# Tumor-Induced Osteomalacia

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**Tumor-induced osteomalacia (TIO) is a rare paraneoplastic form of renal phosphate wasting that results in severe hypophosphatemia, a defect in vitamin D metabolism, and osteomalacia. This debilitating disorder is illustrated by the clinical presentation of a 55-year-old woman with progressive fatigue, weakness, and muscle and bone pain with fractures. After a protracted clinical course and extensive laboratory evaluation, tumor-induced osteomalacia was identified as the basis of her clinical presentation. In this article, the distinctive clinical characteristics of this syndrome, the advances in diagnosis of TIO, and new insights into the pathophysiology of this disorder are discussed.**

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## CASE PRESENTATION

Ms R, who is 55 years old, developed a rare disorder nearly 20 years ago that initially went undiagnosed for more than a year despite numerous physician visits. Since her initial diagnosis, Ms R receives medical therapy that has improved her symptoms; however, definitive therapy has been thwarted because the tumor causing her illness remains obscure.

DR JAN DE BEUR: Back in 1984, when you had onset of this disorder, what difficulties were you experiencing at that time?

MS R: Initially, I experienced pain on the bottom of my right foot that quickly progressed to pain in both feet. Within a month, the pain had progressed to my whole body and had intensified in severity.

DR JAN DE BEUR: What happened when you began seeking medical attention?

MS R: The initial diagnosis was "fallen arches." Then I was told that the excruciating muscle weakness and pain I was experiencing was stress-related. When I persisted, some blood work was sent but I was told that the blood work was "normal." At one point, when I became so debilitated and weak that I was unable to function well in my daily activities, I was given the diagnosis of conversion disorder.

DR JAN DE BEUR: How long did it take before a diagnosis was made?

MS R: Close to a year. I sought medical attention from a podiatrist, internists at 2 different institutions, a psychiatrist, and a family practitioner. I was hospitalized for several days but the evaluation was unrevealing.

DR JAN DE BEUR: What was the initial finding that suggested your diagnosis?

MS R: I saw a rheumatologist at an academic medical center who discovered that I had a low blood phosphorus level.

DR JAN DE BEUR: What were you treated with and how did you respond to treatment?

MS R: Initially, I was treated with phosphorus alone. Despite this treatment, the fractures I had sustained in my ribs and pelvis were not healing, my blood phosphorus was not improving, and my severe pain persisted. Once calcitriol was added to the phosphorus, my symptoms improved substantially within 6 months.

DR JAN DE BEUR: What has been the most difficult part of living with this rare disorder?

MS R: Initially, not knowing what was wrong with me and why I was in so much pain. I wondered if I was losing my mind. I had the sole responsibility for 2 children and I could not function well. I was worried about being able to care for them and for myself. Now, it is frustrating to know the diagnosis but not be able to definitively treat it.

DR JAN DE BEUR: Do you have anyone in your immediate or extended family with similar symptoms, unexplained broken bones, short stature, bowed legs, or low blood phosphorus?

MS R: No—both my sons are alive and well and more than 6 feet tall. There is no one else with low blood phosphorus. My sister and brother are alive and well, with normal height and normal blood phosphorus.

At 37 years of age, Ms R presented with abrupt onset of profound fatigue accompanied by bone pain that became progressive and debilitating. She sought medical attention but was told that her symptoms were psychological, and at one point, was diagnosed as having conversion disorder. Still undiagnosed, she experienced rib and pelvic fractures. Finally, after more than

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a year, an astute physician recognized the connection between her low serum phosphorus levels and her profound fatigue, weakness, bone pain, and fractures, and she was diagnosed as having osteomalacia. Medical therapy was initiated with oral phosphorus alone, with little improvement, then calcitriol was added and significant improvement in her symptoms followed. It was upon transferring her care when she moved to Baltimore, Md (more than 10 years after her original diagnosis) that the diagnosis was refined from osteomalacia to tumor-induced osteomalacia (TIO). The distinguishing clinical features that suggested TIO were the presence of renal phosphate wasting and an inappropriately low 1,25-dihydroxyvitamin D level before treatment with calcitriol. In an effort to locate and remove the causative tumor, Ms R has endured a series of disappointing tumor localization procedures and has had complications of the medical therapy for TIO. Extensive imaging, including octreotide scanning, has been unrevealing in locating the causative tumor. In pursuit of the tumor, she has undergone 2 surgeries—1 to remove a suspected sinus tumor and 1 to remove a suspected tumor near her thyroid. Neither surgery yielded the causative tumor or led to the remission of the biochemical manifestations of TIO. Ms R has experienced complications of long-term treatment with phosphorus and calcitriol; she has developed both nephrolithiasis and tertiary hyperparathyroidism. Currently, the location of Ms R's tumor is unknown.

