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Review Article

Challenges in the management of tumor-induced osteomalacia (TIO)

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ABSTRACT

Tumor-induced osteomalacia (TIO), also known as oncogenic osteomalacia, is a rare acquired paraneoplastic disease, which is challenging to diagnose and treat. TIO is characterized by hypophosphatemia resulting from excess levels of tumor-secreted fibroblast growth factor 23 (FGF23), one of the key physiological regulators of phosphate metabolism. Elevated FGF23 results in renal phosphate wasting and compromised vitamin D activation, ultimately resulting in osteomalacia. Patients typically present with progressive and non-specific symptoms, including bone pain, multiple pathological fractures, and progressive muscle weakness. Diagnosis is often delayed or missed due to the non-specific nature of complaints and lack of disease awareness. Additionally, the disease-causing tumour is often difficult to detect and localize because they are often small, lack localizing symptoms and signs, and dwell in widely variable anatomical locations.

Measuring serum/urine phosphate should be an inherent diagnostic component when assessing otherwise unexplained osteomalacia, fractures and weakness. In cases of hypophosphatemia with inappropriate (sustained) phosphaturia and inappropriately normal or frankly low 1,25-dihydroxy vitamin D, differentiation of the potential causes of renal phosphate wasting should include measurement of FGF23, and TIO should be considered.

While patients experience severe disability without treatment, complete excision of the tumour is typically curative and results in a dramatic reversal of symptoms. Two additional key current unmet needs in optimizing TIO management are: (1 and 2) the considerable delay in diagnosis and consequent delay between the onset of symptoms and surgical resection; and (2) alternative management. These may be addressed by raising awareness of TIO, and taking into consideration the accessibility and variability of different healthcare infrastructures. By recognizing the challenges associated with the diagnosis and treatment of TIO and by applying a stepwise approach with clear clinical practice guidelines, patient care and outcomes will be improved in the future.

1. Introduction

Tumor-induced osteomalacia (TIO) or oncogenic osteomalacia is a rare paraneoplastic syndrome caused by phosphate wasting as a result of excess levels of tumour-secreted fibroblast growth factor 23 (FGF23) [1–4]. The clinical manifestations and symptoms, including bone pain, fractures, muscle weakness and skeletal deformities, can have a severe impact on the quality of life of patients [5,6]. TIO is difficult to diagnose as the manifestations are non-specific, often leading to a delay in diagnosis of many years, which increases the risk of severe disabilities in affected patients [4,6,7]. Although less than 1000 cases have been reported in the literature [5], the exact global incidence and prevalence of the disease remains unclear. The lack of formal epidemiological data and a specific ICD10 code makes it difficult to assess the incidence and to estimate the global clinical burden of TIO [7–9].

To improve timely diagnosis of TIO and specific treatment of affected patients, healthcare providers need to be aware of the options for and challenges of optimal TIO management. With vast heterogeneity in

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terms of healthcare infrastructure, access to services, advanced technologies and disease expertise, there is no agreement on standard of care for optimal TIO management. It is essential to recognize these challenges and offer solutions to facilitate implementing clear guidelines, raising awareness of TIO and improving patient care.

This review summarises the expert opinions of the authors from several working sessions. Key challenges associated with the diagnosis, treatment and management of TIO were identified for the purpose of raising awareness of the pathophysiology and enigmatic clinical presentation of the disease.

2. Overview of TIO etiology and pathophysiology

TIO is predominantly caused by tumors that ectopically secrete FGF23, a primary regulator of phosphate and vitamin D homeostasis [2,4]. Production of FGF23, which escapes feedback control, leads to pathophysiological 'amplified' effects of normal FGF23 function. FGF23 function; specifically decreased renal tubular phosphate reabsorption resulting in hypophosphataemia and a low level of active vitamin D. Furthermore, elevated FGF23 may affect expression of osteopontin, alkaline phosphatase (ALP) and the renal calcium channel transient receptor potential vanilloid 5 (TRPV5) [8,9]. Overall, through the above mechanisms, increased levels of FGF23 lead to defective bone mineralisation (osteomalacia in adults or rickets in the paediatric growing skeleton). Furthermore, FGF23 may directly impair mineralisation [9]. How FGF23 elicits signs and symptoms not directly associated with mineral homeostasis and vitamin D metabolism, e.g. weakness, remains to be understood. Whether additional, yet-to-be identified factors, secreted by the tumour are responsible for these manifestations remains a possibility. Importantly, understanding both the direct and indirect roles of FGF23 in bone and mineral homeostasis and vitamin D metabolism provides important insight into the pathophysiology of TIO.

2.1. Importance of phosphate homeostasis

Phosphate plays a vital role in multiple physiological processes, including energy metabolism, cell signaling, bone mineralization and muscle function [6,16–18]. Phosphate is also important for the delivery of oxygen to the peripheral tissue [19]. Maintaining extracellular and intracellular phosphate levels within a normal range, i.e. phosphate homeostasis, is critical for health and well-being at all ages. Disruption of phosphate homeostasis can lower serum phosphate levels and ultimately lead to chronic hypophosphatemia, resulting primarily in impairment of bone and potentially muscle function, which, accordingly, has a severe detrimental impact on musculoskeletal health and quality of life [6,16,18,20].

The endocrine factors and main regulators of calcium and phosphate homeostasis include parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25(OH)2D) and a group of proteins called phosphatonins, of which FGF23 is best known [7,11,12]. These should, therefore, be considered calciophosphotropic hormones as there is an interconnection between calcium and phosphate pathways. These pathways include a network of humoral interactions and feedback loops required to maintain homeostasis, involving the intestine, kidney, parathyroid gland, and bone [21].

2.1.1. FGF23 role in phosphate homeostasis

Under physiological conditions, FGF23 is expressed predominantly in bone, where it is believed to be primarily produced by osteocytes and osteoblasts [22,23]. Also, recent research reports FGF23 secretion from erythroid progenitor cells [23–25]. Ultimately, intact FGF23 is degraded by proteolytic enzymes [26,27]. FGF23 acts through binding to fibroblast growth factor receptor 1 and co-receptor α-Klotho complex (FGFR1-α-Klotho) to downregulate the activity of sodium-dependent phosphate co-transporter proteins NaPi-IIa and NaPi-IIc, which play a crucial role in reabsorption of phosphate by the renal proximal tubular cells in the kidney [28–30]. By downregulating NaPi-IIa and NaPi-IIc, FGF23 reduces renal phosphate reabsorption and increases renal phosphate excretion, thereby promoting hypophosphatemia [18,31,32]. FGF23 decreases $1,25(OH)_2D$ synthesis by suppressing 1α-hydroxylase and promotes $1,25(OH)_2D$ catabolism by increasing 24-hydroxylase activity leading to reduced gastrointestinal phosphate absorption [29,31]. Thus, in TIO, the excess FGF23 secreted by the tumors greatly reduces phosphate reabsorption and absorption in the kidney and intestine, respectively, resulting in hypophosphatemia and phosphaturia, presenting clinically as osteomalacia and myopathy (Fig. 1) [6,29,33].

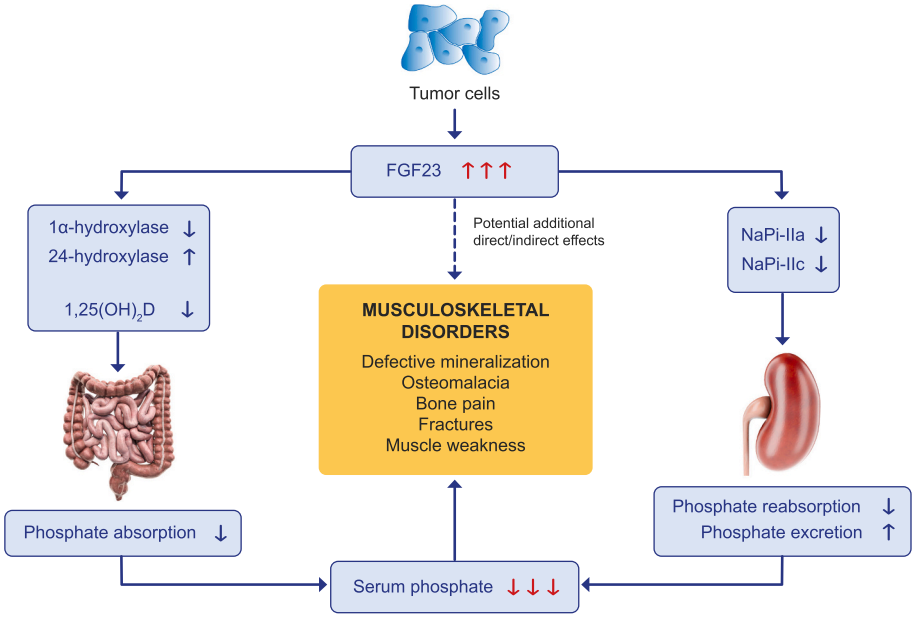

Fig. 1. Effects of pathological increase in FGF23 secreted from tumor cells on phosphate homeostasis.

2.2. Tumors associated with TIO

Typically, tumours associated with TIO are small, slow-growing, mesenchymal tumors, of which the vast majority are classified pathologically as phosphaturic mesenchymal tumors (PMTs) of the mixed connective tissue variant [34,35]. These tumors can be located anywhere in the body, involving either bone or connective tissues [34–37]. In rare instances, FGF23-secreting myopericytomas may be associated with TIO [38].

PMTs are morphologically distinctive neoplasms that are histologically defined by small, bland spindle- to stellate-shaped cells, embedded within a myxoid or myxochondroid matrix with 'grungy' calcification that resembles chondroid or osteoid, with a high vascularity of variable vessel size and pattern. PMTs express FGF23 and other phosphatonins at both the ribonucleic acid (RNA) and the protein level [35,39,40].

In one study, fusion genes were reported in half of PMTs, the most common of which is the fusion of FN1 (which encodes for fibronectin 1) and FGFR1 (which encodes for fibroblast growth factor receptor 1) [41]. A novel *FN1–FGF1* fusion gene was also identified without FN1–FGFR1 fusion. The *FN1-FGFR1* fusion gene is thought to play a key role in FGFR1-signaling pathways, leading to FGF23 over-expression and tumor growth. Although this gene has been found to be ineffective as a diagnostic marker, it may be useful as a potential therapeutic target [40–43].

PMTs are typically benign and singular but, in rare cases, can be multifocal, malignant, or metastatic [35,37,44–46]. Occasionally, secondary TIO presents as a paraneoplastic syndrome in association with several advanced cancers, including colon, ovarian, breast, lung, and prostate cancer [6,47–50].

3. Clinical presentation of patients with TIO

The mean age of TIO onset is 40–45 years [8,37]; however, it can occur in children and the elderly (>70 years) [51–53]. TIO affects men and women equally [37].

The main symptoms of TIO are usually not related to the tumor itself but are the consequence of the FGF23 that the tumors secrete, with resultant severe chronic hypophosphatemia [6,7,54]. Analyses of 144 cases of TIO revealed the most common signs and symptoms of the disease to be bone pain, difficulty walking, muscle weakness, pathological fractures, and height loss, all of which can profoundly affect patients' mobility and quality of life (Table 1) [55]. In some instances, the tumor may cause local symptoms, though this is dependent on location and size of the lesion. For example, sinonasal tumors may present with nasal obstruction and bleeding [6,55]. A review of 163 patients with head and neck TIO found that 44% experienced local symptoms [56].

In general, the first and predominant symptom experienced in TIO is bone pain, often starting in the lower limbs, most commonly the feet and ankles, and caused by fractures or pseudofractures rather than joint pain [55]. Fatigue is also common in patients with TIO [57,58].

TIO-acquired hypophosphatemia causes a rapid onset of osteomalacia, which if left untreated, subsequently progresses to a decline in overall health. Due to the chronic nature of the hypophosphatemia and the consequent severe and progressive osteomalacia, by the time patients are correctly diagnosed, they may have already developed major skeletal complications, including thoracic and spinal deformity and severe disability [4].

