr1$ receptor</td>
<td>↑</td>
</tr>
<tr>
<td>Osteoglophonic dysplasia</td>
<td>OGD</td>
<td>$FGFR1$</td>
<td>↑</td>
</tr>
<tr>
<td>Raines syndrome</td>
<td></td>
<td>$FAM20C$</td>
<td>?</td>
</tr>
<tr>
<td>Tumor-induced osteomalacia</td>
<td>TIO</td>
<td>$FN-FGFR1$</td>
<td>↑</td>
</tr>
<tr>
<td>Hyperphosphatemic familial tumoral calcinosis</td>
<td>HFTC (1,2,3)</td>
<td>$GALNT3; FGF23; Klotho$</td>
<td>↓</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>CRF</td>
<td>$N/A$</td>
<td>↑↑</td>
</tr>
</tbody>
</table>
Evaluation of Hypophosphatemia

↓ serum phosphate (age-related norms)

confirm renal loss (%TRP, TmP/GFR)

primary renal defect vs: hormonal

check plasma FGF23

↓ FGF23  ↑ FGF23

Fanconi-type tubulopathy
- aminoaciduria
- proteinuria (low MW)
- bicarbonaturia (acidosis)
- calciuria

Genetic (Fanconi syndrome)
Acquired
- Toxins (lead, cadmium, etc)
- Drugs (tenofovir, chemotherapy)

Genetic
- X-linked (PHEX)
- ADHR (FGF23)
- ARHR (DMP-1, others)

Acquired
- TIO
- Metastatic cancers
Tumor-Induced Osteomalacia

↑↑↑ FGF23

TIO
phosphaturic mesenchymal tumor

prodistal renal tubule cell
↓↓↓ NaPi2a/c
↓↓ 1-α ase
↓ serum phosphate
↓ serum 1,25-D

FGFR1
Klotho
FGF23 Action and Regulation

TIO
phosphaturic mesenchymal tumor

↑↑↑FGF23

FGF23
Action and Regulation

FGFR1
Klotho

proximal renal
tubule
cell

↓↓1-α ase
↓↓NaPi2a/c

↓serum phosphate

↓serum 1,25-D

TIO
phosphaturic mesenchymal tumor

↓↓↓serum phosphate

↓↓↓serum 1,25-D

phosphate
Diagnosis, Localization, Cure of TIO

Functional Imaging Study: Octreotide, FDG/PET, DOTA

Suspect single lesion

Anatomical Imaging: CT and/or MRI

Surgical excision

Cure ☺
Diagnosis, Localization, Cure of TIO

Functional Imaging Study: Octreotide, FDG/PET, DOTA

- Suspect single lesion
  - Anatomical Imaging: CT and/or MRI
    - Surgical excision
      - Cure 😊

- Multiple lesions or potentially morbid lesion
  - Anatomical Imaging: CT and/or MRI
    - Venous sampling
      - Surgical excision**
        - Cure 😊

** Wide Margins!!!
Functional Imaging Studies:
Octreoscan, FDG-PET/CT, DOTA

- Octreoscan = $^{111}\text{In}$-Octreotide SPECT/CT – head to toe!!
  - head to toe SPECT takes several hours
- DOTA-TATE, -TOC, -NOC
  - DOTAs = somatostatin analogues, $^{68}\text{Ga}$-labeled PET/CT scans
- Which is better? Which is the best?
- DOTA is best, but FDG PET can be complementary
X-Linked Hypophosphatemic Rickets

- Childhood/family history
- Short stature
- Bowed legs
- Dental abscesses as a child/young adult
- Enthesopathies
- Fractures/pseudofractures
- Calcified longitudinal ligament
Medical Therapy

- Oral Phosphate
  - K-phos neutral tablets or packets (250 mg phos/tab or pack)
  - PhosphoSoda (Fleets™), 128 mg elemental phos/ml
  - 3-5 X/day as tolerated → diarrhea
  - 15-60 mg/kg/d
  - Goal is pre-dose serum phos low normal
  - Causes secondary hyperparathyroidism
Medical Therapy

- Calcitriol
  - prevent/control secondary hyperparathyroidism
  - improves GI calcium (and phosphate) absorption
  - 15-60 ng/kg/d (0.25µg capsules, 3-12/day)
  - Can cause hypercalciuria
  - Check 24 hour urinary calcium
**Medical Therapy**

- **Cinacalcet**
  - FGF23 action is PTH-dependent
  - Without PTH, FGF23 is less effective
  - Adjunct to phosphate + calcitriol
  - Can exacerbate hypercalciuria
  - Monitor 24 hr urinary calcium

---

- **FGF23**
- **PTH**
- **FGF23**
- **Klotho**
- **FGFR1**
- **proximal renal tubule cell**
- ↓**NaPi2a/c**
- ↑**serum phosphate**

---

Gupta et al JCEM, 2004
Alon et al. Ped Nephro 2010
Emerging Medical Therapies

- KRN23 – anti-FGF23 mAb
- In clinical trials for XLH/TIO
- Short term efficacy & safety

