

# Chronic musculoskeletal disorders due to FGF23-mediated hypophosphataemia

TERRENCE DIAMOND MB BCh, MRCP, FRACP  
SHEJIL KUMAR MB BS(Hons1)

*Fibroblast growth factor 23 (FGF23) is a key hormonal regulator of renal phosphate excretion that, in excess, can lead to hypophosphataemia and chronic musculoskeletal symptoms, rickets or osteomalacia. Conditions that cause FGF23 excess can be inherited, such as X-linked hypophosphataemic rickets, or acquired, such as tumours and intravenous iron infusions. These conditions are often misdiagnosed unless serum phosphate is measured and the significance of hypophosphataemia recognised.*

## Key points

- **Measurement of the serum phosphate level is crucial for evaluating patients with musculoskeletal complaints; failure to perform this test often delays diagnosis in patients with X-linked hypophosphataemic rickets (XLH) and tumour-induced osteomalacia.**
- **A thorough history and clinical examination are important; hypophosphataemia is often longstanding and undiagnosed.**
- **Assessment of tubular reabsorption of phosphate is key to determining whether hypophosphataemia is due to renal phosphate wasting, which should be considered if hypophosphataemia is otherwise unexplained, chronic or associated with features of osteomalacia (bone pain, proximal weakness, recurrent stress fractures and mobility or functional decline).**
- **Management of hypophosphataemia mediated by fibroblast growth factor 23 (FGF23) involves a multidisciplinary approach and multiple daily dosing with phosphate and calcitriol.**
- **Burosumab (anti-FGF23 monoclonal antibody) is an effective therapy for XLH and promising in acquired FGF23 excess disorders such as tumour-induced and iron infusion-associated osteomalacia.**



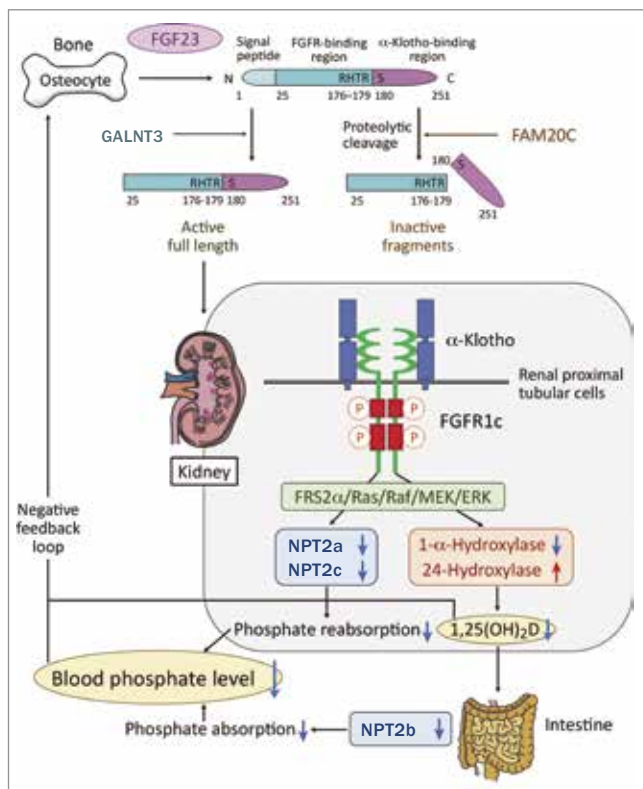
**P**hosphate ( $\text{PO}_4$ ) is an essential anion required for energy metabolism, synthesis of cell membranes and nucleotides, and mineralisation of bones and teeth. Hypophosphataemia can present clinically as an acute syndrome, such as cardiomyopathy and rhabdomyolysis; or a chronic musculoskeletal disorder, such as proximal myopathy and failure of bone mineralisation, leading to rickets (if it occurs before growth plate closure) or osteomalacia (if it occurs after growth plate closure).

Hypophosphataemia is most often caused by impaired gastrointestinal absorption, often in association with malabsorption of other nutrients, or transcellular phosphate shifts, which are common in hospital patients. However, isolated hypophosphataemia is primarily due to excess renal phosphate clearance, termed renal phosphate wasting. A key hormonal regulator of renal phosphate excretion is fibroblast growth factor 23 (FGF23), which can be produced in excess in a range of inherited and acquired conditions, leading to renal phosphate wasting.

This article discusses the causes of FGF23-mediated renal phosphate wasting, their clinical features, diagnosis and management. Three case studies highlight causes that are often misdiagnosed or simply overlooked in patients with chronic debilitating musculoskeletal symptoms. Confirming hypophosphataemia and renal phosphate wasting and establishing the correct diagnosis allowed appropriate management and an overwhelming improvement in the well-being and function of these patients.

ENDOCRINOLOGY TODAY 2022; 11(2): 17-25

Associate Professor Diamond is Associate Professor in the Department of Endocrinology, St George Hospital, Sydney. Dr Kumar is an Endocrinology Advanced Trainee in the Department of Endocrinology, St George Hospital, Sydney, NSW.



