Update on Fibroblast Growth Factor-23

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Learning Objectives

• Discovery of fibroblast growth factor-23 (FGF23).
• Mechanisms of action of FGF23.
• Clinical significance and future directions.

Discovery of FGF23

Hypophosphatemic Syndromes

• Oncogenic osteomalacia
• Autosomal dominant hypophosphatemic rickets
• X-linked hypophosphatemic rickets

Oncogenic Osteomalacia

• Patients present with bone pain, muscle weakness, recurrent fractures, difficulty walking.
• Hypophosphatemia, hyperphosphaturia, low or normal 1,25(OH)\(_2\)D.
• Usually associated with benign tumors of mesenchymal origin.
• Clinical and biological abnormalities resolve with surgical removal of the tumor.

Tumor Resection Cures Oncogenic Osteomalacia
**Autosomal Dominant Hypophosphatemic Rickets**

- Children can present with rickets, lower extremity deformities, and short stature.
- Adults can present with bone pain, weakness, and fractures.
- Hypophosphatemia, hyperphosphaturia, low or normal 1,25(OH)\(_2\)D.
- Improves with phosphate and 1,25(OH)\(_2\)D supplementation.

**Radiologic Findings in XLH**

**X-linked Hypophosphatemic Rickets**

- Lower extremity deformities, rickets, short stature.
- Hypophosphatemia, hyperphosphaturia, low or normal 1,25(OH)\(_2\)D.
- Caused by mutations in the PHEX gene (phosphate regulating gene with homologies to endopeptidases on the X chromosome).
- Improves with phosphate and 1,25(OH)\(_2\)D supplementation.
- Hypophosphatemia persists after renal transplantation in patients with XLH.

**Laboratory Parameters**

<table>
<thead>
<tr>
<th></th>
<th>OHO</th>
<th>ADHR</th>
<th>XLH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Ca</td>
<td>nl or ↓</td>
<td>nl</td>
<td>nl</td>
</tr>
<tr>
<td>Serum Pi</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>1,25(OH)(_2)D</td>
<td>↓ or nl</td>
<td>↓ or nl</td>
<td>↓ or nl</td>
</tr>
<tr>
<td>TMP/GFR</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>PTH</td>
<td>nl or sl↑</td>
<td>nl</td>
<td>nl or sl↑</td>
</tr>
</tbody>
</table>

**“Phosphatonin” – Common Etiologic Factor?**

1. Inhibits renal Pi transport *in vitro and in vivo*.
2. Inhibits 1,25(OH)\(_2\)D formation *in vitro and in vivo*.
3. Expressed in tumor tissues responsible for OHO.
4. Serum concentrations are increased in OHO.
5. Concentrations decrease with tumor removal.
6. Urinary cAMP excretion is normal.
Evidence for a circulating factor in XLH

- Parabiosis between Hyp and normal mice resulted in Pi wasting in the normal mice.
  - (Meyer, JBMR 1989)
- Cross-transplantation of kidneys between Hyp and normal mice resulted in persistent Pi wasting in Hyp mice.
  - (Nesbitt, JCI 1992)

Detecting Phosphatonin in Oncogenic Osteomalacia

- Tumor extracts inhibited Pi uptake in OK cells
  - (Cai, NEJM 1994)
- Infusion of tumor extracts into mice induced phosphaturia and hypophosphatemia
  - (Nitzan, Bone Miner. 1989)

Identifying the Gene for Phosphatonin

- Linkage analysis in a family with ADHR localized the abnormal gene to 12p13.3
- Identified new gene encoding “FGF23”
- Found three missense mutations lying 3 aa apart, postulated to prevent normal FGF23 processing and increase its circulating levels
  - (ADHR consortium, Nature 2000)

Implicating FGF23 in ADHR

- ADHR mutation stabilizes FGF23
  - (White, KI 2001)

Implicating FGF23 in OHO

- OHO tumors expressed ADHR gene product (FGF23)
  - (White, JCEM 2001)

Implicating FGF23 in OHO and XLH

- FGF23 levels decrease after surgery in OHO
- FGF23 levels are increased in patients with XLH
  - (Jonsson, NEJM 2003)
Excess FGF23

Renal phosphate wasting

Hypophosphatemia, Rickets, Osteomalacia

Mechanisms of FGF23
Effects on Mineral Metabolism

Tissue Expression of FGF23

- FGF23 is mainly expressed by bone osteocytes
  - (Liu, 2003)

FGF23 Causes Urinary Phosphate Wasting

- FGF23 transgenic mice over-expressing FGF23 have decreased Na/Pi 2a cotransporter expression in the kidney, resulting in hypophosphatemia.

Vitamin D Metabolism

- Portale, Ped Neph 2000

Prie, NEJM 2010

Liu, J Bio Chem 2003

Shimada, BBRC 2004
FGF23 and Renal Vitamin D Metabolism

- FGF23 administration in normal mice:
  - decreases 1α-hydroxylase mRNA expression
  - increases 24-hydroxylase mRNA expression

Perwad, AJP 2007

Signal Transduction by FGF-23 in the Renal Tubule

- FGF23 regulates renal vitamin D metabolism via the MAP Kinase signaling pathway.
  - Inhibition of the MAPK pathway results in increased 1,25(OH)2D production in Hyp mice.

Ranch, JBMR 2011

FGF23 Inhibits PTH Production in the Parathyroid Gland in Rats

- Treatment with FGF23 decreases serum PTH in rats.
  - Inhibition of the MAP Kinase pathway prevents suppression of PTH by FGF23.