Carpenter et al., JCI, 2014
Imel et al., JCEM, 2015
Zhang et al., J Clin Pharm 2015

Ultragenyx Pharmaceuticals
Kirin Pharmaceuticals (Kyowa Hakko Kirin)
Emerging Therapies – KRN23

Carpenter et al., JCI, 2014
Imel et al., JCEM, 2015
Zhang et al., J Clin Pharm 2015
FGF23 Deficiency: familial tumoral calcinosis (FTC)
Familial tumoral calcinosis: intact FGF23 deficiency

FGF23 maintains tonic inhibition of 1α-hydroxylase activity

n=8, bar = 1 SD

= normal range

Ramnitz, JBMR, 2016
Broader implications for FGF23 in health and disease

Fibroblast Growth Factor 23 and Mortality among Patients Undergoing Hemodialysis


200/10,044 dialysis patients who died compared to 200 case controls
Patients with the highest FGF23 levels → highest mortality

FGF23 levels

- <1090
- 1090-1750
- 1751-4010
- >4010

FGF23 exerted an independent effect on mortality
FGF23 induces left ventricular hypertrophy

Christian Faul,1,2 Ansel P. Amaral,1,2 Behzad Oskouei,3 Ming-Chang Hu,4,5,6 Alexis Sloan,1,2 John W. Kusek,26 Martin G. Keane,18 and Myles Wolf1


Renal failure patients

FGF23-treated mice

Klotho-independent, FGFR4 mediated
The Associations of Fibroblast Growth Factor 23 and Uncarboxylated Matrix Gla Protein With Mortality in Coronary Artery Disease: The Heart and Soul Study

Benjamin D. Parker, MD; Leon J. Schurgers, PhD; Vincent M. Brandenburg, MD; Robert H. Christenson, PhD; Cees Vermeer, PhD; Markus Ketteler, MD; Michael G. Shlipak, MD, MPH; Mary A. Whooley, MD; and Joachim H. Ix, MD, MAS

n = 833, 12 outpatient cardiology clinics in SF CA
### Appendix Table 3. Association Between Baseline Factors and In-FGF23, ucMGP, and Fetuin-A Levels*

<table>
<thead>
<tr>
<th>Variable</th>
<th>In-FGF23</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>β (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Age (per 10 y)</td>
<td>−0.05 (−0.11 to 0.01)</td>
<td>0.107</td>
</tr>
<tr>
<td>Women</td>
<td>0.40 (0.23 to 0.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nonwhite race</td>
<td>−0.04 (−0.18 to 0.10)</td>
<td>0.56</td>
</tr>
<tr>
<td>Smoking status</td>
<td>0.36 (0.19 to 0.53)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.14 (−0.01 to 0.29)</td>
<td>0.077</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.27 (0.12 to 0.42)</td>
<td>0.001</td>
</tr>
<tr>
<td>Estimated GFR†</td>
<td>−0.32 (−0.39 to −0.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist-to-hip ratio†</td>
<td>−0.03 (−0.10 to 0.04)</td>
<td>0.36</td>
</tr>
<tr>
<td>Total cholesterol level†</td>
<td>0.01 (−0.06 to 0.08)</td>
<td>0.82</td>
</tr>
<tr>
<td>HDL cholesterol level†</td>
<td>−0.05 (−0.11 to 0.02)</td>
<td>0.184</td>
</tr>
<tr>
<td>In-hsCRP level†</td>
<td>0.20 (0.13 to 0.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction†</td>
<td>−0.11 (−0.18 to −0.05)</td>
<td>0.001</td>
</tr>
<tr>
<td>Max METS†</td>
<td>−0.23 (−0.30 to −0.16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Medication use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>0.04 (−0.10 to 0.18)</td>
<td>0.55</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>0.12 (−0.02 to 0.25)</td>
<td>0.092</td>
</tr>
<tr>
<td>Aspirin</td>
<td>−0.23 (−0.39 to −0.06)</td>
<td>0.006</td>
</tr>
<tr>
<td>Statin</td>
<td>−0.13 (−0.27 to 0.01)</td>
<td>0.079</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>0.63 (0.38 to 0.89)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Fibroblast Growth Factor 23 and Cause-Specific Mortality in the General Population: The Northern Manhattan Study

Nao Souma, MD, PhD, Tamara Isaakova, MD, MMSc, David Lipiszko, BA, Ralph L. Sacco, MD, MS, Mitchell S.V. Elkind, MD, MS, Janet T. DeRosa, MPH, Shonni J. Silverberg, MD, Armando J. Mendez, PhD, Chuanhui Dong, PhD, Clinton B. Wright, MD, MS, Myles Wolf, MD, MMSc

Fibroblast Growth Factor 23 Is Associated With Stroke April 2016
Subclinical Cerebrovascular Damage
The Northern Manhattan Study