**Figure 1. Fibroblast growth factor 23 (FGF23) processing, signalling and actions.**

Reproduced with permission from Takashi Y, Fukumoto S. FGF23 beyond phosphotropic hormone. *Trends Endocrinol Metab* 2018; 29: 755-767.<sup>4</sup>

Abbreviations: 1,25(OH)<sub>2</sub>D = 1,25-dihydroxyvitamin D<sub>3</sub>; FAM20C = family with sequence similarity 20, member C; FGF23 = fibroblast growth factor 23; FGFR = FGF receptor; FRS2α = FGF receptor substrate 2; GALNT3 = polypeptide N-acetylgalactosaminyltransferase 3; NPT2a, 2b and 2c = sodium-phosphate cotransporters 2a, 2b and 2c; Ras/Raf/MEK/ERK = MAPK/ERK signalling pathway.

### Phosphate homeostasis

The plasma phosphate concentration shows a marked diurnal rhythm; it is lowest in the morning and highest in the evening. The normal serum phosphate range is age-related:

- 0.8 to 1.5 mmol/L in adults
- 0.9 to 1.8 mmol/L at ages 1 to 16 years
- 1.3 to 2.6 mmol/L at age under 1 year.

The determinants of serum phosphate include dietary intake, gastrointestinal absorption, cellular shifts and renal excretion. Key hormonal regulators of serum phosphate include:

- 1,25-dihydroxyvitamin D<sub>3</sub> (calcitriol), which promotes gastrointestinal phosphate absorption
- parathyroid hormone (PTH) and FGF23, which promote renal phosphate excretion.

### Phosphate and the gastrointestinal tract

Phosphate is present in high concentrations in many foods, especially dairy products, meat and vegetables. Thus hypophosphataemia due to reduced dietary phosphate intake is uncommon.<sup>1</sup>

## 1. Causes of hypophosphataemia

### Increased renal phosphate excretion

#### FGF23-mediated conditions

- X-linked hypophosphataemia (*PHEX* mutation)
- Autosomal dominant hypophosphataemic rickets (*FGF23* mutation)
- Autosomal recessive hypophosphataemic rickets (*DMP1* mutation)
- Sodium-phosphate cotransporter NPT2a mutation
- Tumour-induced osteomalacia
- Fibrous dysplasia, McCune-Albright syndrome
- Renal transplantation
- Ferric carboxymaltose treatment

#### Non-FGF23-mediated conditions

- Hyperparathyroidism
- Hereditary hypophosphataemic rickets with hypercalciuria
- Diuretics
- Disorders of the proximal convoluted tubule (e.g. Fanconi syndrome)
- Medications (ifosfamide, cisplatin, imatinib, tenofovir, bisphosphonates)

### Impaired intestinal phosphate absorption or intake (calcipenic rickets)

- Reduced dietary phosphate intake
- Phosphate binders
- Antacids
- Alcoholism
- Malabsorption
- Vitamin D deficiency
- Vitamin D-dependent rickets type 1A/B (defect in 25-hydroxylase or 1- $\alpha$ -hydroxylase enzymes)
- Vitamin D-dependent rickets type 2A/B (vitamin D receptor defect)

### Transcellular phosphate shift

- Refeeding syndrome
- Glucose infusion
- Salicylate poisoning
- Hyperventilation
- Respiratory alkalosis
- Hungry bone syndrome (most often occurs after parathyroidectomy for primary hyperparathyroidism)

Abbreviations: DMP1 = dentin matrix acidic phosphoprotein; FGF23 = fibroblast growth factor 23; PHEX = phosphate regulating gene with homologies to endopeptidases on the X chromosome.

Phosphate is absorbed throughout the small intestine and colon by an active and a passive pathway. Active transport occurs via sodium-phosphate cotransporter 2b (NPT2b) in the brush border of enterocytes; its expression is increased by 1,25-dihydroxyvitamin D<sub>3</sub>. In people with vitamin D deficiency, only 50 to 60% of phosphate can be absorbed from ingested food.

Conversion of 25-hydroxyvitamin D<sub>3</sub> to the active form 1,25-dihydroxyvitamin D<sub>3</sub> is catalysed by the enzyme 1- $\alpha$ -hydroxylase. PTH increases expression of this enzyme, indirectly increasing gastrointestinal phosphate absorption. Conversely, FGF23 decreases expression of 1- $\alpha$ -hydroxylase and also stimulates the

## Diagnostic approach to patients with hypophosphataemia

**Patient has a low serum phosphate concentration**

### Assess

- History
- Medications
- Physical examination
- Serum 25-hydroxyvitamin D3 level

### Cellular shifts

- Refeeding syndrome
- Insulin and dextrose infusion
- Hungry bone syndrome

### Reduced gastrointestinal absorption

- Gastrointestinal losses
- Inflammatory bowel disease
- Short bowel syndrome
- Vitamin D deficiency
- Phosphate binders

