FGF23 & Other Emerging Diagnostic Markers

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Disclosures: Abbott, Amgen, Keryx, Luitpold, OPKO, Pfizer, Sanofi, Shire
PHYSIOLOGY and EPIDEMIOLOGY
Classic actions and stimuli of FGF23

- Stimulates phosphaturia
- Inhibits CYP27B1
- Stimulates CYP24A1
- Inhibits PTH

Classic actions require “permissive” serum calcium

Stimuli:
  - phosphate intake, 1,25-dihydroxyvitamin D, PTH, calcium

Lower 1,25-dihydroxyvitamin D
CKD Chickens and Eggs

Primary klotho deficiency with FGF23 resistance

Primary FGF23 excess with klotho down regulation

↑ FGF-23
↓ klotho
↑ klotho
↑ FGF-23

Early CKD

Early CKD
FGF23 by CKD stage in CRIC

Isakova et al. Kidney Int 2011
FGF23, phosphate and PTH in CRIC

% of Population

Estimated glomerular filtration rate, ml/min/1.73 m²

- Hyperphosphatemia, serum phosphate ≥ 4.6 mg/dl
- Secondary hyperparathyroidism, PTH ≥ 65 pg/ml
- FGF23 excess, FGF23 ≥ 100 RU/ml

Isakova et al. Kidney Int 2011
Disordered Mineral Metabolism in Rats with Anti-GBM Nephritis

Hasegawa et al. Kidney Int 2010
Effects of Anti-FGF23 Antibodies

- Increase serum P
- Normalize 1,25D
- Decrease phosphaturia: FEPi
- Reverse CYP regulation

Hasegawa et al. Kidney Int 2010
Emerging views on the pathogenesis of disordered mineral metabolism in CKD

Isakova, Wolf, Kidney Int 2010
OUTCOMES STUDIES
Mortality
CVD Events
CKD Progression
FGF23 and Mortality in Incident ESRD

cFGF-23 vs. Phosphate Quartiles & Mortality

Two-year survival according to FGF23: Prevalent hemodialysis

Jean et al. Nephrol Dial Transplant 2009; e-pub ahead of print
FGF23 Tertiles & Composite Risk of Death or Allograft Loss

FGF23 vs. PTH, Phosphate, Hgb as Risk Factor for Composite Outcome

Hazard Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tertile 1</th>
<th>Tertile 2</th>
<th>Tertile 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>FGF23</td>
<td>REF</td>
<td>REF</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PTH</td>
<td>REF</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Phosphate</td>
<td>REF</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>REF</td>
<td>REF</td>
<td>NS</td>
</tr>
</tbody>
</table>

HOST: Higher FGF23 Associated With Greater Risk of All-Cause Mortality in CKD 4

Model 1: age, race, gender.
Model 2: Model 1 + smoking status, alcohol intake, DM, HTN, CVD, BMI, SBP, GFR, treatment assignment, homocysteine, hemoglobin, folate, B12, albumin, calcium, 25(OH)D, 1,25(OH)\(_2\)D, iPTH, phosphorus, HDL, LDL, triglycerides, and total cholesterol.
Model 3: Model 2 + use of medications.

FGF23 and Mortality in CKD 2-4: 266 events, 20.3/1000 person-years

Cumulative incidence of death, %

- FGF23 Quartile 1: 1.0
- FGF23 Quartile 2: 1.3
- FGF23 Quartile 3: 2.0
- FGF23 Quartile 4: 3.0

Years of follow up

Isakova et al. JAMA 2011.
FGF-23 and CVD in non-CKD: Heart & Soul

N=833 with history of CAD

Parker et al. Ann Intern Med 2010
FGF23 and outcomes in CHS

- N=3107; 1128 with CKD (eGFR<60 or ACR>30 mg/g)
- Strongest association: death, CHF
- No association of FGF23 with MI
- Greater risks in CKD vs. non-CKD

Ix J et al. JACC 2012
FGF23 and risk of cardiovascular disease events in CKD stages 2 – 4

N=3860; Median follow-up, 3.7 years

Congestive Heart Failure
360 events (27/1000 person-years)

Atherosclerosis
287 events (22/1000 person-years)

Adjusted for demographics, kidney function, traditional CVD risk factors, medications

