A Rare Cause of Persistent Hyperphosphatemia

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1. Dpt. of Endocrinology, Royal Melbourne Hospital
2. Dpt. of Nephrology Research, Royal Melbourne Hospital
51yo male, a refugee from Syria was referred to Endocrinology clinic for management of hyperphosphatemia (PO$_4$ = 2.34 mmol/L)

- Normal renal function.
- L1 vertebral fracture (60% height reduction)

<table>
<thead>
<tr>
<th>DXA</th>
<th>T-score</th>
<th>Z-score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>-1.23</td>
<td>-0.87</td>
</tr>
<tr>
<td>Left forearm</td>
<td>-4.30</td>
<td>-3.87</td>
</tr>
</tbody>
</table>
Presenting symptoms

- Polyarthalgia and joint stiffness since childhood
  - Knees, hips, elbows, hands
- Nodules in elbows – progressive increase in size since age 16
- Gradual change in posture (kyphotic) noted 5 years ago
- Antalgic gait – single point stick and electric scooter
- Dry gritty eyes
- No rash/photosensitivity/Raynaud phenomenon/ history of serositis/neurological symptoms
Medical History

1. **IHD:** mild coronary artery disease
   - Risk Factors: Dyslipidaemia, Hypertension

2. Abdominal/internal carotid artery aneurysm
   - infra-renal abdominal aortic aneurysm repair

4. Gastritis

5. Past history of **nephrolithiasis**

**Medication:** Aspirin, Atorvastatin, Fosinopril

PRN Paracetamol
Family History

- Parents are 1\textsuperscript{st} cousins
- Brother died aged 23
  - ? complication of Rheumatoid Arthritis
- Elder sister has nodules and polyarthropathy
Examination

- Stooped posture
- BP 120/85, PR 76bpm + regular
- **Eye:** White deposits in the corneal margin (left eye)
  - Visual Acuity: normal
- **Mouth:** 4 short and bulbous teeth

Example of corneal calcification
Examination

- **Limb examination**
  - Large, hard nodules over bilateral elbows
  - Bony proliferation DIP/PIP joints bilaterally
  - Fixed flexion deformity knees
  - Flexed lumbar spine with loss of lordosis
  - No synovitis
Examination

- **Abdomen**: no pulsatile mass.
- **Neurological exam**: unremarkable
- **Cardiovascular/Respiratory**: unremarkable
- **Skin**: no rash
## Investigations

<table>
<thead>
<tr>
<th></th>
<th>Result</th>
<th>Unit</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>137</td>
<td>mmol/L</td>
<td>135 – 145</td>
</tr>
<tr>
<td>K⁺</td>
<td>4.3</td>
<td>mmol/L</td>
<td>3.5 – 4.2</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>101</td>
<td>mmol/L</td>
<td>95 – 110</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>25</td>
<td>mmol/L</td>
<td>22 – 29</td>
</tr>
<tr>
<td>Creatinine</td>
<td>87</td>
<td>µmol/L</td>
<td>60 – 110</td>
</tr>
<tr>
<td>eGFR</td>
<td>90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea</td>
<td>8</td>
<td>mmol/L</td>
<td>3.3 – 7.4</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>2.68</td>
<td>mmol/L</td>
<td>2.1 – 2.6</td>
</tr>
<tr>
<td>corrected Ca²⁺</td>
<td>2.74</td>
<td>mmol/L</td>
<td>2.1 – 2.6</td>
</tr>
<tr>
<td>PO₄⁻</td>
<td>2.34</td>
<td>mmol/L</td>
<td>0.75 – 1.5</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>0.78</td>
<td>mmol/L</td>
<td>0.66 – 1.07</td>
</tr>
<tr>
<td>Albumin</td>
<td>38</td>
<td>µg/L</td>
<td>35 – 50</td>
</tr>
</tbody>
</table>

- ESR 21, CRP 26.1mg/L
- Urate 0.29 mmol/L (RR 0.21-0.42), ANA/anti-CCP/RF negative
DDx of hyperphosphatemia
DDx of hyperphosphatemia

