Approach to hypophosphataemia

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Disclosures

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- Consulting fees from Bayer

- All honoraria directed to research
Overview

- Osteomalacia
- Regulation of Phosphate
- Approach to hypophosphataemia

‘I miss the days I used to worry about getting swine flu’
Osteoporosis vs osteomalacia

- **Osteoporosis** is deficiency of bone (low BV/TV)

- **Rickets/osteomalacia** is deficiency of mineralized bone (high osteoid)

Osteomalacia

- Presents with **bone pain, fractures** (usually stress-type), **myopathy** (waddling gait)

- Elevated **ALP** (usual)

- Look for:
  - Calcium, phosphate, 25OHD, PTH levels
  - Urinary phosphate (TmP/GFR)
  - Bone biopsy may be needed

Glendenning P, Bell DA, Clifton-Bligh RJ BMJ. 2014;348:g3172
Osteomalacia

Vitamin D deficiency
- Nutritional
- Malabsorption
- Liver disease
- Renal disease
- Nephrotic syndrome
- Anti-epileptics
- Genetic causes
  - VDR
  - CYP27B1
  - 25-hydroxylase

Hypophosphataemia
- Fanconi syndrome
- Tumour-induced osteomalacia
- Genetic causes
  - XLH (PHEX)
  - ADHR (FGF23)
  - ARHR (DMP1)
  - HHRH (NaPi2c)

Others
- Severe calcium deficiency
- Aluminium toxicity
- Cadmium toxicity
- Etidronate
- Hypophosphatasia (ALPL)
Phosphate

- Measured by colorimetry
- CV <1%
- Normal adult range 0.75-1.50 mmol/L
- Newborns and young children have a higher reference limit and therefore age-specific intervals are necessary.

- Pre-analytical or analytical interference
  Spurious hypophosphataemia:
  (a) physiological (acid base/fasting status)
  (b) sample related factors (plasma/serum, delayed testing etc)
  (c) para-proteinemia, and transiently with respiratory alkalosis or following meals.

Glendenning, Bell, Clifton-Bligh BMJ 2014;348:g3172
How common is hypophosphataemia in hospital?

- ~4770 measurements at RNSH in Sep 2015

- Serum phosphate <0.75 mmol/L in 405 measures (8.5%)

With thanks to Dr Peter Ward, PaLMS
Causes of hypophosphatemia

Decreased intestinal absorption

- antacids
- vit D deficiency
- malabsorption
- starvation

Increased urinary loss

- hyperparathyroidism
- renal tubular D: Fanconi defects of vit D metabolism
- alcoholism
- DKA
- drugs: diuretics, steroids

Transcellular shift

- refeeding syndrome
- recovery from metab acidosis
- sepsis (esp gram negative)

“Hungry-bone” syndrome

Diet

Gut

Faeces

Extracellular Fluid Pi

Bone

Urine
Clinical consequences of hypophosphataemia

- Related to severity and chronicity of low phosphate

- Common settings
  - chronic alcoholism
  - re-feeding syndrome
  - treatment of DKA
  - critical illness

- Acute severe
  - Muscle weakness
  - Delirium
  - Rhabdomyolysis
  - Cardiac failure
  - Haemolytic anaemia

- Chronic
  - Bone pain
  - Myopathy
  - Fractures
Parathyroid-bone-kidney axis

**Parathyroid:**
Most phosphate is stored in bone

**Bone:**

**Intestine:**
65% dietary phosphate is absorbed in proximal SI

**Kidney:**
85–95% of filtered phosphate is reabsorbed
Parathyroid-bone-kidney axis

Parathyroid:

\[ \uparrow \text{PTH} \]

Bone:

\[ \uparrow \text{FGF23} \]

\[ \downarrow \text{PO}_4^{2-} \text{ reabsorption} \]

\[ \downarrow \text{PO}_4^{2-} \text{ absorption} \]

\[ \downarrow [1,25(OH)_2D] \]
Discovery of the hormone FGF23

**ADHR**
- *Activating* mutations in *FGF23* cause autosomal dominant hypophosphataemic rickets: hypophosphataemia, bone deformity, short stature, dental abscesses

**TIO**
- Mesenchymal tumours that cause humoral osteomalacia
- An RNA clone in TIO = FGF23
- FGF23 mRNA ↑ in TIO
- Removal of tumour ↓ circulating FGF23 levels