Clinical presentation of TIO in children includes rickets and growth retardation, however, pediatric TIO cases are extremely rare. A review of 163 cases of head and neck TIO revealed only three pediatric cases [56]. Out of approximately 160 TIO cases identified in the literature in 2011, less than 20 occurred during childhood and adolescence [59]. Given the rarity of paediatric TIO, means it is often misdiagnosed as hereditary hypophosphatemia [4,51]. Nevertheless, iin the paediatric population, genetic testing to rule out hereditary hypophosphatemia should be performed before the diagnosis of TIO is made.

4. Challenges of TIO diagnosis

The diagnosis of TIO can be extremely challenging and significantly delayed, mainly due to its non-specific clinical presentation and the lack of awareness among healthcare professionals of this rare insidious disease. This delay can lead to a considerable and prolonged physical and psychological burden for patients. Establishing the correct diagnosis can take years. The average duration from onset of symptoms to diagnosis of hypophosphatemia is 2.9 years and to tumor resection is 5.4 to 5.7 years [55,60], although the delay between symptom onset and curative surgery can take up to 40 years [60]. One of the primary issues that account for this diagnostic delay is the failure to measure serum phosphate in the evaluation of patients with fracture or with widespread pain and fatigue, or a suspicion of osteomalacia [23]. It would be wise therefore to measure fasting serum phosphate among the panel of tests done to evaluate a patient with such clinical features or one suspected of having bone disease.

In general, symptomatic patients initially seek help from primary care physicians, who if unaware of this extremely rare disease, may not know that early referral is vital as the disease is progressive. Furthermore, as the non-specific symptoms of TIO overlap with other more common disorders, almost all cases of TIO (up to 95%) are misdiagnosed in the first instance [55,57], often with a variety of musculoskeletal, rheumatological, oncological, and even psychiatric disorders [7,55,57,58]. The most common misdiagnoses include intervertebral disc herniation (19%), spondyloarthritis (16%), and osteoporosis (15%) [55], and even disseminated malignancy of unknown cause [61]. This generally leads to ineffective treatment and a delay in potentially curing the disease. Due to the progressive nature of the disease, a delay in appropriate treatment leads to severe osteomalacia and ultimately irreversible disability. Accordingly, access to appropriate high-quality medical care appears critical for optimal diagnostic and therapeutic patient management. The diagnosis of TIO relies on a combination of

Table 1
Clinical manifestations in 144 TIO patients.

Clinical manifestations	Number (%)	Sites
Bone pain	143 (99%)	Lower limbs (54%), lumbar and back pain (26%), sternocostal pain (13%), diffuse bone pain (3%), shoulder pain (2%), neck ache (1%)
Difficulty in walking	134 (93%)	–
Pathological fracture	115 (80%)	Vertebrae (58%), ribs (43%), femur (24%), pelvis (20%)
Height loss	99 (69%)	–
Muscle weakness	94 (65%)	–
Thoracic deformity	48 (33%)	–
Spinal deformity	39 (27%)	–
Tooth loss or loose tooth	25 (17%)	–
Local lump	21 (15%)	–

TIO, tumor-induced osteomalacia.
Adapted from Feng et al. [55].

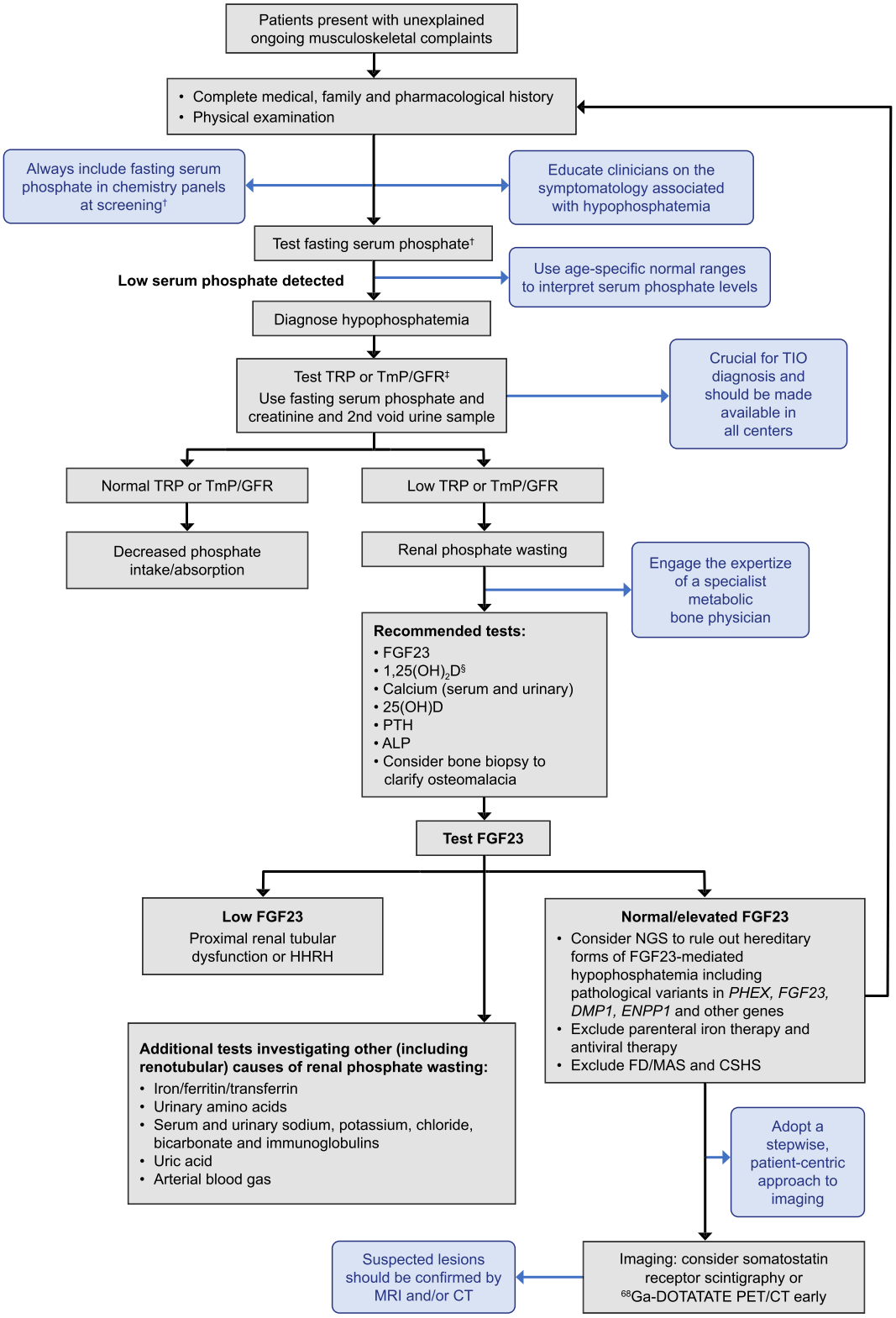

Fig. 2. Biochemical diagnostic algorithm showing the clinical and biochemical approach to the diagnosis of TIO and solutions to diagnostic challenges.
†Mild hypophosphatemia might be missed by a non-fasting serum phosphate measurement; ‡TRP and TmP/GFR must be measured off phosphate replacement; §1,25 $(OH)_2D$ should be supplemented if reduced.
1,25$(OH)_2D$, 1,25-dihydroxyvitamin D (calcitriol); 25(OH)D, 25-hydroxyvitamin D; ^{68}GA-DOTATATE PET/CT, ^{68}Gallium; ALP, alkaline phosphatase; CSHS, cutaneous skeletal hypophosphatemia syndrome; CT, computed tomography; DMP1, dentin matrix protein 1; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; FD/MAS, fibrous dysplasia; FGF23, fibroblast growth factor 23; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; MAS, McCune-Albright syndrome; MRI, magnetic resonance imaging; NGS, next generation sequencing; PET, positron emission tomography; PHEX, phosphate-regulating endopeptidase homolog on the X chromosome; PTH, parathyroid hormone; TIO, tumor-induced osteomalacia; TmP/GFR, ratio of tubular maximum reabsorption of phosphate to glomerular filtration rate; TRP, tubular reabsorption of phosphate.

extensive clinical evaluation, biochemical testing, specialized imaging, and surgical expertise to confirm osteomalacia and ultimately locate and completely resect the tumor. The definitive diagnosis is established once the causative tumor has been identified and biochemical symptoms resolve following complete surgical resection (Fig. 2) [4,6,58].

The diagnostic challenges may further be reflected by the difference in healthcare settings in various countries and how readily patients can access healthcare, the nature of the primary care work-up, the ease of referral to specialists, and the configuration of secondary care.

4.1. Challenges of diagnostic testing

Due to the ambiguous clinical presentation of TIO, biochemical findings play a crucial role in diagnosis.

4.1.1. Phosphate

The first step should be to establish the presence of hypophosphatemia in patients with unexplained ongoing musculoskeletal complaints, such as bone pain, multiple fractures, muscle weakness, fatigue, and decreased mobility, at which time serum phosphate should be tested (Fig. 2). It is noteworthy that, owing to the direct relationship between dietary phosphate and serum phosphate measurements, the degree of hypophosphatemia can be underestimated if serum phosphate is not tested in the fasting state [16,62]. As osteomalacia is usually associated with abnormalities in calcium and vitamin D, serum phosphate assessment may not be part of the routine evaluation in many clinical centers and hypophosphatemia may be missed. Consequently, this leads to a delay in recognizing hypophosphatemia, ultimately delaying the diagnosis of TIO [7,58].

4.1.2. TmP/GFR

The next key step is to confirm the presence of renal phosphate wasting (Fig. 2). This is assessed by calculating either the percentage TRP, or the ratio of tubular maximum phosphate reabsorption to glomerular filtration rate (TmP/GFR), which is low in patients with TIO. TmP/GFR requires measuring phosphate and creatinine levels in the fasting state from blood and urine or collection of urine over two consecutive 1-hour sample periods, with blood sampling midpoint of urine collection [4,6,63]. (TmP/GFR calculation available at: http://baspath.co.uk/calculations/renal_tubular_reabsorption_of_ph.htm.)

In addition to low serum phosphate and decreased TmP/GFR or TRP, further laboratory tests should be performed and repeated if necessary, to identify the following typical biochemical indicators of TIO: low/inappropriately normal $1,25(OH)_2D$, normal/low serum calcium, low urinary calcium, normal PTH elevated ALP, and elevated/inappropriately high serum FGF23 (Fig. 2 and Table 2) [6,27,58]. It is important to note that renal tubular glucose, bicarbonate and low molecular weight protein reabsorption are not affected in TIO.

4.1.3. $1,25(OH)_2D$

Testing for $1,25(OH)_2D$ should be performed to identify whether renal phosphate wasting is FGF23-mediated, as indicated by either lowered or inappropriately low normal levels of $1,25(OH)_2D$ levels in relation to hypophosphatemia. In addition, urinary calcium levels preclude a diagnosis of HHRH (Table 2) [6].

4.1.4. PTH

In some cases, PTH levels can be high due to secondary hyperparathyroidism caused by concomitant 25-hydroxyvitamin D deficiency and 'inappropriately' low $1,25(OH)_2D$ (in response to the increased FGF23 levels), even though FGF23 itself reduces PTH secretion [27,58,72]. Prolonged secondary hyperparathyroidism in TIO can lead to tertiary hyperparathyroidism due to extended stimulation of the parathyroid glands, causing parathyroid autonomy [6,58,73]. Thus, PTH testing should be carried out to rule out secondary and tertiary hyperparathyroidism, which can potentiate renal phosphate wasting and hypophosphatemia [4–7].

4.1.5. FGF23

Serum or plasma FGF23 measurement plays an essential role in the diagnosis and ongoing management of TIO. As the test is not available in every center, sample shipment following diligent pre-analytical handling or patient referral should be considered. In most patients with TIO, FGF23 levels are increased but, depending on the individual's

Table 2
Typical biochemical indicators of acquired and inherited conditions of hypophosphatemia.

