FGF23 in CKD and ESRD

Regulator of phosphorus balance, or much more than that?

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Learning Objectives

• Review the pathogenesis of disordered mineral metabolism in CKD from the traditional perspective of the PTH-Vitamin D axis and the new FGF23-based paradigm.

• Examine the physiologic regulation and function of FGF23 and its molecular mechanisms of action.

• Explore the pathologic role of FGF23 in CKD and ESRD, and the effects of various strategies to lower FGF23 level.
Classical Paradigm of CKD-MBD

Bone Disease
- osteitis fibrosa
- demineralization
- fractures
- bone pain

Renal Failure

Systemic Toxicity
- nervous system
- cardiac
- endocrine
- immunologic
- cutaneous

↑ PTH

↓ Ca++

↑ Pi

↓ 1,25 D

↑ PTH
PTH-Vitamin D Axis

• The mammalian FGF family comprises 22 polypeptides grouped into 7 subfamilies.
• Classical FGFs exert their biological activity locally as paracrine factors via binding to one of four distinct FGF receptor tyrosine kinase gene products (Fgfr1 to Fgfr4) in a process that requires heparin as a cofactor.
• The FGF19 subfamily members (consisting of FGF19, FGF21, and FGF23) are heparin independent, resulting from unique structural features permitting them to circulate and act as endocrine factors:
  – FGF19: energy and bile acid homeostasis;
  – FGF21: glucose and lipid metabolism;
  – **FGF23**: phosphate and vitamin D homeostasis
FGF23

- FGF23 is a ~32 kDa (251 amino acids) circulating protein that has phosphaturic activity *in vivo*.
- Located on Chr 12p13.
- Predominately expressed in osteocytes, but also ventrolateral thalamic nucleus, central venous sinusoids and thymus.
Clinical Spectrum Of Disordered Phosphate Homeostasis and Mineralization

FGF23 Excess

- Hereditary/Acquired Hypophosphatemic Rickets
- FGF23 administration to mice.
- FG23 overexpressing mouse models.
  - Hyp mice
  - Dmp1 null mice
  - FGF23 transgenic mice

FGF23 Deficiency

- Hereditary Tumoral Calcinosis
- FGF23 deficient mouse models

Phenotypes

FGF23 Excess
- Low serum phosphate
- Aberrant vitamin D metabolism/low vitamin D
- Rickets/Osteomalacia

FGF23 Deficiency
- Hyperphosphatemia
- Elevated 1,25(OH)2D production
- Soft tissue calcifications
- Hyperostosis
Comparison of PTH/Vitamin D and FGF23/Klotho Bone-Kidney Axis

A PTH = Calcemic Hormone

PTH/1,25(OH)₂D axis

Parathyroid gland

^-\text{Ca}^{2+}\quad\text{(Primary decrease)}

1,25(OH)₂D secretion

1,25(OH)₂D

Small intestine

Bone

Kidney

25-OH-D

1α-hydroxylase

1,25(OH)₂D

NaPi-IIa

NaPi-IIc

\text{Ca}^{2+}\quad\text{PO}_4\quad\text{Urine}

\text{Ca}^{2+}\quad\text{PO}_4\quad\text{reabsorption}

\text{Ca}^{2+}\quad\text{PO}_4\quad\text{absorption}

\text{Ca}^{2+}\quad\text{PO}_4\quad\text{efflux}

\text{(Normal range restored)}

B FGF23 = Vitamin D Counter-regulatory/Phosphaturic Hormone

FGF23/Klotho axis

1,25(OH)₂D

Small intestine

Bone

Kidney

25-OH-D

1α-hydroxylase

S1c34a1

S1c34a3

\text{PO}_4

\text{Na}^+/\text{K}^-\text{-ATPase}

\text{Klotho: FGFR1}

\text{Klotho: TRPV5}

\text{Secreted Klotho}

\text{Kidney nephron, proximal tubule}

\text{Kidney nephron, distal tubule}

* This Bone-Kidney axis may also provide a mechanism to link changing phosphate requirements for bone mineralization with renal phosphate handling?