- No cause identified
- Recurrent or chronic hypophosphataemia
- Osteomalacia present
- Renal phosphate wasting suspected

### Determine tubular reabsorption of phosphate (TRP)

- Paired measurements of serum and urine phosphate and creatinine

TRP <95% (i.e. inappropriately decreased)

TRP ≥95% (i.e. appropriately increased)

Renal phosphate wasting

Measure iFGF23, PTH and 1,25-dihydroxyvitamin D3\*

- iFGF23 increased or normal (inappropriate)
- 1,25-dihydroxyvitamin D3 decreased or normal (inappropriate)
- PTH concentration often elevated

- iFGF23 decreased (appropriate)
- 1,25 dihydroxyvitamin D3 increased (appropriate)

FGF23-mediated hypophosphataemia

- Proximal tubular dysfunction (e.g. Fanconi syndrome)
- PTH-mediated conditions (e.g. hyperparathyroidism)

### Acquired

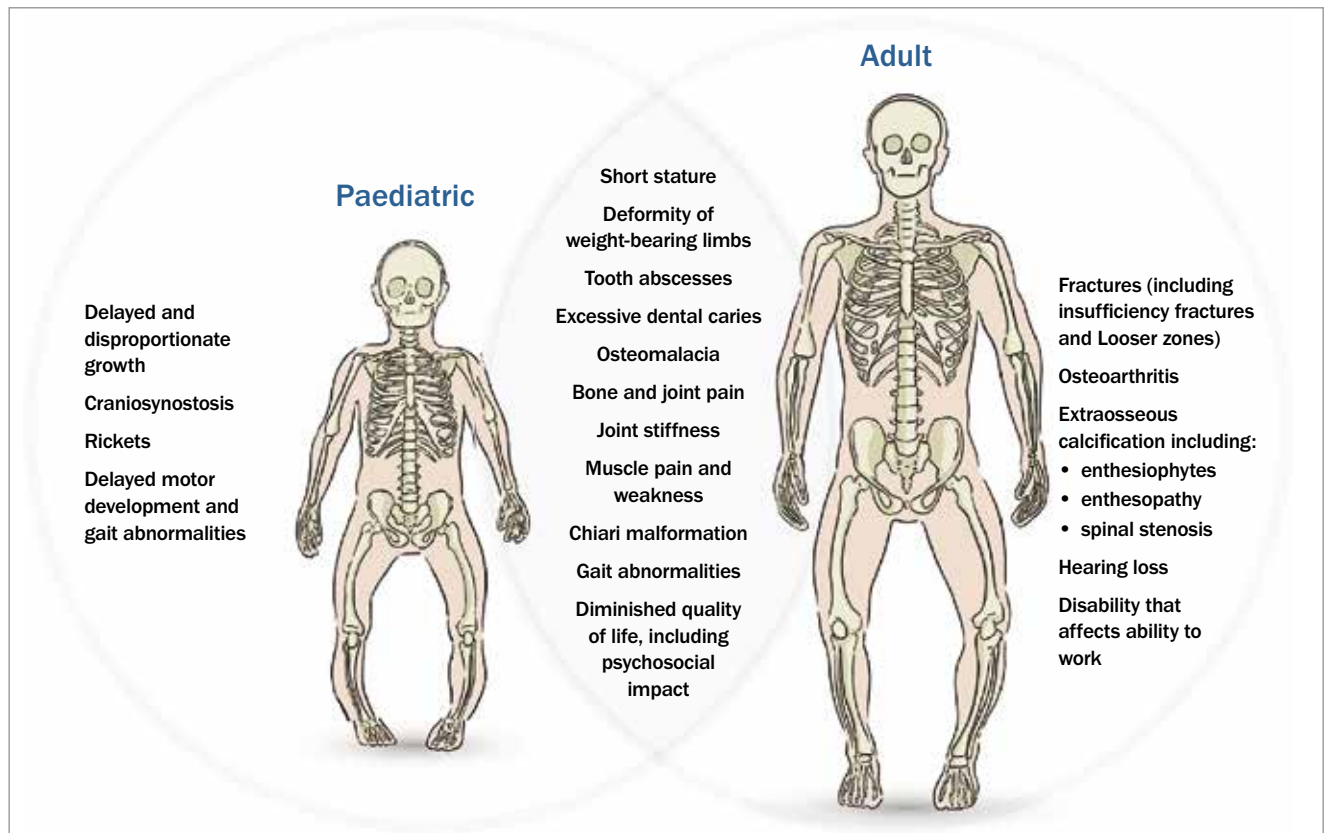
- Tumour-induced osteomalacia
- Iron infusion-associated osteomalacia

### Inherited

- X-linked hypophosphataemic rickets
- Autosomal dominant hypophosphataemic rickets
- Autosomal recessive hypophosphataemic rickets

Abbreviations: iFGF23 = intact fibroblast growth factor 23; PTH = parathyroid hormone.