Renal hypophosphatemia	P	sCa	uCa	PTH	25(OH)D	$1,25(OH)_2D$	TRP or TmP/GFR[a]	ALP	FGF23
Acquired causes									
TIO	↓	N	↓	N or ↑	N	↓ or N[b]	↓↓	N or ↑	Inappropriately N, ↑ or ↑ ↑
Vitamin D deficiency	↓ or N	↓ or N	↓	↑	↓	↓ or N or ↑	↓ or N	N or ↑	↓ or N
CSHS	↓	↓ or N	↓	N or ↑	N	N[b]	↓	↑	N or ↑
FD/MAS	N or ↓	↓ or N	↓	N or ↑	N	N[b]	↓	N or ↑	N or ↑
Acquired Fanconi syndrome[c,d]	↓	–	↓	N or ↑	–	↓ or N	↓	↑	↓
Intravenous iron infusion [68,70]	↓	↓ or N	–	↑	N	↓ or N	↓	N or ↑	↓ or N or ↑
Inherited causes									
XLH	↓	↓ or N	↓	N or ↑	N	↓ or N	↓↓	↑	N or ↑
ADHR	↓	↓ or N	↓	N	N	↓ or N	↓	↑	N or ↑
ARHR	↓	↓ or N	↓	N	N	↓ or N	↓	↑	N or ↑
HHRH	↓	N	N or ↑	↓ or N	N	↑	↓	↑	↓ or N
HRHPT	↓	↑	↓	↑	N	N	↓	↑	↑
Fanconi syndrome type 2[d]	↓	N	↑	N	N	↓ or N	↓	↑	↓ or N

↑, increased levels; ↑↑, markedly increased levels; ↓, decreased levels; ↓↓, markedly decreased levels; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; ADHR, autosomal-dominant hypophosphatemic rickets; ALP, alkaline phosphatase; ARHR, autosomal-recessive hypophosphatemic rickets; CSHS, cutaneous skeletal hypophosphatemia syndrome; FD/MAS, fibrous dysplasia/McCune-Albright syndrome; FGF23, fibroblast growth factor 23; HHRH, hereditary hypophosphatemic rickets with hypercalciuria; HRHPT, hypophosphatemic rickets with hyperparathyroidism; N, normal levels; P, phosphate; PTH, parathyroid hormone; TIO, tumor-induced osteomalacia; TmP/GFR, ratio of tubular maximum phosphate reabsorption to glomerular filtration rate; sCa, serum calcium; uCa, urinary calcium; XLH, X-linked hypophosphatemia.

[a] TRP and TmP/GFR must be measured off phosphate replacement.

[b] Decreased relative to serum phosphate concentration.

[c] Can result from certain antivirals, chemotherapeutic agents, immunosuppressives, antibiotics, monoclonal gammopathy, heavy metal exposure or lymphoblastic leukemia [126,127].

[d] Generalized aminoaciduria is a key metabolic feature of Fanconi syndrome [126].

Adapted from Minisola et al. [6] and Haffner et al. [118].

ability to cleave FGF23, some patients may have 'normal' FGF23 levels – but inappropriately so in the biochemical context. As such, FGF23 levels should always be interpreted in the context of the fasting serum phosphate and TRP or TmP/GFR. Different FGF23 assays are available. A general distinction is being made between those measuring the intact molecule and those detecting the carboxy-terminal (C-terminal) fragment of FGF23. Although C-terminal FGF23 assays are more widely used and considered less susceptible to pre-analytical flaws, they do not indicate the amount of the biologically active intact FGF23 molecule [6,7].

Elevated FGF23 levels exclude a diagnosis of acquired or hereditary renal Fanconi syndrome (unless there is concomitant renal failure or dysfunction), vitamin D deficiency, and hereditary hypophosphatemic rickets with hypercalciuria (HHRH) (Table 2) as causes of hypophosphatemia [4,6,64].

While FGF23-mediated hypophosphataemia occurs in virtually all patients with TIO, it is non-specific with similar biochemical profiles being found as a result of some other inherited or acquired disorders, as shown in Table 2 [4,6,7,65–67]. Although the mechanism is not fully known, acquired FGF23-mediated hypophosphatemia can develop from repeated treatment with some forms of parenteral iron, the subject now of an extensive number of case reports and case series in the literature [68–70]. Recent evidence suggests that iron carboxymaltose may impair FGF23 cleavage [71].

4.1.6. Genotyping

In the differential diagnosis of hypophosphatemia, where the plasma FGF23 is either directly elevated or inappropriately normal, genetic causes should be excluded as some are essentially phenocopies of TIO [4]. The differentiation between FGF23-dependent and FGF23-independent forms of hypophosphatemia is challenging in daily practice and in these instances genotyping of pathological variants by next generation sequencing (NGS), particularly for *PHEX, FGF23, DMP1* and *ENPP1* genes, is indicated to rule out inherited forms of hypophosphatemia [4,7,74,75].

Therefore, if TIO is suspected, a thorough medical and family history, including age of onset, a detailed physical examination, and a biochemical diagnosis of FGF23-mediated hypophosphatemia, is required for a full differential diagnosis to encompass all causes of acquired and genetically determined hypophosphatemia [4,7,76]. In some instances, genetic testing for inherited forms of hypophosphataemic rickets may be indicated [7,58].

4.2. Challenges in tumor localization

Once TIO is suspected, the next crucial step is to accurately localize the causal tumor so that a cure can be achieved with complete surgical resection [6,7]. This can be a major diagnostic challenge because PMTs are often small, slow-growing, and elusive, occurring anywhere in the body in both bone and soft tissue. A review of 308 TIO cases found that most tumors originated in the lower extremities (42%) and the craniofacial region (21%) but could also occur in the hip and pelvic area (12%), abdomen, thorax and neck (11%), and upper extremities (9%) [37]. A thorough medical history and physical examination may, on some occasions, reveal a recent lump [6]. However, in most cases, radiographic imaging is required to localize the tumor.

In cases where a tumor cannot be located to confirm TIO, other inherited and acquired forms of FGF23-dependent hypophosphatemia must be revisited and ruled out, including genetic testing (Table 2).

4.3. Diagnostic imaging challenges

Once the biochemical diagnosis is confirmed and an FGF23-producing PMT is suspected, a structured and stepwise approach to imaging is used to avoid unnecessary radiation and superfluous imaging. To localize PMTs, the entire body (from the top of the head to the fingertips and the tips of the toes) needs to be scanned, including the whole head and distal extremities where tumors are frequently located [6,37]. This should start with functional (nuclear medicine) imaging to detect potential PMTs followed by anatomical imaging in areas of uptake detected on functional imaging, for more precise tumor localization and characterization for surgery [4,6,7,77].

An overview of common functional imaging techniques is provided in Table 3. Several functional imaging techniques exploit the fact that somatostatin receptors (SSTRs), in particular SSTR type 2 (SSTR2), are highly expressed in PMTs. SSTRs can be detected with functional nuclear medicine imaging employing somatostatin analogs (e.g. octreotide, pentetreotide, and octreotide derivatives) bound to various radionuclides, and imaged using either single photon emission computed tomography (SPECT) or positron emission tomography (PET) scanning – termed somatostatin receptor scintigraphy (SRS).

Evolving evidence shows that ^{68}Ga-DOTA-Phe^{1}-Tyr^{3}-Thr^{8}-octreotate (^{68}Ga-DOTATATE) PET/computed tomography (CT) is superior to older SRS techniques (e.g. ^{111}In-pentetreotide [OctreoScan™]) and to ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET/CT in locating PMTs [78–84]. This is likely due to the higher affinity of ^{68}Ga-DOTATATE binding to SSTR2 combined with the advantages of PET [85]. Based on pooled values from two recent meta-analyses, the detection rate of culprit PMTs using ^{68}Ga-DOTATATE-PET/CT is 88–90% [83,84]. Other SSTR binding ('DOTA') radiopharmaceuticals have now been developed, and a recent retrospective study indicated a 94.1% sensitivity and 90.5% accuracy of PMT detection using ^{68}Ga-DOTA-NOC PET/CT [81]. Thus, ^{68}Ga-DOTATATE-PET/CT should probably be considered the first-line functional imaging method of choice as its high PMT detection rate could reduce the need to progress through multiple different modalities and would ultimately lessen the potential radiation burden. However, ^{68}Ga-DOTATATE-PET/CT is generally limited to large nuclear medicine departments and its widespread use is currently limited [85]. Hence, more widely available and cost-effective imaging modalities are often used in the first instance.

When SRS is not available, ^{18}F-FDG PET/CT can be used. FDG is a competitive glucose analog and its use is based on the increased glucose metabolic activity of tumor cells. Although ^{18}F-FDG PET/CT is less sensitive and less specific than OctreoSPECT, the former can be complementary in many cases [86]. As ^{18}F-FDG PET/CT is not specific for detecting PMTs, its use is therefore limited to identifying areas of increased metabolism that deserve further evaluation when the suspected tumor cannot be located with SRS techniques [6,36,77,86,87].

Not all countries have access to or are reimbursed for more advanced imaging technologies, if available, specialized imaging may require approval from governmental agencies. Therefore, patients are often required to undergo multiple, sometimes complementary but often ultimately unhelpful, imaging techniques to locate an elusive tumor, which can lead to a high radiation burden and a delay in diagnosis.

A recent head-to-head comparison of ^{64}Cu-DOTATATE-PET/CT and ^{68}Ga-DOTATATE-PET/CT in 59 patients with neuroendocrine tumors (NETs) found equal sensitivity on a per patient-basis, but ^{64}Cu-DOTATATE-PET/CT identified significantly more lesions and its longer half-life made it easier to use in a clinical setting [88].

Once potential PMTs have been located using functional imaging

Table 3
Functional (nuclear medicine) imaging techniques used in diagnosing TIO.

Functional imaging technique	Radiopharmaceutical	PET/SPECT	Advantages	Disadvantages
Somatostatin receptor scintigraphy (SRS)				
OctreoScan™	^{111}In-pentetreotide	Planar imaging +SPECT/CT	• PMTs with strong expression of SSTR can be effectively localized with OctreoScan-SPECT/CT	• False negatives can occur due to: – poor spatial resolution of planar imaging – small lesion size – suboptimal expression of SSTR – adjacent location of bone fracture • Long radiopharmaceutical injection-to-scan time • Full body SPECT/CT imaging is very time consuming • ^{111}In has a long half-life (2.8 days) and emits high-energy gamma rays • Tracer uptake in inflammatory conditions such as arthritis could lead to false positives
Hynic-TOC scan	^{99m}Tc-hydrazinonicotinyl-Tyr^3-octreotide	Planar imaging +SPECT/CT	• Good sensitivity and selectivity in detecting PMTs • Quicker injection-to-scan time compared with OctreoScan™ and allows for a one-day imaging protocol • ^{99m}Tc has lower energy gamma rays and a shorter half-life (6 h) than ^{111}In leading to a lower radiation burden	• Poor spatial resolution of planar imaging may not be sensitive enough to detect a tumor • Tracer uptake in inflammatory conditions such as arthritis could lead to false positives
DOTA-Scan	^{68}Ga-DOTA-Tyr^3-octreotate (DOTATOC) ^{68}Ga-DOTA-1-Nal^3-octreotide (DOTANOC) ^{68}Ga-DOTA-Phe^1-Tyr^3-Thr^8 octreotide (DOTATATE)	PET/CT	• A high binding affinity to SSTR2 leads to superior PMT localization compared with OctreoScan™ and ^{18}F-FDG-PET-CT • Short acquisition time and low radiation exposure due to short half-life of ^{68}Ga (68 mins)	• Osteoblasts also express SSTR and the presence of pseudofractures in TIO patients may lead to tracer uptake and false positives • Not widely available or reimbursed in all centers
Glucose transporter imaging				
^{18}F-FDG PET/CT	^{18}F-FDG	PET/CT	• High sensitivity • Excellent co-registration between PET and CT images, helps to map PMTs and guide surgery	• Not specific to PMTs and will identify other areas of increased metabolic activity including healing fractures, which are often evident in patients with TIO • Benign slow-growing PMTs tend to have a low ^{18}F-FDG uptake, making it difficult to distinguish them from other tumors and physiologic uptakes • Common head and neck infections such as sinusitis, dental abscess, tonsillitis and mastoiditis can lead to ^{18}F-FDG uptake and false positives

CT, computed tomography; ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; ^{111}In, ^{111}Indium; ^{68}Ga, ^{68}Gallium; PET, positron-emission tomography; PMTs, phosphaturic mesenchymal tumors; SPECT, single-photon emission computed tomography; SSTR, somatostatin receptor; ^{99m}Tc, ^{99m}Technetium; TIO, tumor-induced osteomalacia. Source [4,6,7,77,80,82,87].

techniques, anatomical imaging techniques must be applied to delineate tumor location in more detail and to obtain precise characterization regarding vascularity, neural structures, and the involvement of surrounding tissue to plan and guide surgical resection. These techniques include conventional radiography, ultrasound, CT or (angio-) magnetic resonance imaging (MRI) [7,89].