New Paradigm of CKD-MBD
FGF23 Physiology
Physiologic Regulators and Functions of FGF23

Kovesdy CP and Quarles LD, Nephrol Dial Transplant 2013
Additional regulators of FGF23

- Calcium
- Corticosteroids
- Leptin
- Estrogen
- Iron metabolism/HIF
- Inflammation
- Local regulators (Phex, Dmp1, Enpp1, FGFR1 and HMW-FGF2)

Kovesdy CP and Quarles LD, Nephrol Dial Transplant 2013
Bhattacharyya N et al, Trends Endocrinol Metab. 2012
FGF23 Binding to FGFR: α-Klotho Imparts Tissue Specificity

- **Tissue Expression**
- **Functions**
  - Beta-glucuronidase that deglycosylates steroid beta-glucuronides and TRPV5 calcium channel (permits membrane insertion).
  - Forms trimeric complex with FGF receptor and FGF23.
  - Ectodomain shedding (ADAM-13 & 17) → circulating hormonal actions.

**References**
- Asada, M Biochim Biophys Acta 2009;1790:40-8
FGF23 Binding to FGFR: α-Klotho Imparts Tissue Specificity

Paracrine

Systemic

Chondroitin sulfate
Heparin, Heparan sulfate

FGFR1(IIIc)

FGF receptor tyrosine kinase

Signal transduction

Kidney

PTG

Choroid Plexus

Pituitary?

Other?

On target

Off target?

Npt2- cotransporter
\(^{1\alpha}\)-hydroxylase (Cyp27b1)
Cyp24

医疗机构зовелю

PTH

? Function

? Function

Asada, M Biochim Biophys Acta 2009;1790:40-8
Effects of FGF23 in CKD and ESRD: Adaptive vs. Maladaptive
Which Comes First: FGF23 or PTH?

Isakova T, Kidney Int 79:1370, 2011
FGF23 is Markedly and Variably Elevated in ESRD

Intact FGF23 levels in ESRD

- Normals
  - Median 42 pg/ml
  - Range 8.2-54.3 pg/ml
- ESRD
  - Median 2621 pg/ml
  - Range 26-62,639 pg/ml

Serum FGF23 Levels in Normal and Disordered Phosphorus Homeostasis

Effects of FGF23 on Vitamin D metabolism

Dai B et al., Kidney Int 82, 1061–107, 2012
FGF23 and Outcomes in CKD

Causal or Epiphenomenon?
FGF23 Associated with Mortality in ESRD

FGF23 Associated with Mortality in CKD


Model 1: age, race, gender.
Model 2: Model 1 + smoking, alcohol, DM, HTN, CVD, BMI, SBP, GFR, treatment arm, homocysteine, Hgb, folate, B12, albumin, calcium, 25(OH)D, 1,25(OH)2D, iPTH, phosphate, HDL, LDL, triglycerides, total cholesterol.
Model 3: Model 2 + use of medications.
FGF23 Associated with Outcomes Post-Transplant


Cumulative Incidence, Composite Outcome (%)

Analysis time (years)

N = 984
Enrolled 6 years PTx
FGF23 Associated with ESRD in CKD

FGF23 Associated with CHF and CVD in CKD

FGF23 and Adverse Outcomes: Mechanisms of Action
Elevated circulating FGF23 levels are associated with LVH in patients with CKD

Faul, C et al, JCI 121:4393-408, 2011
FGF23 and LVH – Direct vs. indirect effects