\* FGF23 measurement is useful to determine whether renal phosphate wasting is FGF23-mediated. However, it is not crucial as serum hypophosphataemia associated with renal phosphate wasting plus a low or inappropriately normal 1,25-dihydroxyvitamin D3 level is highly indicative of FGF23 excess.



**Figure 2. Clinical presentation of X-linked hypophosphataemic rickets in children and adults.**

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enzyme 24-hydroxylase, which degrades 1,25-dihydroxyvitamin D3, thereby indirectly decreasing gastrointestinal phosphate absorption.<sup>2</sup>

### Phosphate and the kidneys

About 90% of the phosphate filtered by the kidneys is reabsorbed, mostly in the proximal convoluted tubule. Phosphate reabsorption is mediated by sodium-phosphate cotransporters 2a and 2c (NPT2a and NPT2c). PTH reduces expression of these cotransporters, and FGF23 promotes their degradation, thereby decreasing renal phosphate reabsorption.<sup>2</sup>

FGF23 is released primarily by osteocytes. Its expression is stimulated by a high dietary phosphate intake and high serum phosphate and 1,25-dihydroxyvitamin D3 concentrations. Its expression is inhibited by the products of phosphate regulating gene with homologies to endopeptidases on the X chromosome (*PHEX*) and the dentin matrix acidic phosphoprotein-1 (*DMP1*) gene. Hence, inactivating mutations in *PHEX* and *DMP1* result in excess circulating FGF23. After translation, FGF23 also undergoes significant modification and cleavage; it can be protected from this cleavage by the protein GALNT3 or marked for destruction by the protein FAM20C. Hence, circulating FGF23

concentrations are determined by gene expression and also post-translational modification and cleavage (Figure 1).<sup>3-5</sup>

### Diagnosis of hypophosphataemia

In adults, a plasma phosphate concentration less than 0.80 mmol/L is defined as hypophosphataemia, and less than 0.30 mmol/L as severe hypophosphataemia.

### Cause of hypophosphataemia

Possible causes of hypophosphataemia are listed in Box 1. The diagnostic pathway to differentiate the various causes of hypophosphataemia is summarised in the Flowchart.

Most cases of hypophosphataemia are secondary to cellular shifts or impaired gastrointestinal absorption.<sup>1</sup> Hypophosphataemia is seen in about 2 to 5% of hospital inpatients, commonly as a result of acute transcellular phosphate shifts. Abnormalities in gastrointestinal phosphate absorption are often associated with calcium and vitamin D deficiency and potentially other nutritional deficits. Detailed history taking, physical examination and measurement of the serum 25-hydroxyvitamin D3 concentration are usually sufficient to identify these causes.

If no clear cause of hypophosphataemia is identified or it is

chronic or associated with clinical features of osteomalacia then renal phosphate wasting should be excluded. Determination of the tubular reabsorption of phosphate (TRP) can confirm abnormal regulation of renal phosphate excretion.

### Assessment of tubular reabsorption of phosphate

TRP determination requires simultaneous measurement of fasting serum and spot urine phosphate and creatinine levels. Spot urine samples for phosphate determination should be obtained after patients have been off phosphate supplements for at least 24 hours. TRP is calculated from the equation:

$$\text{TRP} = 100 \times [1 - (\text{spot urine phosphate level} \times \text{serum creatinine level}) / (\text{serum phosphate level} \times \text{spot urine creatinine level})]$$

Automated calculators to determine TRP are available online (e.g. [www.scymed.com/en/smnxps/pshpd274.htm](http://www.scymed.com/en/smnxps/pshpd274.htm)). Ensure correct units are used in the calculator (incorrect units are a common error).

When the serum phosphate concentration is normal, the normal range for TRP is 85 to 95%. In cases of hypophosphataemia, renal phosphate reabsorption should be maximal, with a TRP of 95% or higher. Reduced TRP in the presence of hypophosphataemia indicates a renal defect in phosphate reabsorption (renal phosphate wasting).

### Hypophosphataemic osteomalacia and rickets

Hypophosphataemia due to renal phosphate wasting is often chronic and overlooked and may result in myopathy and metabolic bone disorders, termed hypophosphataemic osteomalacia or rickets. This condition is defined by a low serum phosphate level (less than 0.80 mmol/L) plus an inappropriately reduced TRP (less than 95%). Unlike nutritional rickets, hypophosphataemic osteomalacia and rickets cannot be cured with nutritional vitamin D supplementation.

Hypophosphataemic osteomalacia or rickets may be either FGF23 or non-FGF23-mediated. FGF23-mediated renal phosphate wasting is further characterised by elevated or inappropriately normal FGF23 concentrations and suppressed 1,25-dihydroxyvitamin D3 concentrations. It occurs in a range of inherited and acquired conditions.

### Inherited causes of FGF23-mediated hypophosphataemia

Several inherited syndromes can cause FGF23-mediated hypophosphataemia. Clues to an inherited cause include disproportionate short stature, early onset, positive family history and skeletal deformities such as bowing of the femur and tibia.<sup>6</sup>

### X-linked hypophosphataemic rickets

The most common inherited cause of renal phosphate wasting is X-linked hypophosphataemic rickets (XLH), with an incidence of one in 20,000 live births. It is caused by an inactivating *PHEX* mutation that increases the expression of FGF23. Clinical characteristics include rickets, disproportionate short stature, osteomalacia and odontomalacia.