On physical examination, her vital signs are normal; her height is 66 in. Her physical examination results are normal. In particular, she has no bowed legs or sequelae of rickets. She has no palpable masses with special attention to the extremity examination and oral cavity examination.

Ms R's laboratory evaluation before treatment included a normal calcium level of 8.4 mg/dL (2.1 mmol/L) (normal range, 8.4-10.5 mg/dL [2.1-2.6 mmol/L]), a normal creatinine level of 1.1 mg/dL (97 μmol/L), a low phosphorus level of 1.2 mg/dL (0.36 mmol/L)(normal range, 2.5-4.5 mg/dL [0.81-1.45 mmol/L]), an elevated alkaline phosphatase level of 137 U/L (normal range, 30-120 U/L), and an inappropriately low 1,25-dihydroxyvitamin D level of less than 5 pg/mL (normal range, 9-52 pg/mL). Her tubular reabsorption of phosphate was very low at 10% (normal range, 78%-98%), indicating renal phosphate wasting. Her 25-hydroxyvitamin D level was normal. Her intact parathyroid hormone (PTH) level, which was reportedly normal before initiation of therapy, was elevated at 124 pg/mL (normal range, 10-65 pg/mL) when she was evaluated in Baltimore, after she had been treated for several years. Fibroblast growth factor 23 (FGF-23) levels measured during treatment were markedly elevated at 3768 relative units/mL (normal range, 0-150 relative units/mL). Of note, Ms R had previously documented normal serum phosphorus levels.

## DISCUSSION

Ms R's case is instructive for 2 reasons: first, it shows that an internist should consider TIO in any patient with persistent, enigmatic bone pain accompanied by low serum phosphorus levels. Second, basic investigation of TIO is providing exciting breakthroughs in understanding of the pathogenesis of TIO and other metabolic disorders of phosphate homeostasis.

### Phosphate Homeostasis: Current Understanding

Phosphorus is a critical element in skeletal development, bone mineralization, membrane composition (phospholipids), nucleotide structure (adenosine triphosphate, which provides energy and serves as components of DNA and RNA), and cellular signaling (phosphorylated intermediates).

The serum phosphorus level is maintained within the normal range through a complex interplay among intestinal absorption, exchange with intracellular and bone storage pools, and renal tubular reabsorption. Hypophosphatemia stimulates calcitriol synthesis via 25-hydroxyvitamin D–1α-hydroxylase in the kidney, leading to increased calcium and phosphorus absorption in the intestine and enhanced mobilization of calcium and phosphorus from bone (FIGURE 1). The resultant increased serum calcium and increased calcitriol inhibit PTH secretion, with a subsequent increase in urinary calcium excretion and increased tubular reabsorption of phosphorus. Thus, normal serum calcium levels are maintained and serum phosphorus levels are returned to normal. In addition, hypophosphatemia is a potent stimulator of renal tubular reabsorption of phosphate.

The kidney is the principal organ that regulates phosphate homeostasis. Serum inorganic phosphorus is filtered by the glomerulus and 80% of the filtered load is reabsorbed predominantly along the proximal nephron. Regulation of proximal renal tubular reabsorption of phosphate is achieved through changes in the activity, number, and intracellular location of the brush border membrane type IIa sodium-phosphate cotransporter ($NaP_iIIa$).

Parathyroid hormone is the best-characterized physiological regulator of phosphorus reabsorption, but its principal function is to maintain calcium homeostasis. Parathyroid hormone increases urinary phosphate excretion via cyclic adenosine monophosphate–dependent inhibition of $NaP_iIIa$ expression. This effect is rapid and is achieved by internalization of $NaP_iIIa$ transporters from the brush border membrane and enhanced lysosomal degradation. However, this classic PTH–vitamin D axis does not account for all the complexities of phosphate homeostasis, and the study of renal phosphate-wasting syndromes has revealed several novel regulators.