FGF23 and LVH – Direct vs. indirect effects

Transcriptome Analysis of FGF23 Regulated Genes in Kidney

## Renal genes modified in models of excess FGF23

<table>
<thead>
<tr>
<th>Gene Name</th>
<th>Symbol</th>
<th>Col4a3-/</th>
<th>Hyp</th>
<th>FGF23tg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lipocalin 2</td>
<td>Lcn2</td>
<td>53.8</td>
<td>NM</td>
<td>2.0</td>
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<tr>
<td>vascular cell adhesion molecule 1</td>
<td>Vcam1</td>
<td>11.5</td>
<td>1.4</td>
<td>1.4</td>
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<tr>
<td>complement component factor i</td>
<td>Cfi</td>
<td>3.2</td>
<td>3.2</td>
<td>1.6</td>
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<tr>
<td>tumor-associated calcium signal transducer 2</td>
<td>Tacstd2</td>
<td>2.5</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>lectin, galactoside-binding, soluble, 3 binding protein</td>
<td>Lgals3bp</td>
<td>2.1</td>
<td>1.3</td>
<td>1.3</td>
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<tr>
<td>phospholipase A2, group VII</td>
<td>Pla2g7</td>
<td>1.7</td>
<td>1.9</td>
<td>2.0</td>
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<tr>
<td>immediate early response 3</td>
<td>Ier3</td>
<td>1.6</td>
<td>1.8</td>
<td>2.2</td>
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<tr>
<td>transporter 1, ATP-binding cassette, sub-family B</td>
<td>Tap1</td>
<td>1.6</td>
<td>1.5</td>
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<tr>
<td>receptor (calcitonin) activity modifying protein 2</td>
<td>Ramp2</td>
<td>1.5</td>
<td>1.5</td>
<td>1.6</td>
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<td>phospholipid scramblase 1</td>
<td>Plscr1</td>
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<td>1.4</td>
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<td>guanylate binding protein 2</td>
<td>Gbp2</td>
<td>1.3</td>
<td>1.6</td>
<td>1.3</td>
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<tr>
<td><strong>Decreased</strong></td>
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<tr>
<td>deoxyribonuclease I</td>
<td>Dnase1</td>
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<td>-4.3</td>
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<td>carbonic anhydrase 14</td>
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<td>-1.6</td>
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<td>afamin</td>
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<td>klotho</td>
<td>Ki</td>
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<td>abhydrolase domain containing 14A</td>
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<td>angiotensin I converting enzyme 2</td>
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<td>-1.9</td>
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<tr>
<td>solute carrier family 2, member 2</td>
<td>Slc2a2</td>
<td>-1.6</td>
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<td>-1.3</td>
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<tr>
<td>thioesterase superfamily member 2</td>
<td>Them2</td>
<td>-1.6</td>
<td>-1.4</td>
<td>-1.3</td>
</tr>
</tbody>
</table>

Putative Mechanisms of FGF23s Adverse Effects

$\uparrow$FGF23

$\downarrow$1,25(OH)$_2$D $\rightarrow$ RAAS $\rightarrow$ Klotho expression $\rightarrow$ Inflammation $\rightarrow$ LVH

CV disease, metabolic disorders, infections, malignancies
CV disease, metabolic disorders
Vascular and metabolic disorders
CV disease, protein-energy wasting
Arrhythmias, CV mortality

Kovesdy CP and Quarles LD, Nephrol Dial Transplant 2013
Dietary and Pharmacologic Modification of FGF23 Levels
# Phosphorus binders and FGF23 in CKD