- Increased tubular reabsorption of phosphate
  - Familial tumoral calcinosis
  - Vitamin D toxicity
  - Hypoparathyroidism

- Acute phosphate load
DDx of hyperphosphatemia

- Increased tubular reabsorption of phosphate
  - Familial tumoral calcinosis
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DDx of hyperphosphatemia

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- Acute phosphate load
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<th>Result</th>
<th>Unit</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1,25-OH Vit D</strong></td>
<td>220</td>
<td>pmol/L</td>
<td>78 – 190</td>
</tr>
<tr>
<td><strong>25-OH Vit D</strong></td>
<td>25</td>
<td>nmol/L</td>
<td></td>
</tr>
<tr>
<td><strong>iPTH</strong></td>
<td>5.6</td>
<td>pmol/L</td>
<td>1.7 – 7.5</td>
</tr>
<tr>
<td><strong>P1NP</strong></td>
<td>30.9</td>
<td>μg/L</td>
<td>15 – 80</td>
</tr>
<tr>
<td><strong>CTX</strong></td>
<td>0.36</td>
<td>ng/ml</td>
<td>0.1 – 0.6</td>
</tr>
<tr>
<td><strong>24 hr Urine (2.2L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr Clearance</td>
<td>91</td>
<td>mL/min</td>
<td>90 – 150</td>
</tr>
<tr>
<td>Calcium</td>
<td>4.2</td>
<td>mmol/D</td>
<td>2.5 – 7.5</td>
</tr>
<tr>
<td>Ca(^{2+})/Cr</td>
<td>0.33</td>
<td>mmol/mmol</td>
<td></td>
</tr>
<tr>
<td>Phosphate</td>
<td>22.2</td>
<td>mmol/D</td>
<td>12.9 - 42</td>
</tr>
<tr>
<td>PO(_4)(^{-})/Cr</td>
<td>0.18</td>
<td>mmol/mmol</td>
<td></td>
</tr>
</tbody>
</table>

**CTX**: C-terminal telopeptide of type 1 collagen  
**P1NP**: Procollagen type 1 N propeptide
TmP/GFR

<table>
<thead>
<tr>
<th>Result</th>
<th>Unit</th>
<th>RR&lt;sup&gt;1&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>TmP/GFR *</td>
<td>2.52</td>
<td>0.90 – 1.35</td>
</tr>
</tbody>
</table>

- Reflects the renal phosphate transport
- Paired urine and serum creatinine and phosphate
- **Algorithm<sup>2</sup>:**

\[
\text{TmP/GFR} = 0.3 \times \frac{\text{TRP}}{1 - (0.8 \times \text{TRP})} \times \frac{\text{P}_p}{\text{P}_{cr}}
\]

\[
\text{TRP} = 1 - \left(\frac{\text{U}_p}{\text{P}_p}\right) \times \left(\frac{\text{P}_{cr}}{\text{U}_{cr}}\right)
\]

- **http://www.baspath.co.uk/test_directory/tindex/TmPGFR.htm**

**TmP/GFR**: renal tubular maximum reabsorption of phosphate per litre of GFR

### Diagnostic Investigation

<table>
<thead>
<tr>
<th>Diagnostic</th>
<th>Result</th>
<th>RR(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intact FGF 23(^1)</td>
<td>&lt; 10</td>
<td>20 – 65 pg/mL</td>
</tr>
<tr>
<td>C-terminal FGF 23(^2)</td>
<td>180</td>
<td>38 – 95 RU/mL</td>
</tr>
</tbody>
</table>

**Intact FGF-23 = bioactive form of FGF-23**

**FGF-23 : fibroblast growth factor 23**

Nephrology Research Dpt at RMH

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\(^1\)Kainos Intact assay (*Japan*)

\(^2\)Immunotopics C-terminal Assay (*St Clemente, CA*)

\(^3\)Smith ER. Et al  JCEM (2012)
Case Summary

Clinical
- Polyarthropathy
- Periarticular nodules
- Corneal calcification, dental short bulbous