### Tumor-Induced Osteomalacia

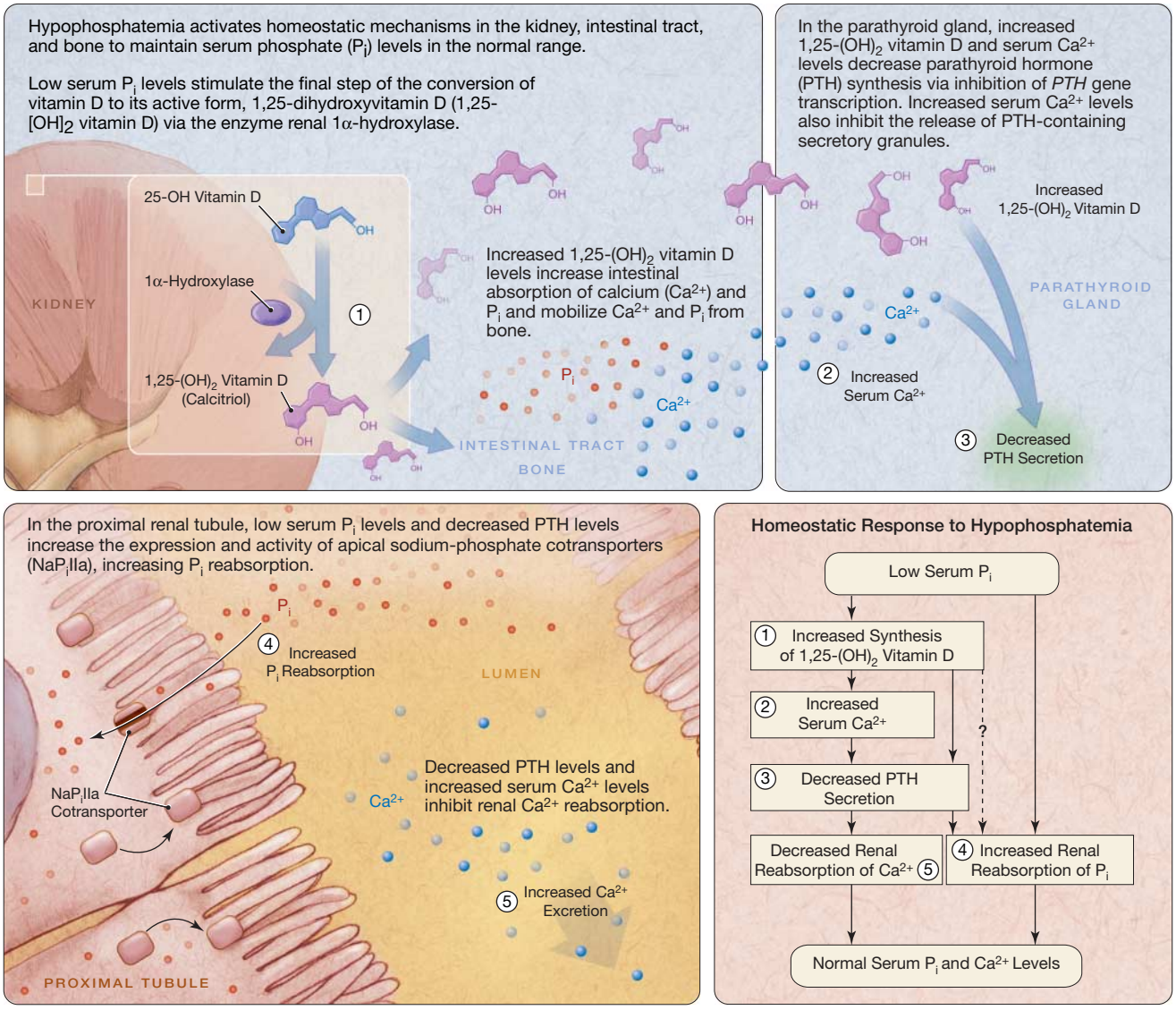
Tumor-induced osteomalacia, or oncogenic osteomalacia, is a paraneoplastic syndrome of renal phosphate wasting (FIGURE 2). Since the initial observation by McCrance,[1] clinical and ex-

perimental studies implicate the humoral factor(s) propagated by tumors in the profound biochemical and skeletal alterations observed in TIO. Tumor-induced osteomalacia is a rare disorder, with approximately 120 cases reported in the literature (undoubtedly, there are many more cases that have not been reported),[2] yet progress in understanding its pathogenesis is contributing to understanding of hypophosphatemic disorders and normal phosphate homeostasis.