The combination of functional and anatomical imaging is usually sufficient to localize PMTs. However, venous sampling may be considered if confirmation is required or if there are multiple suspicious lesions that need to be differentiated [6,7,90].

Overall, we believe that given the extent and detail of biochemical investigation required in making a diagnosis of TIO, the breadth of knowledge needed to exclude alternative diagnoses and the access to, and interpretation of, specialist imaging, it is clear that relevant specialist expertise should be sought from a metabolic bone specialist early in the diagnostic process (Box 1).

5. Review of current treatment options

Complete tumor resection is the only definitive treatment of TIO that cures the disease [6,54,86,91]. This is accompanied by a rapid normalization of fasting serum phosphate, FGF23, and 1,25$(OH)_2$D levels within days in most patients, and a remarkable improvement in clinical manifestations once phosphate homeostasis is restored [4,6,92,93]. Accurate pathological diagnosis may be challenging as PMTs share overlapping histologic features with other types of tumors [94]. Therefore, FGF23-in-situ hybridization assay should be performed on resected tumors to confirm FGF23 production.

Radiotherapy or guided ablation may be used as adjuvant therapy in partially resected tumors or as a primary treatment for tumors that are difficult to access or if surgery is deemed too risky [95,96]. When a tumor cannot be found or if complete removal is not possible, then conventional medical treatment (phosphate supplementation and active vitamin D analogs) is initially required to counteract the phosphate loss, with the aim of normalizing serum phosphate levels and mineral metabolism [4,6,7]. Octreotide has also been proposed as possible treatment for TIO due to the presence of SSTRs on PMTs [97]. However, evidence to suggest improvements is not clear and a small study with five patients showed a lack of efficacy using octreotide to treat TIO short term [98,99].

5.1. Challenges of surgical treatment

The location of the tumor and the experience of the surgeon are the two main factors required to ensure a successful resection [105]. Bone tumors are more difficult to remove than soft tissue tumors as they have a stronger invasive ability and involve more complex surgery [105,106]. As tumors can be located anywhere in the body, surgeons from different specialties and with varying experience may be involved in the operation. Resection of the tumor with appropriately wide margins (R0

Box 1

Solutions to selected challenges associated with making a TIO diagnosis.

- Educate clinicians on the presenting features and differential diagnosis of TIO
- Promote key aspects of testing phosphate to doctors and laboratories, as recognizing hypophosphatemia is imperative to achieve a TIO diagnosis:
  - Fasting serum phosphate testing should always be performed in a general 'bone health'/'bone profile' screening set and any abnormality should not be ignored
  - Promote the clinical requesting of a 'bone profile' panel to physicians when they are assessing patients with ongoing musculoskeletal pains
  - Include serum phosphate assays on all multichannel chemistry panels; mild hypophosphatemia may be missed if the samples are non-fasting
  - Ensure that age-specific reference ranges are used to interpret fasting serum phosphate levels to prevent a misdiagnosis of hypophosphatemia [16,63]
- Implement or promote a healthcare infrastructure that facilitates the opportunity for patients with ongoing musculoskeletal complaints and low serum phosphate to be referred to a specialist metabolic bone physician early in the diagnostic process
- Ensure that the expertise and resources to undertake the calculation of TRP or TmP/GFR are available in all centers, as this calculation is crucial for TIO diagnosis
- Educate more widely that FGF23 should be tested in cases of unexplained persistent hypophosphatemia to aid the diagnosis of TIO and its differential diagnoses
- Adopt the most efficient, evidenced-based stepwise approach to imaging, minimizing overall radiation exposure where possible (Table 3)
- Consider genetic testing in children and when the tumor cannot be located to confirm TIO (and parenteral iron therapy is not considered a likely cause)

resection) is crucial to avoid leaving or spreading any residual tumor cells that could lead to persistent serum biochemical abnormalities or tumor recurrence. One retrospective study of 230 patients with TIO revealed that after primary surgery, 83% of patients recovered, the disease persisted in 11% of patients, and the tumor recurred in 7% of patients with a median time to recurrence of 33 months [105]. Where cases were refractory due to incomplete removal of the tumor, repeat/multiple surgery was found to be effective in approximately half of cases, resulting in an overall cure rate of 88% [105]. Female sex, spinal tumors, bone tissue-involved tumors, malignancy, and lower pre-operative serum phosphate levels were found to be risk factors for refractory outcomes [105].

Although rare (occurring in <5% of TIO cases), late recurrence of metastatic disease can occur and is usually due to incomplete resection or spreading of the primary tumor. The lung is a common site for metastasis so should be closely evaluated if biochemical evidence indicates a recurrence without evidence of local disease [45,107]. Currently, there is no established chemotherapy regimen for treating metastatic TIO [93].

Multifocal PMTs have been described in several patients and may result from incomplete removal and spreading of cells from the initial tumor. This condition can be difficult to manage and would require multiple complete tumor resections to achieve a cure [6,46,108].

If complete resection of the causal tumor is successfully achieved, bone healing starts immediately but depending on severity of disease it may take up to a year for significant clinical improvement [4,93]. In some cases, despite successful tumor resection and restoration of phosphate homeostasis, residual clinical deficits may unfortunately be irreversible if the diagnosis was delayed following prolonged illness.

Perioperative challenges and complications in patients with TIO are a direct result of severe hypophosphatemia and include impaired contractility of the diaphragm and related mechanical ventilation issues, cardiovascular complications during surgery, and the risk of pathological fractures while handling the patient. As a result, severely ill patients may require supplementation with oral phosphate and active vitamin D analogs prior to surgery. However, patients are often taken into surgery with suboptimal serum phosphate levels due to poor responses to medical treatment [109].

Post-surgery complications can include prolonged, severe hypocalcemia, with the complication of hungry bone syndrome due to the rapid re-mineralization of the bone once phosphate and FGF23 return to normal levels and $1,25(OH)_2D$ increases dramatically. Therefore, all patients should be closely monitored and supplemented with vitamin D and calcium following surgery, based on laboratory findings [51].

Patients should also be monitored for recurrence following initial surgery. Although currently there are no established standard follow-up procedures, measurement of fasting serum phosphate levels initially every 6 months and then yearly are recommended [6]. In cases where the causal tumor has not been located, patients should initiate medical treatment and be followed-up regularly as clinically appropriate including medical history, physical examination and imaging in the hope that the tumor may eventually be located [4,6,7].

Most unresectable tumors are located in the spine because it is extremely difficult to fully remove them without post-surgical complications, such as spinal instability and neurological injury [105,110,111].

5.2. Challenges of radiotherapy and ablation

Unresectable or partially resected tumors can be treated with less invasive modalities, such as radiotherapy or image-guided ablation. These modalities can be used as adjuvant treatment in cases of partial resection or as a primary treatment in cases of tumors that are inaccessible or where surgery is deemed too risky [95,96].

A literature review of 160 found to have a tumour in their head or neck revealed that only two patients radiotherapy as their primary treatment and two patients had radiotherapy as adjuvant treatment to surgery. Although some biochemical resolution was demonstrated with radiotherapy, the response was considered slow [56].

Several case reports describe the use of image-guided ablation of tumors using different techniques, such as radiofrequency ablation, cryoablation, and percutaneous ethanol injection. Biochemical and

Box 2

The key challenges of conventional medical treatment in TIO.

- Remaining aware of monitoring and actively managing the effects of long-term treatment with phosphate and active vitamin D:
  - Secondary and tertiary hyperparathyroidism
  - Hypercalcemia
  - Hypercalciuria leading to nephrolithiasis (kidney stones) and nephrocalcinosis (calcium deposits in renal parenchyma)
  - Abnormal renal function (decreased GFR) as a result of calcium-induced kidney disease
  - Gastrointestinal intolerance of phosphate supplementation (diarrhoea)
- Recognising that normalisation of serum phosphate is rarely achieved and is limited by complications of therapy.
- Achieving the balance between optimizing clinical improvement and minimizing treatment complications requires frequent monitoring and sometimes therapy dose adjustments
  - Serum calcium, phosphate, vitamin D, PTH, ALP, eGFR, and urinary calcium must be checked every 3–6 months
  - Fasting morning urine calcium measurements should be taken
- Optimizing taking phosphate supplements
  - Short half-life of oral phosphate means that multiple daily doses are sometimes necessary
  - Burdensome dosing regimen, combined with the poor taste of phosphate preparations and gastro-intestinal side effects, can lead to suboptimal adherence with treatment [118,119]
  - Optimizing phosphate supplementation can be achieved by dissolving the tablets in a large water bottle and sipped during the day
- In patients intolerant or non-adherent on phosphate supplements, active vitamin D doses may need to be adjusted higher, despite not sufficiently addressing the deficient phosphate intake, thereby increasing the risk of hypercalcemia and hypercalciuria

clinical improvements were demonstrated following treatment. However, due to insufficient long-term effectiveness data, it is currently not known whether recurrence rates are equivalent to those of surgical resection [6,112–116]. Surgery, therefore, remains the treatment of choice.

5.3. Challenges of conventional medical treatment

Where tumours are unresectable, partially resectable, multifocal, unlocalised, or where TIO relapses, optimal management is unknown and has not been defined by consensus. Medical intervention is the mainstay of treatment for these patients and is required long term and ultimately up to the time of tumor localization, which can be from months to years in some cases. Medical treatment aims to restore phosphate and vitamin D homeostasis to alleviate clinical symptoms, improve myopathy, improve or prevent further deterioration in mobility, and should aim to normalize bone mineralization [4,6,7].

Medical therapy for TIO involves phosphate and active vitamin D analog supplementation with the goal being to increase serum phosphate levels towards the lower end of the age-appropriate normal range. Normalization of incidental serum phosphate levels should not be the target. The overarching treatment goal is to normalize bone and mineral metabolism as reflected by the absence of clinical issues (fractures, weakness, pain) along with compensated ALP activity, improved calcium without hypercalcemia, and maintaining PTH and vitamin D levels within the normal range. However, conventional medical therapy comes with many challenges as outlined in Box 2 [4,61,117–119].

In patients with poor tolerability to phosphate or imminent phosphate-induced hyperparathyroidism, the calcimimetic agent, cinacalcet, may be considered as adjuvant therapy. Cinacalcet reduces PTH levels and renal phosphate wasting, thereby reducing the need for phosphate supplements. However, treatment can lead to hypercalciuria necessitating the use of a thiazide diuretic and lowering PTH further reduces already compromised 1α-hydroxylase activity. Additional studies are needed to confirm the efficacy and safety of cinacalcet [120], which has restricted use in many countries based on the grounds of cost and indication.

5.4. Other aspects of medical management

Dual energy X-ray absorptiometry (DXA) scans assessing bone density in patients with TIO can lead to a misdiagnosis of osteoporosis [121]. DXA scans cannot distinguish between osteoporosis and other metabolic bone disorders including types of osteomalacia as causes of the detected ‘low bone mass’ [122].

Patients with TIO are often misdiagnosed with osteoporosis resulting in erroneous treatment with anti-resorptive agents, such as bisphosphonates [55,121]. Crucially, bisphosphonates induce hypophosphatemia via increased urinary phosphate excretion and may exacerbate symptoms in patients with TIO [123]. Therefore, routine testing for fasting serum phosphate levels should be included in the baseline diagnostic work-up of patients presenting with DXA values within the osteoporotic range, to ensure that patients with TIO or other phosphate-wasting disorders are not missed and erroneously prescribed treatment that could aggravate symptoms. In selected cases where the osteomalacia from TIO cannot be clarified based on clinical, laboratory, and imaging results, bone biopsy may be considered to obtain a histological confirmation of osteomalacia and to exclude other bone pathology [6,58].