Biochemical
- Phosphate, 1-25 Vitamin D
- FGF 23

Radiology
- Vascular calcification
- Soft tissue calcification

Hyperphosphatemic Familial Tumoral Calcinosi
(hFTC)
Mr AN Progress

- Commenced on **sevelamer** 800mg TDS, **dietary phosphate restriction** & **acetazolamide** 250mg BD
- Genetic counselling
- **Management of:**
  - a) **High risk of cardiovascular event:** BP control and lipid profile
  - b) **Osteoporosis:** commenced on alendronate
  - c) **Corneal calcification:** regular ophthalmology review
  - d) **Vascular aneurysm:** ongoing surveillance under Vascular team
Sevelamer 800mg TDS 10/2/16

Acetazolamide
250mg BD, alendronate 25/5/16

Acetazolamide Ceased 22/6/16

<table>
<thead>
<tr>
<th>Dec-15</th>
<th>Mar-16</th>
<th>Jun-16</th>
<th>Sep-16</th>
<th>Dec-16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mmol/L)</td>
<td>2.78</td>
<td>2.81</td>
<td>2.85</td>
<td>2.70</td>
</tr>
<tr>
<td>Phosphate (mmol/L)</td>
<td>2.11</td>
<td>2.12</td>
<td>2.09</td>
<td>1.76</td>
</tr>
<tr>
<td>TmP/GFR</td>
<td>2.52</td>
<td></td>
<td>2.53</td>
<td></td>
</tr>
</tbody>
</table>
Discussion

1. Role of FGF-23
2. Hyperphosphatemic Familial Tumoral Calcinosis (hFTC)
3. Pathophysiology in hFTC (Gene Mutations)
FGF-23

- Previously known as phosphatonin
- Identified by Japanese researchers in 2000

**Osteocyte**

2. Econs MJ. Et al. NEJM (1994)
7. White et al JCEM (2001)
FGF-23 – Diagnostic Evaluation

Intact FGF-23
- ELISA assay
- two monoclonal antibodies to epitopes on either side of the cleavage site
- Measures intact FGF-23 (bioactive)

C-terminal FGF-23
- ELISA assay
- polyclonal antiserum vs two epitopes on C-terminus of the RXXR cleavage site
- Measures both full-length FGF23 (bioactive) and C-terminal cleavage fragments (inactive)
Role of FGF-23
Parathyroid-bone-kidney-gut axis

65% dietary phosphate is absorbed

90% of filtered phosphate is reabsorbed

Adapted from Aline Martin et al. Physiol Rev (2012)
Role of FGF-23
Parathyroid-bone-kidney-gut axis

↑ phosphate absorption
↑ FGF-23
↑ PTH

Adapted from Aline Martin et al. Physiol Rev (2012)
Role of FGF-23
Parathyroid-bone-kidney-gut axis

↑PTH

↓phosphate re-absorption

↑FGF-23

Adapted from Aline Martin et al. Physiol Rev (2012)
Role of FGF-23
Parathyroid-bone-kidney-gut axis

↓ phosphate/calcium absorption

↑ FGF-23

↓ 1,25(OH)₂D

Adapted from Aline Martin et al. Physiol Rev (2012)
hFTC

↑ phosphate/calcium

↓ FGF-23

↑ 1,25(OH)₂D

Adapted from Aline Martin et al. Physiol Rev (2012)
Discussion

1. Role of FGF-23

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Hyperphosphatemic Familial Tumoral Calcinosis (hFTC)

- Autosomal recessive inheritance
- First described in 1898 by Giard and Duret (dermatologists)
- Rare and prevalence is unknown
- Ethnicity – African and middle Eastern background
- Onset in the first 2 decades of life
Clinical Features in hFTC

- Deposition of calcifications in periarticular cutaneous/subcutaneous tissues

Ramnitz et al. J Bone Miner Res; May 2016; epub
Clinical Features in hFTC

- Deposition of calcifications in periarticular cutaneous and subcutaneous tissues

<table>
<thead>
<tr>
<th>Head and Neck</th>
<th>Eyes</th>
<th>Calcium deposits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Teeth</td>
<td>Short bulbous tooth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obliterated tooth pulp cavities</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Disturbed root development</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>Vascular</th>
<th>Vascular calcifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genitourinary</td>
<td>Kidneys</td>
<td>Calcinosis of the renal parenchyma</td>
</tr>
</tbody>
</table>
Discussion