Clinton B. Wright, MD, MS; Nirav H. Shah, MD; Armando J. Mendez, PhD; Janet T. DeRosa, MPH; Mitsuhiro Yoshita, MD, PhD; Mitchell S.V. Elkind, MD, MS; Ralph L. Sacco, MD, MS; Charles DeCarli, MD; Tatjana Rundek, MD, PhD; Shonni Silverberg, MD, PhD; Chuanhui Dong, PhD; Myles Wolf, MD, MMSc

Fibroblast Growth Factor 23 Is Associated With Carotid Plaque Presence and Area September 2015
Arterioscler Thromb Vasc Biol
The Northern Manhattan Study

Nirav H. Shah, Chuanhui Dong, Mitchell S.V. Elkind, Ralph L. Sacco, Armando J. Mendez, Barry I. Hudson, Shonni Silverberg, Myles Wolf, Tatjana Rundek, Clinton B. Wright

Fibroblast Growth Factor 23, Cardiovascular Disease Risk Factors, and Phosphorus Intake in the Health Professionals Follow-up Study

Gutiérrez OM, Wolf M, Taylor EN.
Summary

- FGF23 is a bone-derived hormone
- Disease of excess (osteomalacia), deficiency (ectopic calcification)
- Acts at the kidney to lower Pi and 1,25-D
- Regulated by Pi, 1,25-D, others
- Complex FGF23/PTH/1,25-D axis
- May play a role in renal mortality via LVH
- Role in “normal physiology” is evolving
Return to our Case

111In octreoscan

plantar view feet

whole body planar view
Venous sampling of FGF23 for tumor localization

= catheter course/tip

FGF23 (pg/ml)

peripheral veins

cranial veins

plantar veins
Tumor excision/resolution of tumor-induced osteomalacia

\[ t_{1/2} \approx 45 \text{ min} \]
NIH Clinical Center
William Chong
Mary Scott Ramnitz
Diana Ovejero
Beth Brillante
Diala El-Maouche
Alison Boyce
Andrea Estrada
Andrea Burke
Lori Guthrie
Nisan Bhattacharyya

Former Trainees
Azar Khosravi
Claudia Dumitrescu
Penny Andreopoulou
William H. Chong
Tarek Metwally

NIH Clinical Center
Richard Chang
Clara Chen
Jenny Blau

Surgeons
Felasfa Wodajo
Johnathan Forsberg

Rachel Gafni
Recommendations for Treatment of Hypophosphatemia

Goal:
To provide enough phosphate substrate to allow mineralization. In disorders of pure phosphate deficiency (XLH, TIO, etc.), this is achieved when the alkaline phosphatase is normalized. In fibrous dysplasia, it is not possible to normalize the alk phos, so a trough serum phosphorus in the age-appropriate, low end of the normal range is the goal.

Treatment:
Phosphorus: 15-60 mg/kg/d, elemental phosphorus divided, 3-5 times/d. Compliance can be an issue, due to side effects. Phosphorus treatment sometimes causes secondary hyperparathyroidism. 1,25 vitamin D (calcitriol) is usually needed.

Supplements:
K-phos neutral tablets or packets: 250 mg phos/tab or pack; Most concentrated form is Fleets PhosphoSoda, 128 mg elemental phos/ml
1,25 vitamin D: up to 30 ng/kg/d, range 15-60 ng/kg/d. 1,25 vitamin D prevents secondary hyperparathyroidism and may increase GI phosphorus absorption.
Cinacalcet: FGF23 action is PTH dependent. Medicinal hypoparathyroidism with cinacalcet will increase renal phosphate reabsorption. Dose 30 mg/d (increase as needed/tolerated).

Possible Complications:
Hypercalciuria (due to calcitriol): with resultant nephrocalcinosis, nephrolithiasis and decreased creatinine clearance.
Hypercalcemia: less common than hypercalciuria.
GI upset (common): Due to the phosphate. Dividing the doses over 4-5 times per day and taking with food may help.
Hypocalcemia: if cinacalcet is used. May need to increase calcitriol.
Hypercalciuria: if cinacalcet is used. May need to add a thiazide diuretic.

Follow-up:
1. Baseline ultrasound to rule out nephrolithiasis (which some patients are at risk for at the outset).
2. q3 month urine (second A M void) for calcium and creatinine, if Ca/Cr ≥ 0.20, dip urine for heme, if + decrease 1,25 D, and obtain 24 hour urine for calcium and creatinine with the goal to keep urinary calcium in the normal range. If it is high, decrease 1,25 D again. If Ca/Cr ≤ 0.20 and serum phos and PTH ok, maintain regimen (pediatric urinary calcium: Ca/Cr upper limit: < 7mo 0.86, 7-18 mo 0.6, 19 mo – 6 y 0.42: 24 hr urine: <4mg/kg/24hr)
3. once dosing is stable, q3 month serum calcium, phosphorus, and PTH

Craniofacial and Skeletal Diseases Branch
National Institute of Dental and Craniofacial Research
National Institutes of Health, Bethesda, MD