XLH usually presents in children within the first two years of life. Delayed diagnosis in adulthood is often the result of the diversity of

## 2. A middle-aged woman with presumed ankylosing spondylitis

A 45-year-old woman presented with a 20-year history of persistent back pain, joint stiffness and proximal muscle weakness. This had been treated with NSAIDs and immunosuppressants for presumed ankylosing spondylitis.

Endocrine review was recommended because of an incidental finding of hypophosphataemia (serum phosphate level 0.56 mmol/L) and suspected osteomalacia. Detailed laboratory investigations confirmed hypophosphataemic osteomalacia and renal phosphate wasting (Table 1). FGF23 levels were elevated, and 1,25-dihydroxyvitamin D3 concentrations were inappropriately normal in the setting of hypophosphataemia.

Dual energy x-ray absorptiometry showed the bone mineral density at the femoral neck was low (T score -2.8). Transiliac bone biopsy and histomorphometry confirmed osteomalacia. Genotyping showed a deletion mutation (c.842T>A) in the *PHEX* gene, consistent with X-linked hypophosphataemic rickets.

**Table 1. Results of endocrine investigations in a 45-year-old woman**

Investigations	Reference range	Baseline
Serum phosphate (mmol/L)	0.8 to 1.5	0.56 L
Urine phosphate excretion (mmol/day)	13 to 42	47 H
%TRP	85 to 95%	49% L
Serum calcium (mmol/L)	2.15 to 2.55	2.04
25-hydroxyvitamin D3 (nmol/L)	50 to 140	53
1,25-dihydroxyvitamin D3 (pmol/L)	60 to 210	130
Parathyroid hormone (pmol/L)	1.6 to 6.9	5.6
Bone-specific ALP (mcg/L)	5.5 to 24.6	85 H
iFGF23 (ng/L)	10 to 54	55 H
Bone area (%)	22 to 28%	20%
Osteoid area (%)	1.3 to 3.1%	14.9% H
Osteoid surface (%)	7.1 to 13.9%	59.6% H
Osteoid thickness (mcm)	9.2 to 14.9	58 H

Abbreviations: ALP = alkaline phosphatase; H = high; iFGF-23 = intact fibroblast growth factor 23; L = low; TRP = tubular reabsorption of phosphate.

clinical manifestations and rarity of the disease.<sup>6</sup> The different clinical presentations in children and adults are shown in Figure 2.<sup>7</sup> The case of a 45-year-old woman with XLH misdiagnosed as ankylosing spondylitis is described in Box 2 and Table 1.

**Autosomal hypophosphataemic rickets**

There are two forms of autosomal hypophosphataemic rickets: a dominant and a recessive form. Autosomal dominant hypophosphataemic rickets is caused by an activating mutation in the *FGF23* gene at the proteolytic cleavage site, which renders FGF23 resistant to cleavage, increasing circulating levels.

Autosomal recessive hypophosphataemic rickets results from inactivating mutations in the *DMP1* and *FAM20C* genes, which increase FGF23 expression and reduce FGF23 cleavage, respectively.

**Acquired causes of FGF23-mediated hypophosphataemia****Tumour-induced osteomalacia**

Tumour-induced osteomalacia is an acquired cause of hypophosphataemic osteomalacia caused by hypersecretion of FGF23, usually by benign neoplasms of mesenchymal origin. These include phosphaturic mesenchymal tumours, nonossifying fibromas, fibroangiomas and giant cell tumours.<sup>7</sup>

Phosphaturic mesenchymal tumours are often benign and slow-growing. The major cause of morbidity in patients with these tumours is delayed diagnosis of the paraneoplastic syndrome of hypophosphataemic osteomalacia, rather than tumour mass effect or metastases.<sup>8</sup> A young man with a four-year history of progressive debilitating musculoskeletal symptoms due to tumour-induced osteomalacia is described in Box 3, Table 2 and Figures 3a to e.

**Iron infusion-associated osteomalacia**

Treatment of iron deficiency with intravenous infusions of iron, particularly ferric carboxymaltose, has become an important and not-so-rare cause of hypophosphataemia. The pathogenic mechanisms remain uncertain. The first evidence linking iron infusion-associated hypophosphataemia to FGF23 excess arose from a prospective New Zealand study on single-dose intravenous iron polymaltose in eight female outpatients.<sup>9</sup> More recent evidence indicates ferric carboxymaltose may reduce cleavage of FGF23.