1. Role of FGF-23
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3. Pathophysiology in hFTC (Gene Mutations)
FGF-23

GALNT3: polypeptide N-acetylgalactosaminyltransferase 3
NPT: Sodium/Phosphate transporter

Genetic Mutations in hFTC

Osteocyte

GALNT3

Intact FGF-23 → 0-glycosylation

Glycosylated intact FGF-23

Bioactive FGF-23

FGF23

Klotho

NPT

↓ FGF 23 activity

GALNT3: polypeptide N-acetylgalactosaminyltransferase 3
NPT: Sodium/Phosphate transporter

## Diagnostic investigation: FGF-23

<table>
<thead>
<tr>
<th></th>
<th>Intact FGF23</th>
<th>C-terminal FGF23</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FGF-23 mutation</strong></td>
<td>Low or low normal</td>
<td>High</td>
</tr>
<tr>
<td><strong>GALNT3 mutation</strong></td>
<td>Low or low normal</td>
<td>High</td>
</tr>
<tr>
<td><strong>Klotho mutation</strong></td>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Summary

- hFTC is associated with decrease in FGF-23 activity
- **Hallmark biochemical markers in hFTC:**
  - a) hyperphosphatemia
  - b) elevated or inappropriately normal levels of 1,25 Vitamin D
  - c) low intact FGF23
- The genetic mutations are heterogeneous (FGF23, GALNT3, Klotho) resulting in impaired FGF23 function
- Management can be challenging & multidisciplinary approach is required
Acknowledgements

1. All of the co-authors
2. Dr. Ie-Wen Sim
3. A/Prof. Shane Hamblin
4. Dr. Vivian Grill
5. Dr. Deepak Dutta
6. Endocrinology consultants at Western Health
7. Prof. Rory Clifton-Bligh (RNSH)
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JCEM, 2002; 87(11):4957-60.


Aline Martin et al. Physiol Rev 2012;92:131-155


Inclan A, Leon P, Camejo MG. Tumoral calcinosis. JAMA. 1943;121:490-496

Urakawa I, Yamazaki et al. Klotho converts canonical FGF receptor into a specific receptor for FGF23. Nature. 2006; 444(7120):770-4
References

References

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Ur ( \text{PO}_4^- )</th>
<th>Serum ( \text{PO}_4^- )</th>
<th>1,25 Vit D</th>
<th>Calcinosis lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-phosphate diet</td>
<td>↓ phosphate</td>
<td>↓</td>
<td>↓</td>
<td>↑ ↔</td>
<td>↓ ↔</td>
</tr>
<tr>
<td>Phosphate binders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>a) Sevelamer</td>
<td>↓ phosphate load</td>
<td>↓</td>
<td>↓</td>
<td>↑ ↔</td>
<td>↓ ↔</td>
</tr>
<tr>
<td>b) Aluminum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>↑ phosphate excretion</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
<td>↓ ↔</td>
</tr>
<tr>
<td>Probenecid</td>
<td>↓ renal phosphate reabsorption</td>
<td>↑</td>
<td>↓</td>
<td>↔</td>
<td>↓</td>
</tr>
<tr>
<td>Anakinra</td>
<td>IL-1 antagonist</td>
<td></td>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Bisphosphonate</td>
<td>↓ phosphate release from bone</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↓ ↔</td>
</tr>
</tbody>
</table>

Ramnitz et al. J Bone Miner Res. (2016)
Management of hFTC

- Surgical excision of ectopic lesions
- Medical (combination)
  a) Decrease phosphate load
  b) Increase phosphate excretion
TmP/GFR to evaluate renal phosphate transport

- based on simultaneous urine and blood creatinine and phosphate concentrations
- TRP: Ratio of phosphate clearance to creatinine clearance \( \left( \frac{C_p}{C_{Cr}} \right) \)

\[
C_p/C_{Cr} = \frac{\text{serum creatinine} \times \text{Urine phosphate}}{\text{Urine creatinine} \times \text{Serum phosphate}}
\]

(This ratio is normally less than 0.15 and is often elevated in primary hyperparathyroidism).