Ben-Dov, JCI 2007

Summary of FGF23 Effects on Mineral Metabolism

- FGF23
  - Increased urinary Pi excretion
  - Hypophosphatemia
  - Low serum 1,25(OH)2D
  - Renal 1α-hydroxylase

FGF23 Influences Renal Vitamin D Metabolism

- Decreases 1α-hydroxylase mRNA expression
- Increases 24-hydroxylase mRNA expression

FGF23 Regulates Renal Vitamin D Metabolism via the MAP Kinase Signaling Pathway

- FGF23 inhibits PTH production in the parathyroid gland in rats.
- Inhibition of the MAPK pathway prevents suppression of PTH by FGF23.

FGF23 in the Renal Tubule

- Signal transduction by FGF-23 in the renal tubule.

Ranch, JBMR 2011

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Summary of FGF23 Effects on Mineral Metabolism

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  - Low serum 1,25(OH)2D
### Hypophosphatemic Syndromes

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<tr>
<th>Disease</th>
<th>Affected Gene</th>
<th>Serum Pi</th>
<th>1,25(OH)2D</th>
<th>Serum FGF23</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autosomal Dominant Hypophosphatemic Rickets</td>
<td>FGF23</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
<td>NI</td>
</tr>
<tr>
<td>X-Linked Hypophosphatemic Rickets</td>
<td>PHEx</td>
<td>Low</td>
<td>Low or NI</td>
<td>High</td>
<td>NI  or High</td>
</tr>
<tr>
<td>Recessive X-Linked Hypophosphatemic Rickets</td>
<td>DMP1</td>
<td>Low</td>
<td>Low or NI</td>
<td>High</td>
<td>NI</td>
</tr>
<tr>
<td>McCune-Albright Syndrome</td>
<td>GNAS</td>
<td>Low</td>
<td>?</td>
<td>High</td>
<td>NI</td>
</tr>
<tr>
<td>Hereditary Hypophosphatemic Rickets with Hypercalciuria</td>
<td>SLC34A3</td>
<td>SI or Low or NI</td>
<td>High</td>
<td>Low or NI</td>
<td>NI</td>
</tr>
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<th>C-terminal FGF23</th>
<th>PTH</th>
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<tbody>
<tr>
<td>Tumoral Calcinosis</td>
<td>FGF23</td>
<td>High</td>
<td>NI or High</td>
<td>Low</td>
<td>High</td>
<td>NI</td>
</tr>
<tr>
<td>Tumoral Calcinosis</td>
<td>GALNT3</td>
<td>High</td>
<td>NI or High</td>
<td>Low</td>
<td>High</td>
<td>NI</td>
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<td>Hyperphosphatemic syndrome</td>
<td>GALNT3</td>
<td>High</td>
<td>NI or High</td>
<td>Low</td>
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<td>NI</td>
</tr>
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<td>Tumoral Calcinosis</td>
<td>KLOTHO</td>
<td>High</td>
<td>NI or High</td>
<td>High</td>
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### FGF23 and Mortality in Hemodialysis Patients

- ArMORR study
- Prospective cohort of 10,044 incident adult hemodialysis patients in the U.S.
- Analyzed nested case-control sample of 200 subjects who died in the 1st year on dialysis vs 200 survivors.
- Increased FGF23 levels were strongly associated with risk of death in the 1st year on dialysis.

### FGF23 and Chronic Kidney Disease Progression

- MMKD study
- Cohort of 177 adult non-diabetic CKD patients, followed for a median of 53 months.
- End-point was doubling of baseline serum Cr or ESRD.
- Higher baseline serum FGF23 was associated with increased risk of disease progression.
FGF23 Increases As Kidney Function Declines

Adults with CKD

Children with CKD

Fiser, JASN 2007; van Husen, KI 2010

Development of Mineral Abnormalities in Chronic Kidney Disease

Development of Mineral Abnormalities in Chronic Kidney Disease

FGF23 and Dietary Phosphate Binding

FGF23 and Dietary Phosphate Binding

Isakova, NDT 2011

Isakova, KI 2011

Pathogenic Role for FGF23 in CKD?

- Possible direct toxicity by FGF23?
  - Increased serum FGF23 levels associated with increased LVMI.
  - FGF23 levels are 15-20 times higher than the upper limit of normal in advanced CKD.

Gutierrez, Circ 2009
**Anti-FGF23 Antibody Treatment in XLH**

- WT, control
- Hyp, control
- Hyp, FGF23Ab (4)
- Hyp, FGF23Ab (18)

**Future Research in FGF23**

- Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community.
  - Mirza, Athero 2009
- FGF-23 as a predictor of renal outcome in diabetic nephropathy.
  - These, JASN 2011
- Decrease in serum FGF23 levels after intravenous infusion of pamidronate in patients with osteogenesis imperfecta.
  - Klaase, JBMM 2011
- Sorafenib may induce hypophosphatemia through a fibroblast growth factor-23 (FGF23)-independent mechanism.
  - Ann Oncol 2011
- Leptin stimulates fibroblast growth factor 23 expression in bone and suppresses renal 1alpha,25-dihydroxyvitamin D3 synthesis in leptin-deficient mice.
  - Tsuji, JBMR 2010

**Take-Home Points**

- FGF23 is produced mainly from bone osteocytes.
- Excess FGF23 causes:
  - Renal phosphate wasting and hypophosphatemia.
  - Decreased 1,25(OH)₂D.
- Lack of FGF23 causes:
  - Hyperphosphatemia, increased 1,25(OH)₂D.
- FGF23 is increased in chronic kidney disease.