6. Future outlook

More widespread availability and use of ^{68}Ga-DOTATATE PET/CT imaging could improve timely diagnostic capabilities and tumor localization. Recent meta-analyses provide evidence-based data that could be used towards supporting medical insurance coverage of this imaging method in TIO. Further prospective, multicenter and cost-effective studies could strengthen this prospect [83,84].

Burosumab is not globally accessible for patients with TIO. Once registration is approved in other regions treatment with burosumab will remain a challenge given restricted and varied funding across healthcare systems, with little experience of using the treatment outside a few specialized centers. Conclusive recommendations on the use of burosumab are also required as this new therapy has only been tested in clinical trials, and the long-term safety data will need to be considered.

Additional real-world data, further education and evidence-based

practises combined with better access to burosumab, should improve the management of TIO patients.

Recognition that chromosomal translocation - causing an FN1-FGFR1 or FN1-FGF1 fusion gene - is a molecular driver of PMT growth might drive therapeutic development [41–43]. It is, therefore, notable that a pan-FGFR kinase inhibitor (BGJ398) is considered one possible treatment option for TIO [124]. In a Phase II study of patients with FGFR altered tumours, BGJ398 (infigratinib) demonstrated anti-tumour activity and normalised serum FGF23 and phosphate levels in one patient with metastatic TIO, and normalised serum FGF23 and phosphate levels in another patient with no identifiable tumour but presenting with symptomatic metabolic manifestations [88]. In a more recent case report of a 66-year-old man with an FN1–FGFR1 fusion gene PMT, the use of the FGFR1–3 tyrosine kinase inhibitor, infigratinib, resulted in a favorable biochemical and structural tumor response, confirming the role of FGFR1 signaling in PMT growth and FGF23 production. However, treatment was interrupted and ceased due to tyrosine kinase inhibitor-related side effects [125].

Finally, should long-term follow-up from studies on ablation therapy demonstrate a potential cure, then it may provide a less invasive option to surgery, but only in cases where tumors are surgically inaccessible or where an attempted surgical excision might be too risky [114,115].

Burosumab, a fully human, monoclonal antibody to FGF23, recently received approval by the US Food and Drug Administration (FDA) for the treatment of patients with TIO who cannot undergo surgical removal of tumors [100,101]. Approval was based on two single-arm Phase II studies (NCT02304367, NCT02722798), in which burosumab was associated with improvements in serum phosphate, osteomalacia, mobility, quality of life, and fatigue [102,103]. In a recent case report, a 52-year-old female patient with two unresectable TIO lesions of the brain, who had failed a course of oral phosphate supplementation, was treated with burosumab. Pain symptoms had improved after 7 weeks, allowing her to stand from her wheelchair. By Week 23, she was able to use a walker. Serum phosphate concentrations also normalized and were 4.3 mg/dL after 5 months [104]. Currently, burosumab is only licensed for the management of TIO in Japan and the USA. Burosumab, although not curative, may represent an effective alternative to conventional medical treatment in patients whose tumors are unresectable, cannot be localized or where surgery might be too risky or otherwise unfeasible.

7. Conclusion

Optimal TIO management includes early recognition and then diagnosis of the disease, followed by identification and complete removal of the PMT. Accordingly, mineral homeostasis is restored and clinical symptoms resolve.

However, there are challenges in managing patients when the tumor cannot be either located or resected, or who unfortunately relapse after surgery. These patients require pharmacological intervention and long-term medical management to restore their phosphate levels and prevent chronic disease manifestations (osteomalacia, bone pain and myopathy).

There is a clear need to improve the time to suspicion, referral, and diagnosis of TIO, as well as to subsequently engage appropriately resourced specialized units or teams, to either take over from referring doctors, or to closely supervise the remainder of the diagnostic pathway and ongoing management of patients. The authors believe that an increased awareness of hypophosphatemia and its causes among primary care doctors and specialists, should lead to greater knowledge of TIO. It is hoped that this review of the challenges of managing TIO might help to focus opinion, effort, and resource towards establishing a broad consensus on how to manage patients who might potentially have or have been diagnosed as having TIO.

All stakeholders within the healthcare community, coupled with the introduction of clinical practice guidelines, will help to establish an acceptable standard of care for this challenging and rare disease. A systematic and stepwise approach to the management of TIO, taking into consideration current and novel modalities, will ultimately mitigate the challenges caused by the variability in healthcare provision and improve patient outcomes.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study. Any data referred to in the text is available from the cited references.

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Declaration of competing interest

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GPRC has served as advisory board member for Novartis, Eli Lilly and Kyowa Kirin.

PH has served as a speaker and taken part in advisory board meetings for Shire, Kyowa Kirin and Takeda.

SMJDB has taken part in advisory boards for Ultragenyx, Kyowa Kirin. She is a consultant for Ultragenyx, Kyowa Kirin, Inozyme and has received research grants from Ultragenyx.

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References

[1] R. Kumar, Tumor-induced osteomalacia and the regulation of phosphate homeostasis, Bone. 27 (2000) 333–338, https://doi.org/10.1016/s8756-3282(00)00334-3.
[2] T. Shimada, S. Mizutani, T. Muto, T. Yoneya, R. Hino, S. Takeda, Y. Takeuchi, T. Fujita, S. Fukumoto, T. Yamashita, Cloning and characterization of FGF23 as a causative factor of tumor-induced osteomalacia, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 6500–6505, https://doi.org/10.1073/pnas.101545198.
[3] S.M. Jan de Beur, R.B. Finnegan, J. Vassiliadis, B. Cook, D. Barberio, S. Estes, P. Manavalan, J. Petroziello, S.L. Madden, J.Y. Cho, R. Kumar, M.A. Levine, S. C. Schiavi, Tumors associated with oncogenic osteomalacia express genes important in bone and mineral metabolism, J. Bone Miner. Res. 17 (2002) 1102–1110, https://doi.org/10.1359/jbmr.2002.17.6.1102.
[4] W.H. Chong, A.A. Molinolo, C.C. Chen, M.T. Collins, Tumor-induced osteomalacia, Endocr. Relat. Cancer 18 (2011) R53–R77, https://doi.org/10.1530/erc-11-0006.
[5] P. Florenzano, R.I. Gafni, M.T. Collins, Tumor-induced osteomalacia, Bone Rep. 7 (2017) 90–97, https://doi.org/10.1016/j.bonr.2017.09.002.
[6] S. Minisola, M. Peacock, S. Fukumoto, C. Cipriani, J. Pepe, S.H. Tella, M. T. Collins, Tumour-induced osteomalacia, Nat. Rev. Dis. Primers. 3 (2017) 17044, https://doi.org/10.1038/nrdp.2017.44.
[7] P. Florenzano, I.R. Hartley, M. Jimenez, K. Roszko, R.I. Gafni, M.T. Collins, Tumor-induced osteomalacia, Calcif. Tissue Int. 108 (2021) 128–142, https://doi.org/10.1007/s00223-020-00691-6.
[8] I. Endo, S. Fukumoto, K. Ozono, N. Namba, D. Inoue, R. Okazaki, M. Yamauchi, T. Sugimoto, M. Minagawa, T. Michigami, M. Nagai, T. Matsumoto, Nationwide