Two identical randomised controlled trials of single-course iron infusions in adults with iron deficiency anaemia found the incidence of hypophosphataemia was significantly greater after ferric carboxymaltose (74.4%) compared with iron isomaltoside (8.0%) infusions.<sup>10</sup> Ferric carboxymaltose resulted in increased circulating FGF23 concentrations within 24 hours of the infusion, and nadir TRP, serum phosphate and 1,25-dihydroxyvitamin D3 levels after two weeks, with hypophosphataemia persisting to six to 12 weeks.<sup>10</sup>

Randomised controlled trials indicate 50 to 70% of patients treated with ferric carboxymaltose develop incident hypophosphataemia. However, data on severe, persistent or symptomatic hypophosphataemia are scarce.<sup>10-12</sup> A patient with hypophosphataemic osteomalacia associated with iron infusions is described in Box 4, Figure 4 and Table 3.

**Non-FGF23-mediated causes of renal phosphate wasting and hypophosphataemia**

Non-FGF23-mediated causes of renal phosphate wasting leading to hypophosphataemia include primary hyperparathyroidism, in which

PTH increases renal phosphate excretion, primary and secondary renal tubular disorders (e.g. Fanconi syndrome and amyloidosis) and medications that affect the proximal convoluted tubule (e.g. ifosfamide, cisplatin and tenofovir).

**Specialised investigations****FGF23 assay**

Measurement of the FGF23 level is useful in determining whether renal phosphate wasting is FGF23-mediated. However, it is not crucial as serum hypophosphataemia associated with renal phosphate wasting and a low or inappropriately normal 1,25-dihydroxyvitamin D3 level is highly indicative of FGF23 excess.

Several FGF23 immunoassays are commercially available.<sup>13</sup> The automated intact FGF23 assay (iFGF23) is used in Australian clinical practice but is not rebatable by Medicare. This chemiluminescence immunoassay measures intact 251 amino acid-length protein (iFGF23) by simultaneous recognition of epitopes on the N- and C-terminal domains. In healthy adults, the reference range for the plasma iFGF23 level is 10 to 54 ng/L. Blood samples for this test should be collected in EDTA tubes and centrifuged, and the EDTA plasma frozen at -20°C for transport to the laboratory.

The C-terminal FGF23 assay (cFGF23) detects both intact FGF23 and the inactive C-terminal fragment. However, this assay is not routinely used in Australia.

**Bone biopsy**

The skeletal complications of hypophosphataemia include recurrent stress fractures, low bone mineral density and hypomineralising bone disorders.<sup>14</sup> A tetracycline-labelled bone biopsy is the 'gold standard' diagnostic tool to characterise osteomalacia and carefully evaluate the rate of bone mineralisation. Histomorphometric features consistent with osteomalacia include elevated osteoid area, surface and thickness (hyperosteooidosis). Although bone biopsy is highly specialised, not readily available and not necessary to make a diagnosis of osteomalacia, it can be useful in this clinical context.

**Treatment of hypophosphataemia secondary to FGF23 excess**

Management of chronic hypophosphataemia secondary to excess FGF23 (with or without rickets or osteomalacia) requires a multidisciplinary team approach, with input from endocrinologists, physiotherapists, occupational therapists, geneticists (if an inherited cause is suspected) and orthopaedic surgeons (to correct skeletal deformities or resect tumours in patients with tumour-induced osteomalacia).

Standard treatment involves oral phosphate replacement, which is often limited by the need for multiple daily doses and gastrointestinal intolerance. Calcitriol replacement is essential to correct 1,25-dihydroxyvitamin D3 deficiency, promote gastrointestinal phosphate absorption and prevent secondary or tertiary hyperparathyroidism. Treatment can be complicated by hypercalcaemia and nephrocalcinosis.<sup>15,16</sup>

### 3. A young man with debilitating musculoskeletal symptoms

A 36-year old man presented to his GP with four years of progressive pain and stiffness of the lower back, knees, hips and shoulders. Despite treatment for presumed ankylosing spondylitis, his condition continued to deteriorate, with progressive debilitating symptoms over 2.5 years. He went from living independently to requiring a walking frame and having to stop work.

He was referred to an endocrinologist for recurrent fractures. Review of his biochemistry results over the previous five years confirmed a chronically low serum phosphate level (0.42 mmol/L) that had not been remarked on. Results of subsequent endocrine investigations confirmed hypophosphataemia, renal phosphate wasting, a suppressed 1,25-dihydroxyvitamin D3 and elevated fibroblast growth factor 23 (FGF23) level and osteomalacia (Table 2).

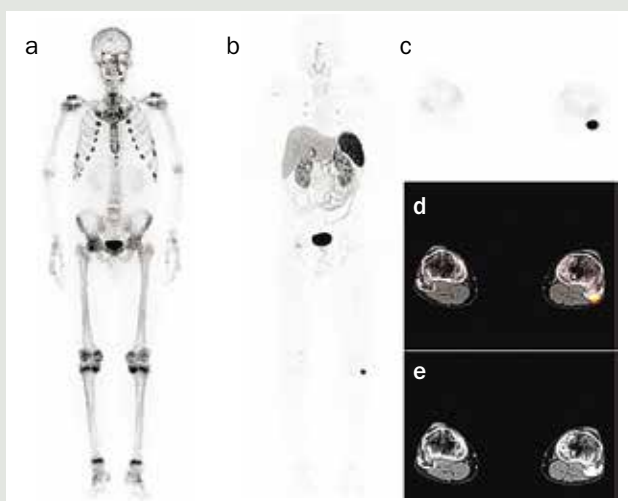
A technetium-99m methyl diphosphonate bone scan showed a 'super-scan' with costochondral beading, increased activity in multiple joints bilaterally, pseudofracture in the right proximal femoral neck and stress fractures in multiple ribs bilaterally (Figure 3a). Dual-energy absorptiometry showed bone mineral density T scores of  $-4.7$  at the lumbar spine and  $-4.1$  at the femoral neck.