## Clinical and Biochemical Features

As Ms R illustrates, most patients with TIO are adults who report long-standing, progressive muscle and bone pain, weakness, and fatigue that often predate the recurrent fractures that complicate TIO. When manifested in childhood, rachitic features including gait disturbances, growth retardation, and skeletal deformities are observed. The occult nature of TIO delays its recognition, and the average time from onset of symptoms to a correct diagnosis often exceeds 2.5 years.[2] Once the syndrome is recognized, inability to locate the underlying tumor[3] further delays definitive treatment by an average of 5 years. In Ms R's case, the tumor remains elusive to date, 19 years after the diagnosis. Until the causative tumor is identified, the diagnosis of TIO is presumptive and other renal phosphate-wasting syndromes must be considered. Therefore, it is important to note that in patients with TIO, a family history of hypophosphatemia and bone disorders is absent

**Figure 1.** Phosphate Homeostasis



and onset and severity of symptoms are more acute than in some other hypophosphatemic syndromes, such as X-linked hypophosphatemia (XLH). Identification of previously normal serum phosphorus levels in an adult patient supports the diagnosis of TIO, although in rare instances patients with autosomal dominant hypophosphatemic rickets (ADHR) may present in adulthood. In cases in whom inherited hypophosphatemic rickets must be excluded, genetic testing for mutations of the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome; defective in XLH) and the *FGF-23* gene (defective in ADHR) is useful. In the management of presumptive TIO, clinical diligence, serial physical examination, and appropriate imaging are required to successfully detect the causal tumor.

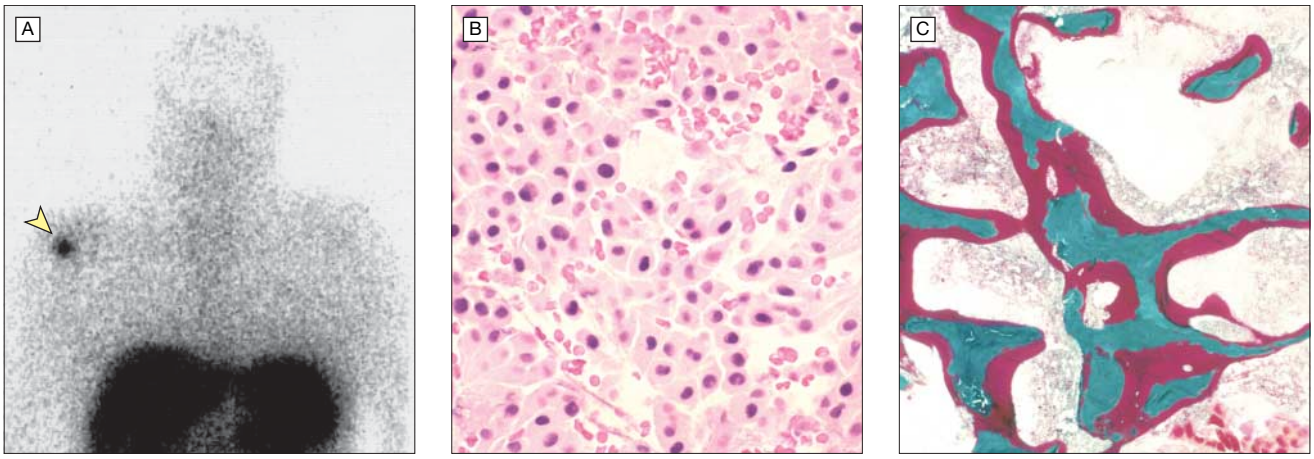
One of the major obstacles to diagnosing TIO is that serum phosphorus measurements are no longer included in the standard comprehensive metabolic panel. Therefore, hypophosphatemia is often not identified unless a physician orders a serum phosphorus measurement specifically. As demonstrated by Ms R, the biochemical hallmarks of TIO are low serum concentrations of phosphorus, phosphaturia secondary to reduced proximal renal tubular phosphorus reabsorption, and frankly low or inappropriate normal levels of serum calcitriol (1,25-dihydroxyvitamin D) that should be elevated in the face of hypophosphatemia. The degree of hypophosphatemia is usually profound and can range from 0.7 to 2.4 mg/dL.[2] Serum calcium and 25-hydroxyvitamin D levels are normal and serum concentrations of intact PTH are only occasionally elevated. Serum alkaline phosphatase is typically elevated and is primarily derived from bone. In TIO, a more global proximal tubular defect (known as Fanconi syndrome) that results in glucosuria and amino aciduria occasionally accompanies phosphaturia. Bone histomorphometry demonstrates osteomalacia, with clear evidence of a mineralization defect with increased mineralization lag time and excessive osteoid (unmineralized bone matrix) (Figure 2). The dual defect of renal phosphate wasting in concert with impaired calcitriol synthesis results in poor bone mineralization and, ultimately, fractures.[2,4] If untreated, severe osteomalacia may lead to fractures of the long bones as well as the vertebra and ribs, with resultant chest wall deformity and respiratory compromise.