survey of fibroblast growth factor 23 (FGF23)-related hypophosphatemic diseases in Japan: prevalence, biochemical data and treatment, Endocr. J. 62 (2015) 811–816, https://doi.org/10.1507/endocrj.EJ15-0275.
[9] B. Abrahamsen, C.D. Smith, S. Minisola, Epidemiology of tumor-induced osteomalacia in Denmark, Calcif. Tissue Int. (2021), https://doi.org/10.1007/s00223-021-00843-2.
[11] Q. Yuan, Y. Jiang, X. Zhao, T. Sato, M. Densmore, C. Schüler, R.G. Erben, M. D. McKee, B. Lanske, Increased osteopontin contributes to inhibition of bone mineralization in FGF23-deficient mice, J. Bone Miner. Res. 29 (2014) 693–704, https://doi.org/10.1002/jbmr.2079.
[12] O. Andrukhova, A. Smorodchenko, M. Egerbacher, C. Streicher, U. Zeitz, R. Goetz, V. Shalhoub, M. Mohammadi, E.E. Pohl, B. Lanske, R.G. Erben, FGF23 promotes renal calcium reabsorption through the TRPV5 channel, EMBO J. 33 (2014) 229–246, https://doi.org/10.1002/embj.201284188.
[16] P. Florenzano, C. Cipriani, K.L. Roszko, S. Fukumoto, M.T. Collins, S. Minisola, J. Pepe, Approach to patients with hypophosphataemia, Lancet Diabetes Endocrinol. 8 (2020) 163–174, https://doi.org/10.1016/S2213-8587(19)30426-7.
[17] J.M. Boland, P.J. Tebben, A.L. Folpe, Phosphaturic mesenchymal tumors: what an endocrinologist should know, J. Endocrinol. Investig. 41 (2018) 1173–1184, https://doi.org/10.1007/s40618-018-0849-5.
[18] M. Goretti Penido, U.S. Alon, Phosphate homeostasis and its role in bone health, Pediatr. Nephrol. 27 (2012) 2039–2048, https://doi.org/10.1007/s00467-012-2175-z.
[19] J.-O.C. Dunn, M.G. Mythen, M.P. Grocott, Physiology of oxygen transport, BJA Educ. 16 (2016) 341–348, https://doi.org/10.1093/bjaed/mkw012.
[20] M.O. Gore, B.J. Welch, W. Geng, W. Kabbani, N.M. Maalouf, J.E. Zerwekh, O. W. Moe, K. Sakhaee, Renal phosphate wasting due to tumor-induced osteomalacia: a frequently delayed diagnosis, Kidney Int. 76 (2009) 342–347, https://doi.org/10.1038/ki.2008.355.
[21] J.E. Blau, M.T. Collins, The PTH-vitamin D-FGF23 axis, Rev. Endocr. Metab. Disord. 16 (2015) 165–174, https://doi.org/10.1007/s11154-015-9318-z.
[22] A. Martin, V. David, L.D. Quarles, Regulation and function of the FGF23/klotho endocrine pathways, Physiol. Rev. 92 (2012) 131–155, https://doi.org/10.1152/physrev.00002.2011.
[23] A.J. van Vuren, C. Gaillard, M.F. Eisenga, R. van Wijk, E.J. van Beers, The EPO-FGF23 signaling pathway in erythroid progenitor cells: opening a new area of research, Front. Physiol. 10 (2019) 304, https://doi.org/10.3389/fphys.2019.00304.
[24] S. Rabadi, I. Udo, D.E. Leaf, S.S. Waikar, M. Christov, Acute blood loss stimulates fibroblast growth factor 23 production, Am. J. Physiol. Ren. Physiol. 314 (2018) F132–f139, https://doi.org/10.1152/ajprenal.00081.2017.
[25] L. Toro, V. Barrientos, P. León, M. Rojas, M. Gonzalez, A. González-Ibáñez, S. Illanes, K. Sugikawa, N. Abarzúa, C. Bascuñán, K. Arcos, C. Fuentealba, A. M. Tong, A.A. Elorza, M.E. Pinto, R. Alzamora, C. Romero, L. Michea, Erythropoietin induces bone marrow and plasma fibroblast growth factor 23 during acute kidney injury, Kidney Int. 93 (2018) 1131–1141, https://doi.org/10.1016/j.kint.2017.11.018.
[26] M. Wolf, K.E. White, Coupling fibroblast growth factor 23 production and cleavage: iron deficiency, rickets, and kidney disease, Curr. Opin. Nephrol. Hypertens. 23 (2014) 411–419, https://doi.org/10.1097/01.mnh.0000447020.74593.6f.
[27] S. Liu, L.D. Quarles, How fibroblast growth factor 23 works, J. Am. Soc. Nephrol. 18 (2007) 1637–1647, https://doi.org/10.1681/asn.2007010068.
[28] H. Kurosu, Y. Ogawa, M. Miyoshi, M. Yamamoto, A. Nandi, K.P. Rosenblatt, M. G. Baum, S. Schiavi, M.C. Hu, O.W. Moe, M. Kuro-o, Regulation of fibroblast growth factor-23 signaling by klotho, J. Biol. Chem. 281 (2006) 6120–6123, https://doi.org/10.1074/jbc.C500457200.
[29] M.S. Razzaque, The FGF23-Klotho axis: endocrine regulation of phosphate homeostasis, Nat. Rev. Endocrinol. 5 (2009) 611–619, https://doi.org/10.1038/nrendo.2009.196.
[30] I. Urakawa, Y. Yamazaki, T. Shimada, K. Iijima, H. Hasegawa, K. Okawa, T. Fujita, S. Fukumoto, T. Yamashita, Klotho converts canonical FGF receptor into a specific receptor for FGF23, Nature. 444 (2006) 770–774, https://doi.org/10.1038/nature05315.
[31] T. Shimada, H. Hasegawa, Y. Yamazaki, T. Muto, R. Hino, Y. Takeuchi, T. Fujita, K. Nakahara, S. Fukumoto, T. Yamashita, FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis, J. Bone Miner. Res. 19 (2004) 429–435, https://doi.org/10.1359/jbmr.0301264.
[32] L. Beck, A.C. Karaplis, N. Amizuka, A.S. Hewson, H. Ozawa, H.S. Tenenhouse, Targeted inactivation of Npt2 in mice leads to severe renal phosphate wasting, hypercalciuria, and skeletal abnormalities, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 5372–5377, https://doi.org/10.1073/pnas.95.9.5372.
[33] M. Courbebaisse, B. Lanske, Biology of fibroblast growth factor 23: from physiology to pathology, Cold Spring Harb. Perspect. Med. 8 (2018), https://doi.org/10.1101/cshperspect.a031260.
[34] N. Weidner, D. Santa Cruz, Phosphaturic mesenchymal tumors. A polymorphous group causing osteomalacia or rickets, Cancer. 59 (1987) 1442–1454, https://doi.org/10.1002/1097-0142(19870415)59:8<1442::aid-cncr2820590810>3.0.co;2-q.
[35] A.L. Folpe, J.C. Fanburg-Smith, S.D. Billings, M. Bisceglia, F. Bertoni, J.Y. Cho, M. J. Econs, C.Y. Inwards, S.M. Jan de Beur, T. Mentzel, E. Montgomery, M. Michal, M. Miettinen, S.E. Mills, J.D. Reith, J.X. O'Connell, A.E. Rosenberg, B.P. Rubin, D. E. Sweet, T.N. Vinh, L.E. Wold, B.M. Wehrli, K.E. White, R.J. Zaino, S.W. Weiss, Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature, Am. J. Surg. Pathol. 28 (2004) 1–30, https://doi.org/10.1097/00000478-200401000-00001.
[36] W.H. Chong, S. Yavuz, S.M. Patel, C.C. Chen, M.T. Collins, The importance of whole body imaging in tumor-induced osteomalacia, J. Clin. Endocrinol. Metab. 96 (2011) 3599–3600, https://doi.org/10.1210/jc.2011-1757.
[37] Y. Jiang, W.B. Xia, X.P. Xing, B.C. Silva, M. Li, O. Wang, H.B. Zhang, F. Li, H. L. Jing, D.R. Zhong, J. Jin, P. Gao, L. Zhou, F. Qi, W. Yu, J.P. Bilezikian, X. W. Meng, Tumor-induced osteomalacia: an important cause of adult-onset hypophosphatemic osteomalacia in China: report of 39 cases and review of the literature, J. Bone Miner. Res. 27 (2012) 1967–1975, https://doi.org/10.1002/jbmr.1642.
[38] N. Muro Bushart, L. Tharun, R. Oheim, A. Paech, J. Kiene, Tumor-induced osteomalacia caused by an FGF23-secreting myopericytoma : case report and literature review, Orthopade. 49 (2020) 1–9, https://doi.org/10.1007/s00132-019-03719-4.
[39] J.M. Carter, B.L. Caron, A. Dogan, A.L. Folpe, A novel chromogenic in situ hybridization assay for FGF23 mRNA in phosphaturic mesenchymal tumors, Am. J. Surg. Pathol. 39 (2015) 75–83, https://doi.org/10.1097/pas.0000000000000290.
[40] Y. Yamada, I. Kinoshita, K. Kenichi, H. Yamamoto, T. Iwasaki, H. Otsuka, M. Yoshimoto, S. Ishihara, Y. Toda, Y. Kuma, N. Setsu, Y. Koga, Y. Honda, T. Inoue, H. Yanai, K. Yamashita, I. Ito, M. Takahashi, S. Ohga, M. Furue, Y. Nakashima, Y. Oda, Histopathological and genetic review of phosphaturic mesenchymal tumours, mixed connective tissue variant, Histopathology. 72 (2018) 460–471, https://doi.org/10.1111/his.13377.
[41] J.C. Lee, S.Y. Su, C.A. Changou, R.S. Yang, K.S. Tsai, M.T. Collins, E.S. Orwoll, C. Y. Lin, S.H. Chen, S.R. Shih, C.H. Lee, Y. Oda, S.D. Billings, C.F. Li, G.P. Nielsen, E. Konishi, F. Petersson, T.O. Carpenter, K. Sittampalam, H.Y. Huang, A.L. Folpe, Characterization of FN1-FGFR1 and novel FN1-FGF1 fusion genes in a large series of phosphaturic mesenchymal tumors, Mod. Pathol. 29 (2016) 1335–1346, https://doi.org/10.1038/modpathol.2016.137.
[42] J.C. Lee, Y.M. Jeng, S.Y. Su, C.T. Wu, K.S. Tsai, C.H. Lee, C.Y. Lin, J.M. Carter, J. W. Huang, S.H. Chen, S.R. Shih, A. Mariño-Enríquez, C.C. Chen, A.L. Folpe, Y. L. Chang, C.W. Liang, Identification of a novel FN1-FGFR1 genetic fusion as a frequent event in phosphaturic mesenchymal tumour, J. Pathol. 235 (2015) 539–545, https://doi.org/10.1002/path.4465.
[43] S. Wöhrle, C. Henninger, O. Bonny, A. Thuery, N. Beluch, N.E. Hynes, V. Guagnano, W.R. Sellers, F. Hofmann, M. Kneissel, D. Graus Porta, Pharmacological inhibition of fibroblast growth factor (FGF) receptor signaling ameliorates FGF23-mediated hypophosphatemic rickets, J. Bone Miner. Res. 28 (2013) 899–911, https://doi.org/10.1002/jbmr.1810.
[44] N. Oyama, K. Kojima-Ishii, N. Toda, T. Matsuo, V. Tocan, K. Ohkubo, U. Oba, Y. Koga, N. Setsu, Y. Yamada, K. Kohashi, Y. Nakashima, Y. Oda, K. Ihara, S. Ohga, Malignant transformation of phosphaturic mesenchymal tumor: a case report and literature review, Clin. Pediatr. Endocrinol. 29 (2020) 69–75, https://doi.org/10.1297/cpe.29.69.
[45] M.P. Yavropoulou, C. Poulios, C. Foroulis, S. Tournis, P. Hytiroglou, K. Kotsa, I. Kessisoglou, P. Zebekakis, Distant lung metastases caused by a histologically benign phosphaturic mesenchymal tumor, Endocrinol. Diabetes Metab. Case Rep. 2018 (2018), https://doi.org/10.1530/edm-18-0023.
[46] A.K. Annamalai, K. Sampathkumar, S. Kane, N.S. Shetty, S. Kulkarni, V. Rangarajan, N. Purandare, P.S. Pai, A.D. Mahuvakar, R. Shanthi, G. Suriyakumar, V. Puri, S. Aram, C. Gopalakrishnan, M. Chelian, K.G. Srinivasan, A.J. Gill, M. Gurnell, R. Clifton-Bligh, Needle(s) in the haystack-synchronous multifocal tumor-induced osteomalacia, J. Clin. Endocrinol. Metab. 101 (2016) 390–393, https://doi.org/10.1210/jc.2015-3854.
[47] D.E. Leaf, R.C. Pereira, H. Bazari, H. Jüppner, Oncogenic osteomalacia due to FGF23-expressing colon adenocarcinoma, J. Clin. Endocrinol. Metab. 98 (2013) 887–891, https://doi.org/10.1210/jc.2012-3473.
[48] H.A. Lin, S.R. Shih, Y.T. Tseng, C.H. Chen, W.Y. Chiu, C.Y. Hsu, K.S. Tsai, Ovarian cancer-related hypophosphatemic osteomalacia–a case report, J. Clin. Endocrinol. Metab. 99 (2014) 4403–4407, https://doi.org/10.1210/jc.2014-2120.
[49] M.P. Mak, V.T. da Costa e Silva, R.M. Martin, A.M. Lerario, L. Yu, P.M. Hoff, G. de Castro Jr., Advanced prostate cancer as a cause of oncogenic osteomalacia: an underdiagnosed condition, Support Care Cancer 20 (2012) 2195–2197, https://doi.org/10.1007/s00520-012-1474-z.
[50] C. Savva, J. Adhikaree, S. Madhusudan, K. Chokkalingam, Oncogenic osteomalacia and metastatic breast cancer: a case report and review of the literature, J. Diabetes Metab. Disord. 18 (2019) 267–272, https://doi.org/10.1007/s40200-019-00398-y.
[51] S. Kumar, R. Shah, V. Patil, S. Ramteke-Jadhav, M. Bal, A. Lila, N. Shah, T. Bandgar, Tumor-induced rickets-osteomalacia: an enigma, J. Pediatr. Endocrinol. Metab. (2020), https://doi.org/10.1515/jpem-2020-0079.
[52] G.H. Jung, J.D. Kim, Y. Cho, S.H. Chung, J.H. Lee, K.R. Sohn, A 9-month-old phosphaturic mesenchymal tumor mimicking the intractable rickets, J. Pediatr. Orthop. B 19 (2010) 127–132, https://doi.org/10.1097/BPB.0b013e32832f59cb.
[53] Z. Adnan, D. Nikomarov, M. Weiler-Sagie, N. Roguin Maor, Phosphaturic mesenchymal tumors among elderly patients: a case report and review of literature, Endocrinol. Diabetes Metab. Case Rep. 2019 (2019), https://doi.org/10.1530/edm-18-01396.
[54] S. Piemonte, E. Romagnoli, C. Cipriani, F. De Lucia, R. Pilotto, D. Diacinti, J. Pepe, S. Minisola, Six-year follow-up of a characteristic osteolytic lesion in a patient with tumor-induced osteomalacia, Eur. J. Endocrinol. 170 (2014) K1–K4, https://doi.org/10.1530/eje-13-0581.

[55] J. Feng, Y. Jiang, O. Wang, M. Li, X. Xing, L. Huo, F. Li, W. Yu, D.R. Zhong, J. Jin, Y. Liu, F. Qi, W. Lv, L. Zhou, X.W. Meng, W.B. Xia, The diagnostic dilemma of tumor induced osteomalacia: a retrospective analysis of 144 cases, Endocr. J. 64 (2017) 675–683, https://doi.org/10.1507/endocrj.EJ16-0587.

[56] R. Shah, A.R. Lila, R.S. Jadhav, V. Patil, A. Mahajan, S. Sonawane, P. Thadani, A. Dcruz, P. Pai, M. Bal, S. Kane, N. Shah, T. Bandgar, Tumor induced osteomalacia in head and neck region: single center experience and systematic review, Endocr. Connect. 8 (2019) 1330–1353, https://doi.org/10.1530/ec-19-0341.

[57] Q.Y. Zuo, H. Wang, W. Li, X.H. Niu, Y.H. Huang, J. Chen, Y.H. You, B.Y. Liu, A. M. Cui, W. Deng, Treatment and outcomes of tumor-induced osteomalacia associated with phosphaturic mesenchymal tumors: retrospective review of 12 patients, BMC Musculoskelet. Disord. 18 (2017) 403, https://doi.org/10.1186/s12891-017-1756-1.

[58] S.M. Jan de Beur, Tumor-induced osteomalacia, JAMA. 294 (2005) 1260–1267, https://doi.org/10.1001/jama.294.10.1260.