Results of histomorphometry of a transiliac bone biopsy specimen were consistent with osteomalacia. This was likely acquired, given the age of onset and lack of family history or skeletal deformities. The patient had no history of intravenous iron infusions.

He was investigated for possible tumour-induced osteomalacia. A  $^{68}\text{Ga}$ -DOTATATE PET-CT scan showed a small area of intensely increased uptake (SUVmax 38.3) at the proximal left fibula (Figures 3b to e). MRI confirmed a 17 mm tumour.

Tumour resection led to normalisation of serum phosphate homeostasis, bone turnover and FGF23 levels. Over the next two years, the patient's debilitating symptoms resolved fully, and he returned to his pre-morbid level of functioning. His bone mineral density increased substantially (100 to 120%) and bone histomorphometry normalised.

The case was confirmed as hypophosphataemic osteomalacia due to renal phosphate wasting and 1,25-dihydroxyvitamin D3 deficiency, induced by an FGF23-producing tumour (tumour-induced osteomalacia).



Figures 3a to e. A technetium-99m methyl diphosphonate bone scan (a) and  $^{68}\text{Ga}$ -DOTATATE PET/CT scans (b to e) in a 36-year-old man.

Table 2. Results of endocrine investigations in a 36-year-old man

Investigation	Reference range	Patient results	
		Baseline	12 months after tumour resection
Serum phosphate (mmol/L)	0.8 to 1.5	0.42 L	1.21
Urine phosphate excretion (mmol/day)	13 to 42	80 H	38
%TRP	85 to 95%	51.1% L	88%
Serum calcium (mmol/L)	2.15 to 2.55	2.23	2.24
25-hydroxyvitamin D3 (nmol/L)	50 to 140	57	65
1,25-dihydroxyvitamin D3 (pmol/L)	60 to 210	27 L	78
Parathyroid hormone (pmol/L)	1.6 to 6.9	5.8	4.0
Bone-specific ALP (mcg/L)	5.5 to 24.6	106 H	18.6
iFGF23 (ng/L)	10 to 54	140 H	10
Bone area (%)	21 to 29%	6.8% L	32.4%
Osteoid area (%)	1.3 to 3.1%	60.4% H	4.8%
Osteoid surface (%)	7.1 to 13.9%	75% H	38.3% H
Osteoid thickness (mcm)	9.2 to 14.9	36.8 H	26.8 H
Bone formation rate (mm <sup>3</sup> /mm <sup>2</sup> /day)	0.03 to 0.09	Tetracycline smearing	0.52 H
Lumbar spine BMD (g/cm <sup>2</sup> )	0.95 to 1.30	0.67 L	1.29
Lumbar spine T score		$-4.7$ L	$+0.4$
Femoral neck BMD (g/cm <sup>2</sup> )	0.85 to 1.25	0.53 L	1.26
Femoral neck BMD T score		$-4.1$ L	$+1.5$

Abbreviations: ALP = alkaline phosphatase; BMD = bone mineral density; H = high; iFGF23 = intact fibroblast growth factor 23; L = low; TRP = tubular reabsorption of phosphate.

**4. A middle-aged man with Crohn’s disease, iron deficiency anaemia and bone pain**

A 45-year-old man presented with progressive bone pain for three to four years involving the ribs, spine and feet. Eventually this prevented his regular employment. He had a history of severe Crohn’s disease since the age of 19 years, treated with resection of 35cm of small bowel, subtotal colectomy and immunosuppressive therapy. His bone mineral density at the lumbar spine was reduced (T score -1.8). He also had a history of chronic iron deficiency anaemia (haemoglobin 62g/L, ferritin 11mcg/L), which had been treated with an intravenous ferric carboxymaltose infusion every eight weeks for the previous four years.

Endocrine referral was recommended to exclude corticosteroid-induced osteoporosis. It was noted that previous blood tests after commencement of the iron infusions showed low serum phosphate concentrations, with a nadir of 0.21mmol/L, that had been overlooked (Figure 4).

Detailed endocrinological investigations confirmed hypophosphataemic osteomalacia, renal phosphate wasting, 1,25-dihydroxyvitamin D3 deficiency and FGF23 elevation caused by long-term intravenous administration of ferric carboxymaltose (Table 3). Replacement with intravenous iron sucrose infusions led to normal phosphate homeostasis and resolution of the patient’s symptoms.