LV Geometry According to Ascending Quartiles of FGF23

Fibrroblast Growth Factor 23 Quartiles

- Quartile 1: Normal 27, Remodeling 35, Eccentric LVH 11, Concentric LVH 27
- Quartile 2: Normal 33, Remodeling 31, Eccentric LVH 12, Concentric LVH 24
- Quartile 3: Normal 38, Remodeling 16, Eccentric LVH 16, Concentric LVH 30
- Quartile 4: Normal 50, Remodeling 21, Eccentric LVH 21, Concentric LVH 10

FGF23 vs. phosphate as risk factors for CAC

N=1501 CRIC participants with CKD stage 2-4

Scialli et al. Kidney Int 2013
Disordered phosphate homeostasis and cardiovascular disease in CKD

High FGF23 → Heart

Klotho deficiency → LVH

Hyperphosphatemia → Vessels

Calcification → CVD events

CKD
Renal progression according to cFGF-23 levels

Interaction between FGF23, eGFR and ESRD

Risk of ESRD

HR per SD ln FGF23, 95%CI

<table>
<thead>
<tr>
<th>eGFR, ml/min/1.73m²</th>
<th>&lt; 30</th>
<th>30 – 44</th>
<th>≥ 45</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.3</td>
<td>1.5</td>
<td>1.9</td>
</tr>
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</table>

N

<table>
<thead>
<tr>
<th></th>
<th>3879</th>
<th>758</th>
<th>1472</th>
<th>1649</th>
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<tbody>
<tr>
<td>FGF23</td>
<td>145</td>
<td>256</td>
<td>161</td>
<td>105</td>
</tr>
<tr>
<td>Events Incidence</td>
<td>410</td>
<td>231</td>
<td>143</td>
<td>36</td>
</tr>
</tbody>
</table>

Isakova et al. JAMA 2011.
FGF23 is a risk factor for ESRD in AASK

Scialla et al. JASN 2012

<table>
<thead>
<tr>
<th>FGF23</th>
<th>+GFR</th>
<th>MV</th>
<th>+MM</th>
<th>+GFR slope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quartile 1</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Quartile 2</td>
<td>1.40</td>
<td>1.47</td>
<td>1.54</td>
<td>1.44</td>
</tr>
<tr>
<td>Quartile 3</td>
<td>1.58</td>
<td>1.67</td>
<td>1.79</td>
<td>1.65</td>
</tr>
<tr>
<td>Quartile 4</td>
<td>2.17</td>
<td>2.24</td>
<td>2.29</td>
<td>2.22</td>
</tr>
<tr>
<td>p-trend</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

MV: adjusted for: age, sex, Rx group; GFR; UPCR; income, prior heart disease, smoking, albumin, BMI, center

+MM: adjusted for PTH, phosphate, 25-hydroxyvitamin D, calcium

+GFR slope: adjusted for year 1 GFR slope

N = 809
ASSAYS and OTHER ODDS AND ENDS
Correlation between cFGF-23 & iFGF-23

Differences in the Proportion of FGF23 Present as C-terminal Fragments

Smith et al. JCEM 2012
Intact Diurnal Variation in Mineral Metabolism in CKD

Isakova T et al. CJASN 2012
Within-Subject Variation: FGF23, PTH, Phosphate

3 monthly measurements in 67 PD patients

Isakova T et al. CJASN 2011;6:2688-2695
## Factors that Modify FGF23

<table>
<thead>
<tr>
<th>Raises FGF23</th>
<th>Lowers FGF23</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD</td>
<td>Kidney transplantation</td>
</tr>
<tr>
<td>Low GFR</td>
<td>Low phosphate diet</td>
</tr>
<tr>
<td>AKI</td>
<td>Hypocalcemia</td>
</tr>
<tr>
<td>High phosphate diet</td>
<td>Non-calcium P-binders</td>
</tr>
<tr>
<td>Calcium</td>
<td>1,25D and analogs</td>
</tr>
<tr>
<td>PTH</td>
<td>Cinacalcet</td>
</tr>
<tr>
<td>Certain IV iron formulations</td>
<td>Certain IV iron formulations</td>
</tr>
</tbody>
</table>
Major unanswered questions

- What stimulates FGF23 production in early CKD?
- Does the FGF23 response differ by CKD etiology?
- What is FGF23 actually regulating?
- How and where is phosphate sensed?
- How and where is FGF23 degraded?
- What are other “off-target” effects of FGF23?
- What are the ideal therapeutic approaches to lower (or slow elevation) FGF23?
- If FGF23 can be modified, can we improve clinical outcomes?