[59] W. Khaliq, P. Cheripalli, K. Tangella, Tumor-induced osteomalacia (TIO): atypical presentation, South. Med. J. 104 (2011) 348–350, https://doi.org/10.1097/SMJ.0b013e31821427db.

[60] D.M. Li, H.W. Wu, J.D. Li, W.B. Xia, Y. Jiang, D.R. Zhong, Clinical and immunohistopathologic study of phosphaturic mesenchymal tumor, Zhonghua Bing Li Xue Za Zhi 47 (2018) 427–431, https://doi.org/10.3760/cma.j.issn.0529-5807.2018.06.008.

[61] G.P. Clunie, P.E. Fox, T.C. Stamp, Four cases of acquired hypophosphataemic ('oncogenic') osteomalacia. Problems of diagnosis, treatment and long-term management, Rheumatology (Oxford) 39 (2000) 1415–1421, https://doi.org/10.1093/rheumatology/39.12.1415.

[62] A.A. Portale, B.P. Halloran, R.C. Morris Jr., Dietary intake of phosphorus modulates the circadian rhythm in serum concentration of phosphorus. Implications for the renal production of 1,25-dihydroxyvitamin D, J. Clin. Invest. 80 (1987) 1147–1154, https://doi.org/10.1172/jci113172.

[63] E.A. Imel, M.J. Econs, Approach to the hypophosphatemic patient, J. Clin. Endocrinol. Metab. 97 (2012) 696–706, https://doi.org/10.1210/jc.2011-1319.

[64] S. Goto, H. Fujii, K. Kono, K. Watanabe, K. Nakai, S. Nishi, Serum FGF23 levels may not be associated with serum phosphate and 1,25-dihydroxyvitamin D levels in patients with Fanconi syndrome-induced hypophosphatemia, Clin. Kidney J. 9 (2016) 677–681, https://doi.org/10.1093/ckj/sfw086.

[65] R. Fuente, H. Gil-Peña, D. Claramunt-Taberner, O. Hernández, A. Fernández-Iglesias, L. Alonso-Durán, E. Rodríguez-Rubio, F. Santos, X-linked hypophosphatemia and growth, Rev. Endocr. Metab. Disord. 18 (2017) 107–115, https://doi.org/10.1007/s11154-017-9408-1.

[66] A. Gohil, E.A. Imel, FGF23 and associated disorders of phosphate wasting, Pediatr. Endocrinol. Rev. 17 (2019) 17–34, https://doi.org/10.17458/per.vol17.2019.gi.fgf23anddisordersphosphate.

[67] Y. Kinoshita, S. Fukumoto, X-linked hypophosphatemia and FGF23-related hypophosphatemic diseases: prospect for new treatment, Endocr. Rev. 39 (2018) 274–291, https://doi.org/10.1210/er.2017-00220.

[68] R.H. Bishay, K. Ganda, M.J. Seibel, Long-term iron polymaltose infusions associated with hypophosphataemic osteomalacia: a report of two cases and review of the literature, Ther. Adv. Endocrinol. Metab. 8 (2017) 14–19, https://doi.org/10.1177/2042018816678363.

[69] J.A. Glaspy, M.Z. Lim-Watson, M.A. Libre, S.S. Karkare, N. Hadker, A. Bajic-Lucas, W.E. Strauss, N.V. Dahl, Hypophosphatemia associated with intravenous iron therapies for iron deficiency anemia: a systematic literature review, Ther. Clin. Risk Manag. 16 (2020) 245–259, https://doi.org/10.2147/tcrm.s243462.

[70] M. Wolf, T.A. Koch, D.B. Bregman, Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women, J. Bone Miner. Res. 28 (2013) 1793–1803, https://doi.org/10.1002/jbmr.1923.

[71] D. Edmonston, M. Wolf, FGF23 at the crossroads of phosphate, iron economy and erythropoiesis, Nat. Rev. Nephrol. 16 (2020) 7–19, https://doi.org/10.1038/s41581-019-0189-5.

[72] H. Olauson, K. Lindberg, R. Amin, T. Sato, T. Jia, R. Goetz, M. Mohammadi, G. Andersson, B. Lanske, T.E. Larsson, Parathyroid-specific deletion of Klotho unravels a novel calcineurin-dependent FGF23 signaling pathway that regulates PTH secretion, PLoS Genet. 9 (2013), e1003975, https://doi.org/10.1371/journal.pgen.1003975.

[73] Q.L. Huang, D.S. Feig, M.E. Blackstein, Development of tertiary hyperparathyroidism after phosphate supplementation in oncogenic osteomalacia, J. Endocrinol. Investig. 23 (2000) 263–267, https://doi.org/10.1007/bf03343720.

[74] J.Q. Feng, L.M. Ward, S. Liu, Y. Lu, Y. Xie, B. Yuan, X. Yu, F. Rauch, S.I. Davis, S. Zhang, H. Rios, M.K. Drezner, L.D. Quarles, L.F. Bonewald, K.E. White, Loss of DMP1 causes rickets and osteomalacia and identifies a role for osteocytes in mineral metabolism, Nat. Genet. 38 (2006) 1310–1315, https://doi.org/10.1038/ng1905.

[75] V. Levy-Litan, E. Hershkovitz, L. Avizov, N. Leventhal, D. Bercovich, V. Chalifa-Caspi, E. Manor, S. Buriakovsky, Y. Hadad, J. Goding, R. Parvari, Autosomal-recessive hypophosphatemic rickets is associated with an inactivation mutation in the ENPP1 gene, Am. J. Hum. Genet. 86 (2010) 273–278, https://doi.org/10.1016/j.ajhg.2010.01.010.

[76] C.A. Wagner, I. Rubio-Aliaga, J. Biber, N. Hernando, Genetic diseases of renal phosphate handling, Nephrol. Dial. Transplant. 29 (Suppl. 4) (2014) iv45–54, https://doi.org/10.1093/ndt/gfu217.

[77] M. Yang, K.B. Doshi, M.C. Roarke, B.D. Nguyen, Molecular imaging in diagnosis of tumor-induced osteomalacia, Curr. Probl. Diagn. Radiol. 48 (2019) 379–386, https://doi.org/10.1067/j.cpradiol.2018.06.005.

[78] K. Agrawal, S. Bhadada, B.R. Mittal, J. Shukla, A. Sood, A. Bhattacharya, A. Bhansali, Comparison of 18F-FDG and 68Ga DOTATATE PET/CT in localization of tumor causing oncogenic osteomalacia, Clin. Nucl. Med. 40 (2015) e6–e10, https://doi.org/10.1097/rlu.0000000000000460.

[79] S. Breer, T. Brunkhorst, F.T. Beil, K. Peldschus, M. Heiland, S. Klutmann, F. Barvencik, J. Zustin, K.F. Gratz, M. Amling, 68Ga DOTA-TATE PET/CT allows tumor localization in patients with tumor-induced osteomalacia but negative 111In-octreotide SPECT/CT, Bone. 64 (2014) 222–227, https://doi.org/10.1016/j.bone.2014.04.016.

[80] D. El-Maouche, S.M. Sadowski, G.Z. Papadakis, L. Guthrie, C. Cottle-Delisle, R. Merkel, C. Millo, C.C. Chen, E. Kebebew, M.T. Collins, (68)Ga-DOTATATE for tumor localization in tumor-induced osteomalacia, J. Clin. Endocrinol. Metab. 101 (2016) 3575–3581, https://doi.org/10.1210/jc.2016-2052.

[81] Q. He, B. Zhang, L. Zhang, Z. Chen, X. Shi, C. Yi, X. Wang, X. Zhang, Diagnostic efficiency of (68)Ga-DOTANOC PET/CT in patients with suspected tumour-induced osteomalacia, Eur. Radiol. (2020), https://doi.org/10.1007/s00330-020-07342-2.

[82] S.M. Jan de Beur, E.A. Streeten, A.C. Civelek, E.F. McCarthy, L. Uribe, S.J. Marx, O. Onobrakpeya, L.G. Raisz, N.B. Watts, M. Sharon, M.A. Levine, Localisation of mesenchymal tumours by somatostatin receptor imaging, Lancet. 359 (2002) 761–763, https://doi.org/10.1016/s0140-6736(02)07846-7.

[83] Y. Jiang, G. Hou, W. Cheng, Performance of 68Ga-DOTA-SST PET/CT, octreoscan SPECT/CT and 18F-FDG PET/CT in the detection of culprit tumors causing osteomalacia: a meta-analysis, Nucl. Med. Commun. 41 (2020) 370–376, https://doi.org/10.1097/mnm.0000000000001163.

[84] M. Meyer, M. Nicod Lalonde, N. Testart, M. Jreige, C. Kamani, S. Boughdad, B. Muoio, F. Becce, N. Schaefer, C. Candrian, L. Giovanella, J.O. Prior, G. Treglia, M. Riegger, Detection rate of culprit tumors causing osteomalacia using somatostatin receptor PET/CT: systematic review and meta-analysis, Diagnostics (Basel) 10 (2019), https://doi.org/10.3390/diagnostics10010002.

[85] E. Pauwels, F. Cleeren, G. Bormans, C.M. Deroose, Somatostatin receptor PET ligands - the next generation for clinical practice, Am. J. Nucl. Med. Mol. Imaging 8 (2018) 311–331. DOI:.

[86] W.H. Chong, P. Andreopoulou, C.C. Chen, J. Reynolds, L. Guthrie, M. Kelly, R. I. Gafni, N. Bhattacharyya, A.M. Boyce, D. El-Maouche, D.O. Crespo, R. Sherry, R. Chang, F.M. Wodajo, G.B. Kletter, A. Dwyer, M.T. Collins, Tumor localization and biochemical response to cure in tumor-induced osteomalacia, J. Bone Miner. Res. 28 (2013) 1386–1398, https://doi.org/10.1002/jbmr.1881.

[87] S.J. Rayamajhi, R. Yeh, T. Wong, S. Dumeer, B.R. Mittal, F. Remotti, I. Chikeka, A. K. Reddy, Tumor-induced osteomalacia - current imaging modalities and a systematic approach for tumor localization, Clin. Imaging 56 (2019) 114–123, https://doi.org/10.1016/j.clinimag.2019.04.007.

[88] C.B. Johnbeck, U. Knigge, A. Loft, A.K. Berthelsen, J. Mortensen, P. Oturai, S. W. Langer, D.R. Elema, A. Kjaer, Head-to-head comparison of (64)Cu-DOTATATE and (68)Ga-DOTATOC PET/CT: a prospective study of 59 patients with neuroendocrine tumors, J. Nucl. Med. 58 (2017) 451–457, https://doi.org/10.2967/jnumed.116.180430.

[89] C. Lapa, F. Genest, A.K. Buck, K. Herrmann, W. Kenn, M. Rudert, F. Jakob, L. Seefried, Diagnostic findings and treatment in a 51-year-old woman with oncogenic osteomalacia, J. Clin. Endocrinol. Metab. 99 (2014) 385–386, https://doi.org/10.1210/jc.2013-3980.

[90] P. Andreopoulou, C.E. Dumitrescu, M.H. Kelly, B.A. Brillante, C.M. Cutler Peck, F. M. Wodajo, R. Chang, M.T. Collins, Selective venous catheterization for the localization of phosphaturic mesenchymal tumors, J. Bone Miner. Res. 26 (2011) 1295–1302, https://doi.org/10.1002/jbmr.316.

[91] L. Li, S.X. Wang, H.M. Wu, D.L. Luo, G.F. Dong, Y. Feng, X. Zhang, Acquired hypophosphatemic osteomalacia is easily misdiagnosed or neglected by rheumatologists: a report of 9 cases, Exp. Ther. Med. 15 (2018) 5389–5393, https://doi.org/10.3892/etm.2018.6106.

[92] A. Khosravi, C.M. Cutler, M.H. Kelly, R. Chang, R.E. Royal, R.M. Sherry, F. M. Wodajo, N.S. Fedarko, M.T. Collins, Determination of the elimination half-life of fibroblast growth factor-23, J. Clin. Endocrinol. Metab. 92 (2007) 2374–2377, https://doi.org/10.1210/jc.2006-2865.