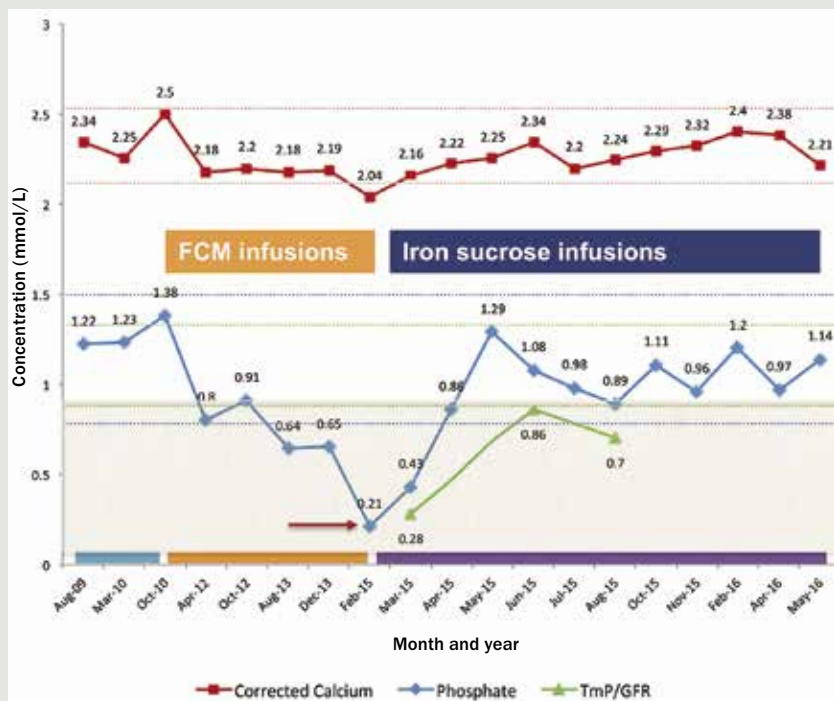


Figure 4. Changes in serum calcium and phosphate and renal tubular maximum reabsorption of phosphate (TmP/GFR) in the patient, who received regular iron infusions of ferric carboxymaltose (FCM), later replaced by iron sucrose. Dotted lines represent reference ranges.

**Table 3. Results of endocrine investigations in a 45-year-old man**

Investigation	Reference range	Patient baseline result
Serum phosphate (mmol/L)	0.8 to 1.5	0.21 L
Urine phosphate excretion (mmol/day)	13 to 42	48 H
%TRP	85 to 95%	31.4% L
Serum calcium (mmol/L)	2.15 to 2.55	2.04
25-hydroxyvitamin D3 (nmol/L)	50 to 140	75
1,25-dihydroxyvitamin D3 (pmol/L)	60 to 210	19 L
Parathyroid hormone (pmol/L)	1.6 to 6.9	8.3
Bone-specific ALP (mcg/L)	5.5 to 24.6	46 H
iFGF23 (ng/L)	10 to 54	289 H
Bone area (%)	21 to 29%	26.8%
Osteoid area (%)	1.3 to 3.1%	20.4% H
Osteoid surface (%)	7.1 to 13.9%	58.6% H
Osteoid thickness (mcm)	9.2 to 14.9	22.4 H

Abbreviations: ALP = alkaline phosphatase; H = high; iFGF23 = intact fibroblast growth factor 23; L = low; TRP = tubular reabsorption of phosphate.

Recent randomised clinical trials have compared burosumab (an anti-FGF23 monoclonal antibody) versus placebo for adults and children with XLH and found significant improvements in phosphate homeostasis, symptoms, quality of life and fracture healing.<sup>17</sup> Burosumab is also being trialled as a treatment for tumour-induced osteomalacia.<sup>18</sup> It has been used successfully in a patient with iron infusion-associated hypophosphataemic osteomalacia.<sup>19</sup>

Burosumab received TGA approval in September 2021 for use in patients aged 1 year or older with XLH. However, it is not PBS-approved for this indication, and its clinical use in Australia is currently limited by cost and availability.

## Conclusion

FGF23-mediated renal phosphate wasting and hypophosphataemia can present with features of osteomalacia, including bone pain, proximal muscle weakness, recurrent stress fractures, and mobility and functional decline. Measurement of the serum phosphate concentration is essential in the assessment of patients presenting with chronic musculoskeletal disorders to ensure timely diagnosis and management of this often overlooked, debilitating disorder. Recent discoveries about the genes that regulate FGF23 have led to better understanding of genetic disorders such as XLH and autosomal hypophosphataemic rickets. Excess circulating FGF23 is also responsible for the

pathogenesis of tumour-induced osteomalacia and hypophosphataemia associated with iron (ferric carboxymaltose) infusions. The anti-FGF23 monoclonal antibody burosumab may have a role in management of XLH and other FGF23 excess syndromes but is currently limited by cost and availability. **ET**

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COMPETING INTERESTS: None.

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