- Subtract this fraction from 1.0 to give the fractional tubular reabsorption of phosphate (TRP).

\[
\text{TRP} = 1 - \frac{\text{serum creatinine} \times \text{Urine phosphate}}{\text{Urine creatinine} \times \text{Serum phosphate}}
\]

- If TRP is \( \leq 0.86 \) then phosphate reabsorption is maximal and there is a linear relationship between plasma phosphate concentration and excretion and TmP/GFR which is calculated by:

\[
\text{TmP/GFR} = \text{TRP} \times \text{serum phosphate}
\]

- If TRP is > 0.86 relationship between plasma phosphate concentration and excretion is curvilinear and TmP/GFR is defined as follows:

\[
\text{TmP/GFR} = a \times \text{serum phosphate}, \quad \text{where } a = \frac{0.3 \times \text{TRP}}{1 - (0.8 \times \text{TRP})}
\]
FGF-23

- Previously known as phosphatonin
- Identified by Japanese researchers in 2000
- Regulation of phosphate levels in balancing mineral ion homeostasis and bone mineralisation
- 32-kDa protein mainly secreted by osteocytes

2. Econs MJ. Et al. NEJM (1994)
7. White et al JCEM (2001)
FGF-23

- Discovered about 16 years ago
- First discovered in the thalamic nucleas of the mouse brain (1)
- then revealed in patients with autosomal dominant hypophosphatemic rickets (2)
- FGF23 is an important hormone in regulating serum phosphate levels
  key role in balancing mineral ion homeostasis and bone mineralisation
- FGF23 is a 32-kDa protein that is mainly secreted by osteocytes
  - Several tissues express FGF-23, such as bone tissue, bone marrow vessels, ventrolateral thalamic nucleus, thymus, and lymph nodes. The relative contribution of those tissues to FGF-23 expression is unknown, but the high levels of expression by osteocytes suggest that the bone tissue is the major source of FGF-23.
- Fgf23 gene is located on the human chromosome 12

5. White et al JCEM (2001)
FGF-23 structure
The first reports on phosphatonin date back to 1994, in studies of patients with tumor-induced osteomalacia. Cultures of tumor cells revealed the presence of a 10 to 30 kDa thermosensitive factor that inhibited the Na-dependent tubular transportation of P, but not that of other substances, such as glucose and amino acids. That thermosensitive factor was named phosphatonin. The result of that phenomenon was the biochemical phenotype of hypophosphatemia, increased P renal excretion, and low calcitriol (1α,25(OH)2D3) concentrations, consistent with the alterations observed in patients with autosomal dominant hypophosphatemic rickets and tumor-induced osteomalacia.

In 2000, Japanese researchers identified, through homology assessment between the fibroblast growth factor 15 (FGF-15) of a mouse embryo and the use of a genetic database (GenBank Nucleotide Sequence Database), a new factor in the fibroblast growth factor family, named FGF-23.

FGF-23: The discovery
Role of FGF-23
Parathyroid-bone-kidney-gut axis

Adapted from Aline Martin et al. Physiol Rev 2012; Ruppe and de Beur. 2013
Genetic Mutations

GALNT3: polypeptide N-acetylgalactosaminyltransferase 3
NPT: Sodium/Phosphate transporter
Recommended treatment by Author Mary Ramnitz, Michael Colllins at NIH

1. Low phosphate diet: <400mg/day

2. Start phosphate binder eg sevelamer 800mfg with all meals and snacks,(uptitrate to as to 1600-2400 mg)

3. Start Probenecid in an effort to induce phosphaturia at a dose of 250-500 mg BID. This can be increased in increments of 500 mg every 4 weeks to a maximum of 2 gm/day. Uric acid levels should be checked at baseline and follow-up and can be used as a dose titration marker.

4. Add acetazolamide at a dose of 250 mg BID. Monitor serum bicarbonate, and titrate acetazolamide up to as high as 500 mg BID with a goal of pushing the bicarbonate into the lower end of the normal range.

5. Monitor bloods /TmP/GFR every 4-6 weeks for safety concern as well as monitoring efficacy.