FGF23 and regulation of phosphate

- **DMP1** mutations cause ARHR
- **PHEX** mutations cause XLH
- Activating **FGF23** mutations cause ADHR
- NaPi2c mutations cause HHRH

Excess FGF23 production
TIO, FD, ENS, OGD

**αKlotho**

Inactivating **GALNT3** mutations
→ tumoral calcinosi

Inactivating **FGF23** mutations
→ tumoral calcinosi

Inactivating **Klotho** mutation
→ tumoral calcinosi

Adapted from Ruppe and de Beur. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 2013;pp 601-612
FGF23 is a bone-derived hormone that regulates phosphate

- Osteocytes secrete **FGF23**
  - ?in relation to ↑serum phosphate or 1,25(OH)2D
  - ?in relation to bone microenvironment

- Bone is an **endocrine** organ

Feng, JQ et al Nat Genet. 2006;38:1310-5
Serum FGF23 in diagnostics: measure if hypophosphataemia and renal phosphate wasting

- "Low" FGF23 is adaptive
- High FGF23 is pathogenic
Serum FGF23 and diagnostics

- **Immunotopics C-terminal assay**
  - polyclonal antiserum vs two epitopes on C-terminus of the RXXR cleavage site
  - recognizes both full-length FGF23 and C-terminal cleavage fragments
  - CV 5-7.3%, lower limit 3 RU/mL

- **Kainos Intact assay**
  - two monoclonal antibodies to epitopes on either side of the cleavage site
  - CV <5%, lower limit 3 pg/mL

Imel et al J Clin Endocrinol Metab 2006;91: 2055–2061
Serum FGF23 and diagnostics

Kainos assay: intact FGF23

Endo et al Bone 2008;42:1235-1239
Serum FGF23 and diagnostics

- **RNSH**: Kainos assay (intact FGF23, pg/ml)
  - 13 patients with TIO: 401 ± 475 (59-1940)
  - 8 patients with XLH: 227 ± 126 (43-358)
  - “random” referrals: 56 ± 43 (56-141)

R Clifton-Bligh, C Wood, P Ward; unpublished
My approach to hypophosphataemia

- Is it **acute** or **chronic**?
  - Intercurrent illness, alcohol, medications?
  - Bone pain, myopathy, fractures?
  - Family history of rickets?

- Is there **renal phosphate wasting**?
  - Fasting urine phosphate, creatinine

- Check serum PTH, 25OHD, 1,25(OH)₂D, EPG, FGF23
Urinary phosphate

- Fasting, second void urine into 25 ml universal container for urine creatinine and phosphate
- Send with serum electrolytes and phosphate
- TRP TmPGFR Calculator - science@NICHD

Table 2 Normal ranges for tubular maximum for phosphate corrected for GFR

<table>
<thead>
<tr>
<th>Age</th>
<th>Male mg/dl (mmol/L)</th>
<th>Female mg/dl (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborn</td>
<td>5.7–6.1 (1.27–2.59)</td>
<td>5.7–6.1 (1.27–2.59)</td>
</tr>
<tr>
<td>1 month–2 years</td>
<td>3.6–5.4 (1.15–1.73)</td>
<td>3.6–5.4 (1.15–1.73)</td>
</tr>
<tr>
<td>2–12 years</td>
<td>3.8–5.0 (1.22–1.80)</td>
<td>3.8–5.0 (1.22–1.80)</td>
</tr>
<tr>
<td>12–16 years</td>
<td>3.4–4.8 (1.09–1.47)</td>
<td>3.4–4.8 (1.09–1.47)</td>
</tr>
<tr>
<td>16–25 years</td>
<td>3.33–5.9 (1.07–1.89)</td>
<td>3.10–6.41 (1.02–2.05)</td>
</tr>
<tr>
<td>25–45 years</td>
<td>3.09–4.18 (0.98–1.34)</td>
<td>2.07–4.45 (0.95–1.42)</td>
</tr>
<tr>
<td>45–65 years</td>
<td>2.78–4.18 (0.89–1.34)</td>
<td>2.72–4.39 (0.87–1.40)</td>
</tr>
<tr>
<td>65–75 years</td>
<td>2.47–4.18 (0.79–1.34)</td>
<td>2.47–4.18 (0.79–1.34)</td>
</tr>
</tbody>
</table>