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Length of Rx</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koiwa et al. <em>Ther Apher Dial</em> 2005</td>
<td>Sevelamer + Ca Carb. Calcium Carbonate</td>
<td>4 weeks</td>
<td>Sevelamer + Ca but not Ca alone reduced FGF23</td>
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<tr>
<td>Oliveria et al. <em>CJASN</em> 2009</td>
<td>Sevelamer Calcium Acetate</td>
<td>6 weeks</td>
<td>Sevelamer but not Ca reduced FGF23</td>
</tr>
<tr>
<td>Isakova et al. <em>NDT</em> 2010</td>
<td>Lanthanum</td>
<td>2 weeks</td>
<td>Lanthanum alone did not reduce FGF23</td>
</tr>
<tr>
<td>Gonzalez-Parra et al. <em>NDT</em> 2011</td>
<td>Lanthanum</td>
<td>4 weeks</td>
<td>Lanthanum reduced FGF23</td>
</tr>
<tr>
<td>Block et al. <em>JASN</em> 2012</td>
<td>Sevelamer Lanthanum Calcium Acetate</td>
<td>36 weeks</td>
<td>Sevelamer but not lanthanum or Ca reduced FGF23</td>
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<tr>
<td>Shigematsu et al. <em>NDT</em> 2011</td>
<td>Lanthanum + Ca Carbonate</td>
<td>16 weeks</td>
<td>Lanthanum + Ca reduced FGF23</td>
</tr>
<tr>
<td>Covic et al. <em>NDT</em> 2013</td>
<td>Calcium-magnesium Sevelamer</td>
<td>24 weeks</td>
<td>CaMg and sevelamer reduced FGF23</td>
</tr>
<tr>
<td>Isakova et al. <em>CJASN</em> 2013</td>
<td>Lanthanum</td>
<td>12 weeks</td>
<td>Lanthanum alone did not reduce FGF23</td>
</tr>
</tbody>
</table>

**Bottom line:** non-calcium based binders reduce FGF23 in CKD patients, with sevelamer showing a more consistent effect than lanthanum.
# Low phosphorus diet and FGF23

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Length of Rx</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moe et al. <em>CJASN 2010</em></td>
<td>Vegetarian vs. meat diets (protein source)</td>
<td>1 week</td>
<td>Vegetarian diet reduced FGF23</td>
</tr>
<tr>
<td>Isakova et al. <em>NDT 2010</em></td>
<td>Low $P_i$ diet</td>
<td>2 weeks</td>
<td>Low $P_i$ Diet did not reduce FGF23</td>
</tr>
<tr>
<td>Sigrist et al. <em>NDT 2013</em></td>
<td>Low $P_i$ Diet Low $P_i$ Diet + aluminum</td>
<td>1 week</td>
<td>Low $P_i$ + Al but not diet alone reduced FGF23</td>
</tr>
<tr>
<td>Isakova et al. <em>CJASN 2013</em></td>
<td>Low $P_i$ diet Low $P_i$ diet + lanthanum</td>
<td>12 weeks</td>
<td>Lanthanum + low $P_i$ diet but not diet alone reduced FGF23</td>
</tr>
</tbody>
</table>

**Bottom line:**
- Dietary phosphorus reduction alone does not seem to be effective in reducing FGF23
- There may be benefit in focusing on vegetable vs. meat sources of phosphorus
Cinacalcet to reduce FGF23

ACHIEVE Study:
91 maintenance hemodialysis patients assigned to receive either cinacalcet + low-dose VDR activators (Cinacalcet-D) or VDR activators (Flex-D) alone

Anti-inflammatory therapy and FGF23

Augustine MV et al, J Clin Endocrinol Metab 2014 Mar 11:jc20133846. [Epub ahead of print]
Effect of anti-FGF23 blocking antibody on phosphate and vitamin D metabolism in anti-GBM CKD rat model

Summary and Conclusions

• Bone is an endocrine organ that produces and secretes FGF23 from osteocytes.

• Physiological role is to suppress renal phosphate reabsorption and 1,25(OH)$_2$D production, thereby creating a Bone-Kidney Axis that:
  – Counters the effects of PTH on 1,25(OH)$_2$D.
  – Coordinates bone mineralization (turnover) and renal phosphate handling, through FGF receptor-mediated mechanism both in the kidney (distal tubule/proximal effect) and in osteoblasts (other FGFs and FGFRs regulates FGF23 production in osteoblasts/osteocytes).

• Pathological effects include:
  – Causative agent in hereditary and acquired hypophosphatemic and hyperphosphatemic disorders.
  – Adaptive role in early CKD and a potential maladaptive role in late stage CKD.

• Many aspects of FGF23’s physiology and pathophysiology, and its role in CKD and ESRD as causal agent vs. risk factor need further studying.