## Diagnostic Evaluation

**Laboratory Studies.** The evaluation of suspected TIO consists of a battery of serum and urine measurements, including fasting serum phosphorus; a chemistry panel with serum calcium, alkaline phosphatase, and creatinine; intact PTH; serum 1,25-dihydroxyvitamin D (calcitriol); and fasting 2-hour urine phosphorus, creatinine, calcium, amino acids, and glucose. The best way to assess phosphate homeostasis is by calculating the maximum tubular resorption of phosphorus factored for glomerular filtration rate ($T_mP$/GFR). This represents the concentration above which most phosphate is excreted and below which most is absorbed. To calculate $T_mP$/GFR, the tubular reabsorption of phosphate is calculated first: 1 – urine phosphorus × serum creatinine/urine creatinine × serum phosphorus (all measured in milligrams per deciliter). With the tubular reabsorption of phosphate calculated and the serum phosphate measured, a nomogram is used to estimate $T_mP$/GFR.[5] When serum phosphorus is low, the $T_mP$/GFR should be relatively high. In renal phosphate wasting, the $T_mP$/GFR is lower than expected for a given serum phosphorus concentration.

In some instances, when confirmation of the diagnosis is warranted, a

**Figure 2.** Radiographic and Histologic Features of Tumor-Induced Osteomalacia




A, Octreotide scan demonstrating small mesenchymal tumor in the head of the humerus (arrowhead). B, Hemangiopericytoma with numerous pericytes and vascular channels (hematoxylin and eosin stain). Original magnification ×100. C, Bone biopsy with Goldner stain. Excessive osteoid or unmineralized bone matrix composed mainly of collagen stains pink. Mineralized bone stains blue. Normal bone usually has a very thin, barely visible layer of osteoid. The presence of excessive osteoid is indicative of osteomalacia. This bone biopsy demonstrates severe osteomalacia. Original magnification ×20.

tetracycline-labeled iliac crest bone biopsy is obtained for bone histomorphometric studies. Bone biopsy reveals prominent features of osteomalacia with increased unmineralized bone or osteoid surface and an increased mineralization lag time, as indicated by a reduced distance between the 2 tetracycline labels in the bone.

**Imaging.** Patients with TIO display radiographic features of osteomalacia including generalized osteopenia, pseudofractures, and coarsened trabeculae. Technecium Tc 99 bone scintigraphy demonstrates diffuse skeletal uptake, referred to as a "superscan," and focal uptake at sites of fractures. In general, plain films demonstrate features of osteomalacia; however, it is impossible to distinguish the underlying etiology of the osteomalacia with these modes.