Case #1

- Aged 36y presented with progressive onset of pain in feet, ribs, mid-back and left hip
- Serum phosphate **0.39** mmol/l (0.85-1.40)
- 1,25(OH)$_2$D **67** pmol/l (NR 54-161)
- ALP **650** U/L
- Renal phosphate wasting
- Bone biopsy confirmed **osteomalacia**
- She improved on phosphate and calcitriol
Case #1:

- continued on calcitriol (0.75mcg/day) and phosphate (1.5g/day) supplementation for the **ensuing 27 years**
- Multiple imaging studies including whole body MRI and CT did not conclusively reveal a tumour site
- She underwent two FGF-23 venous sampling studies which were also inconclusive
Case #1: a diagnostic test was performed

DOTATATE-PET
Australian experience with DOTATATE-PET in TIO

- Six TIO cases
- 68Ga-DOTA octreotate (DOTATATE) somatostatin receptor positron emission tomography (PET)/computed tomography (CT)
- Confirmed **clinical utility** in finding these **small tumours**

Another case: soft tissue - left foot

Case #1: progress

- Surgery: left hip replacement
- Histology: 32 mm phosphaturic mesenchymal cell tumour
- Normophosphataemic on no treatment
Case #2

- 36 yo woman
- Hypophosphataemia diagnosed as a neonate
- Her usual serum phosphate ~**0.5 mmol/L**
- Short stature
- Dental caries
- Bowed tibiae
Inherited hypophosphataemic rickets syndromes

- X-Linked: PHEX
  - Autosomal dominant: FGF23
  - Autosomal recessive type 1: DMP1
  - Autosomal recessive type 2: ENPP1
  - Autosomal recessive type 3: FAM20c
Case #3

- 78 year-old woman
- Bone pain, muscle aches and weakness 3 weeks after iron infusion for chronic anaemia

- 25OHD 42 nmol/L
- Calcium 2.12 mmol/L
- PTH 5.7 pmol/L
- ALP 114 U/L
- Phosphate 0.20 mmol/L

Prompt symptomatic recovery on starting calcitriol 0.25 mcg BD continued for 4 weeks
Iron polymaltose infusions and hypophosphataemia

Osteomalacia: renal phosphate wasting

Humoral causes
**FGF23-mediated:**
- TIO
- Iron polymaltose
- XLH
- ADHR
- ARHR

**PTH-mediated**

Renal phosphate leak
- Fanconi syndrome
- HHRH
- Anti-retrovirals

**PO₄**
Case #4

- A 55 year old man with a head and neck squamous cell carcinoma presented with severe muscle pain and weakness
  - Recently completed chemotherapy
  - Had begun eating solid diet 10 days prior to attendance following resolution of dysphagia

- Creatine kinase 4600 U/L (30-170 U/L)
- Phosphate 0.25 mmol/L
- Potassium 2.6 mmol/L
- Creatinine 89 umol/L
- 25OHD 55 nmol/L

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Case #4

- Re-feeding syndrome

- In view of severity of hypophosphataemia and symptoms
  
  ➔ intravenous replacement

- phosphate, potassium and CK normalised uneventfully and muscle symptoms resolved within 7 days

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Conclusions (1)

○ The clinical significance of hypophosphataemia is often missed
  ● Patients with symptoms of hypophosphataemia may not have a phosphate level ordered
  ● Low phosphate measurements may be misinterpreted

○ Always consider hypophosphataemia in a patient with bone pain and/or myopathy
Conclusions (2)

- Renal phosphate wasting is determined by measurement of **fasting serum phosphate** and **urinary phosphate** (and creatinine)
  - TmP/GFR calculators available on-line!
  - Also measure ALP, PTH, 25OHD, 1,25OH₂D, EPG, FGF23 and U.αα/gluc

- Consider **iatrogenic** causes: iron infusion, antivirals

- **DOTATATE**-PET scan may rapidly identify TIO
Collaborators

- RNSH
  Cameron Wood
  Peter Ward
  Dr Geoff Schembri (PET)
  A/Prof Anthony Gill

- Kolling
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  Dr Dindy Benn

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  Prof Arthur Conigrave
  Prof Rebecca Mason

- Dr Paul Stalley

- New Zealand
  Dr Marianne Elston

- TIO case series
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  A/Prof John Walsh
  Prof Peter Ebeling
  Dr Ie-Wen Sim
  Dr Tricia Wong
  Dr David Darnell