[93] J. Dadoniene, M. Miglinas, D. Miltiniene, D. Vajauskas, D. Seinin, P. Butenas, T. Kacergius, Tumour-induced osteomalacia: a literature review and a case report, World J. Surg. Oncol. 14 (2016) 4, https://doi.org/10.1186/s12957-015-0763-7.

[94] E. Shiba, A. Matsuyama, R. Shibuya, K. Yabuki, H. Harada, M. Nakamoto, T. Kasai, M. Hisaoka, Immunohistochemical and molecular detection of the expression of FGF23 in phosphaturic mesenchymal tumors including the non-phosphaturic variant, Diagn. Pathol. 11 (2016) 26, https://doi.org/10.1186/s13000-016-0477-3.

[95] E. Hesse, H. Rosenthal, L. Bastian, Radiofrequency ablation of a tumor causing oncogenic osteomalacia, N. Engl. J. Med. 357 (2007) 422–424, https://doi.org/10.1056/NEJMc070347.

[96] A.H. Hautmann, M.G. Hautmann, O. Kölbl, W. Herr, M. Fleck, Tumor-induced osteomalacia: an up-to-date review, Curr. Rheumatol. Rep. 17 (2015) 512, https://doi.org/10.1007/s11926-015-0512-5.

[97] J. Seufert, K. Ebert, J. Müller, J. Eulert, C. Hendrich, E. Werner, N. Schuüze, G. Schulz, W. Kenn, H. Richtmann, K.D. Palitzsch, F. Jakob, Octreotide therapy for tumor-induced osteomalacia, N. Engl. J. Med. 345 (2001) 1883–1888, https://doi.org/10.1056/NEJMoa010839.

[98] A. Nair, S. Chakraborty, P. Dharmshaktu, N. Tandon, Y. Gupta, R. Khadgawat, P. K. Jabbar, C.S. Bal, S. Agarwal, M.A. Ganie, Peptide receptor radionuclide and octreotide: a novel approach for metastatic tumor-induced osteomalacia, J. Endocr. Soc. 1 (2017) 726–730, https://doi.org/10.1210/js.2016-1088.

[99] D. Ovejero, D. El-Maouche, B.A. Brillante, A. Khosravi, R.I. Gafni, M.T. Collins, Octreotide is ineffective in treating tumor-induced osteomalacia: results of a short-term therapy, J. Bone Miner. Res. 32 (2017) 1667–1671, https://doi.org/10.1002/jbmr.3162.

[100] Ultragenyx, Ultragenyx and Kyowa Kirin Announce U.S. FDA Approval of Crysvita® (Burosumab) for the Treatment of Tumor-induced Osteomalacia (TIO). https://www.globenewswire.com/news-release/2020/06/18/2050351/0/en/Ultragenyx-and-Kyowa-Kirin-Announce-U-S-FDA-Approval-of-Crysvita-burosumab-for-the-Treatment-of-Tumor-Induced-Osteomalacia-TIO.html, 2020. (Accessed 28 April 2021).

[101] CRYSVITA® (burosumab-twza), Prescribing Information. https://www.ultragenyx.com/file.cfm/29/docs/Crysvita_Full_Prescribing_Information.pdf, 2020. (Accessed 28 April 2021).

[102] Y. Imanishi, N. Ito, Y. Rhee, Y. Takeuchi, C.S. Shin, Y. Takahashi, H. Onuma, M. Kojima, M. Kanematsu, H. Kanda, Y. Seino, S. Fukumoto, Interim analysis of a phase 2 open-label trial assessing burosumab efficacy and safety in patients with tumor-induced osteomalacia, J. Bone Miner. Res. (2020), https://doi.org/10.1002/jbmr.4184.

[103] S.M. Jan de Beur, P.D. Miller, T.J. Weber, M. Peacock, K. Insogna, R. Kumar, F. Rauch, D. Luca, T. Cimms, M.S. Roberts, J. San Martin, T.O. Carpenter, Burosumab for the treatment of tumor-induced osteomalacia, J. Bone Miner. Res. (2020), https://doi.org/10.1002/jbmr.4233.

[104] A.L. Day, O.M. Gutiérrez, B.L. Guthrie, K.G. Saag, Burosumab in tumor-induced osteomalacia: a case report, Joint Bone Spine 87 (2020) 81–83, https://doi.org/10.1016/j.jbspin.2019.07.012.

[105] X. Li, Y. Jiang, L. Huo, H. Wu, Y. Liu, J. Jin, W. Yu, W. Lv, L. Zhou, Y. Xia, O. Wang, M. Li, X. Xing, Y. Chi, R. Jiajue, L. Cui, X. Meng, W. Xia, Nonremission and recurrent tumor-induced osteomalacia: a retrospective study, J. Bone Miner. Res. 35 (2020) 469–477, https://doi.org/10.1002/jbmr.3903.

[106] Z.J. Sun, J. Jin, G.X. Qiu, P. Gao, Y. Liu, Surgical treatment of tumor-induced osteomalacia: a retrospective review of 40 cases with extremity tumors, BMC Musculoskelet. Disord. 16 (2015) 43, https://doi.org/10.1186/s12891-015-0496-3.

[107] S. Qiu, L.L. Cao, Y. Qiu, P. Yan, Z.X. Li, J. Du, L.M. Sun, Q.F. Zhang, Malignant phosphaturic mesenchymal tumor with pulmonary metastasis: a case report, Medicine (Baltimore) 96 (2017) e6750, https://doi.org/10.1097/md.0000000000006750.

[108] R. Arai, T. Onodera, M.A. Terkawi, T. Mitsuhashi, E. Kondo, N. Iwasaki, A rare case of multiple phosphaturic mesenchymal tumors along a tendon sheath inducing osteomalacia, BMC Musculoskelet. Disord. 18 (2017) 79, https://doi.org/10.1186/s12891-017-1446-z.

[109] A. Verma, S. Tewari, A. Kannaujia, Perioperative management of patients with severe hypophosphataemia secondary to oncogenic osteomalacia: our experience and review of literature, Indian J. Anaesth. 61 (2017) 590–593, https://doi.org/10.4103/ija.IJA_57_17.

[110] S. Liu, X. Zhou, A. Song, Z. Huo, Y. Wang, Y. Liu, Surgical treatment of recurrent spinal phosphaturic mesenchymal tumor-induced osteomalacia: a case report, Medicine (Baltimore) 99 (2020), e18603, https://doi.org/10.1097/md.0000000000018603.

[111] X. Wang, J. Gao, S. Han, Y. Li, Spinal phosphaturic mesenchymal tumors: case report and literature review, J. Clin. Neurosci. 63 (2019) 234–239, https://doi.org/10.1016/j.jocn.2019.01.010.

[112] S. Cowan, S.A. Lozano-Calderon, R.N. Uppot, D. Sajed, A.J. Huang, Successful CT guided cryoablation of phosphaturic mesenchymal tumor in the soft tissues causing tumor-induced osteomalacia: a case report, Skelet. Radiol. 46 (2017) 273–277, https://doi.org/10.1007/s00256-016-2548-7.

[113] S. Jadhav, R. Kasaliwal, N.S. Shetty, S. Kulkarni, K. Rathod, B. Popat, H. Kakade, A. Bukan, S. Khare, S. Budyal, V.S. Jagtap, A.R. Lila, T. Bandgar, N.S. Shah, Radiofrequency ablation, an effective modality of treatment in tumor-induced osteomalacia: a case series of three patients, J. Clin. Endocrinol. Metab. 99 (2014) 3049–3054, https://doi.org/10.1210/jc.2013-4515.

[114] S.K. Mishra, M.S. Kuchay, I.B. Sen, A. Garg, S.S. Baijal, A. Mithal, Successful management of tumor-induced osteomalacia with radiofrequency ablation: a case series, JBMR Plus 3 (2019), e10178, https://doi.org/10.1002/jbm4.10178.

[115] S.H. Tella, H. Amalou, B.J. Wood, R. Chang, C.C. Chen, C. Robinson, M. Millwood, L.C. Guthrie, S. Xu, E. Levy, V. Krishnasamy, R.I. Gafni, M. T. Collins, Multimodality image-guided cryoablation for inoperable tumor-induced osteomalacia, J. Bone Miner. Res. 32 (2017) 2248–2256, https://doi.org/10.1002/jbmr.3219.

[116] S. Tutton, E. Olson, D. King, J.L. Shaker, Successful treatment of tumor-induced osteomalacia with CT-guided percutaneous ethanol and cryoablation, J. Clin. Endocrinol. Metab. 97 (2012) 3421–3425, https://doi.org/10.1210/jc.2012-1719.

[117] E.A. Imel, K.E. White, Pharmacological management of X-linked hypophosphataemia, Br. J. Clin. Pharmacol. 85 (2019) 1188–1198, https://doi.org/10.1111/bcp.13763.

[118] D. Haffner, F. Emma, D.M. Eastwood, M.B. Duplan, J. Bacchetta, D. Schnabel, P. Wicart, D. Bockenhauer, F. Santos, E. Levtchenko, P. Harvengt, M. Kirchhoff, F. Di Rocco, C. Chaussain, M.L. Brandi, L. Savendahl, K. Briot, P. Kamenicky, L. Rejnmark, A. Linglart, Clinical practice recommendations for the diagnosis and management of X-linked hypophosphataemia, Nat. Rev. Nephrol. 15 (2019) 435–455, https://doi.org/10.1038/s41581-019-0152-5.

[119] A. Linglart, M. Biosse-Duplan, K. Briot, C. Chaussain, L. Esterle, S. Guillaume-Czitrom, P. Kamenicky, J. Nevoux, D. Prié, A. Rothenbuhler, P. Wicart, P. Harvengt, Therapeutic management of hypophosphatemic rickets from infancy to adulthood, Endocr. Connect. 3 (2014) R13–R30, https://doi.org/10.1530/ec-13-0103.

[120] J.L. Geller, A. Khosravi, M.H. Kelly, M. Riminucci, J.S. Adams, M.T. Collins, Cinacalcet in the management of tumor-induced osteomalacia, J. Bone Miner. Res. 22 (2007) 931–937, https://doi.org/10.1359/jbmr.070304.

[121] J. Paul, K.E. Cherian, N. Kapoor, T.V. Paul, Treating osteoporosis: a near miss in an unusual case of FGF-23 mediated bone loss, BMJ Case Rep. 12 (2019), https://doi.org/10.1136/bcr-2018-228375.

[122] A. Bhan, S. Qiu, S.D. Rao, Bone histomorphometry in the evaluation of osteomalacia, Bone Rep. 8 (2018) 125–134, https://doi.org/10.1016/j.bonr.2018.03.005.

[123] G. Liamis, H.J. Milionis, M. Elisaf, Medication-induced hypophosphatemia: a review, QJM. 103 (2010) 449–459, https://doi.org/10.1093/qjmed/hcq039.

[124] M.C. Brennan, B. Clemens, B. Jenny, B. Alison, G.R. I, G. Lori, P.G. Z, M. Flora, S. E. Daniel, G.-P. Diana, H. Christine, G. Erica, I. Randi, C.M. T., Response of tumor-induced osteomalacia (TIO) to the FGFR inhibitor BGJ398, J. Clin. Oncol. 34 (2016), https://doi.org/10.1200/JCO.2016.34.15_suppl.e22500 e22500-e22500.

[125] I.R. Hartley, C.B. Miller, G.Z. Papadakis, C. Bergwitz, J. Del Rivero, J.E. Blau, P. Florenzano, J.A. Berglund, J. Tassone, K.L. Roszko, S. Moran, R.I. Gafni, R. Isaacs, M.T. Collins, Targeted FGFR blockade for the treatment of tumor-induced Osteomalacia, N. Engl. J. Med. 383 (2020) 1387–1389, https://doi.org/10.1056/NEJMc2020399.

[126] J.W. Foreman, Fanconi syndrome, Pediatr. Clin. N. Am. 66 (2019) 159–167, https://doi.org/10.1016/j.pcl.2018.09.002.

[127] P. Keefe, S.R.A. Bokhari, Fanconi Syndrome, StatPearls, Treasure Island (FL), 2020.