Complete surgical resection cures TIO and, thus, underscores the importance of early detection and localization of the culprit tumor. Localization is often accomplished through serial physical examination with attention to palpable masses (especially in the extremities and the oral cavity) and appropriate imaging. The barrier to localization with conventional imaging techniques is that the tumors are often small, slow-growing, and frequently situated in unusual anatomical sites. Tumors associated with TIO are more commonly found in craniofacial locations and in the extremities; therefore, special attention to these areas is indicated when conventional imaging such as magnetic resonance imaging or computed tomography is used. In vitro studies demonstrate that some mesenchymal tumors express somatostatin receptors (SSTRs)[6] and, therefore, can be detected with a scanning technique that uses a radiolabeled somatostatin analog, indium In 111–pentetreotide scintigraphy (octreotide scan).[3,7] The mesenchymal tumors that express SSTRs are not limited to those associated with TIO; thus, careful biochemical confirmation of the syndrome is necessary before embarking on exhaustive imaging.[6] Some tumors associated with TIO do not express SSTRs and, therefore, are not localized by octreotide scanning. Successful tumor localization has been reported in a few patients with other imaging techniques, such as whole-body magnetic resonance imaging[8] and positron emission tomography.[9] In 1 instance, venous sampling for FGF-23 was used to confirm that a groin mass was the source of FGF-23 and, thus, the causative tumor in a patient with TIO.[10] Unfortunately, in Ms R, octreotide scanning, whole-body magnetic resonance imaging, and computed tomography have been unsuccessful in locating a tumor.

## Tumors

The mesenchymal tumors that are associated with TIO are characteristically slow-growing, complex, polymorphous neoplasms, which have been subdivided into 4 groups based on their histological features: (1) phosphaturic mesenchymal tumor, mixed connective tissue type (PMTMCT); (2) osteoblastoma-like tumors; (3) ossifying fibrous-like tumors; and (4) nonossifying fibrous-like tumors.[11] The PMTMCT subtype, which includes hemangiopericytomas, is the most common and comprises approximately 70% to 80% of the mesenchymal tumors associated with TIO.[11,12] Characterized by an admixture of spindle cells, osteoclast-like giant cells, prominent blood vessels, cartilage-like matrix, and metaplastic bone, these tumors occur equally in soft tissue and bone. Although typically benign, malignant variants of PMTMCT have been described.

## Differential Diagnosis

Osteomalacia in adults and rickets in children may arise from a variety of conditions, including abnormal vitamin D metabolism (which, in itself, has a long differential diagnosis), abnormal bone matrix, enzyme deficiencies (such as hypophosphatasia), inhibitors of mineralization (such as aluminum, fluoride, bisphosphonates), calcium or phosphorus deficiency, and renal phosphate wasting (such as cadmium, TIO, inherited hypophosphatemic rickets). Impaired renal phosphorus reabsorption is one common mechanism that leads to hypophosphatemia. Tumor-induced osteomalacia is a disorder of impaired renal phosphorus reabsorption; therefore, the discussion of the differential diagnosis will be focused on other renal phosphate-wasting disorders and differentiating them from TIO.

In contrast with more common forms of osteomalacia that share clinical features with TIO, patients with TIO have normal serum calcium, normal serum 25-hydroxyvitamin D, normal intact PTH, low 1,25-dihydroxyvitamin D, and inappropriately elevated urinary phosphorus (reduced tubular reabsorption of phosphorus) levels. With the appropriate battery of biochemical tests, TIO is readily distinguishable from the most common forms of osteomalacia; however, TIO is biochemically indistinguishable from several inherited forms of hypophosphatemic rickets, XLH and ADHR.[13] X-linked hypophosphatemia and ADHR typically present in childhood, although ADHR can exhibit a variable and delayed age of onset. This underscores the importance of eliciting a careful family history in patients with hypophosphatemia. In contrast with XLH, patients with TIO exhibit symptoms of weakness, pain, and fractures that are more severe, with rapid progression to disability. However, patients with adult-onset ADHR may present with severe pain and weakness. Stress and insufficiency fractures are a more prominent feature of TIO and lower-extremity deformity and short stature are characteristic of XLH and ADHR. When a definitive diagnosis is imperative, genetic testing of the *PHEX* and *FGF-23* genes, which are defective in XLH and ADHR, respectively, is commercially available. The definitive diagnosis of TIO is established by identification of the causative tumor and remission of the syndrome after complete tumor resection. The features that support the diagnosis of TIO in Ms R are an adult onset with previously documented normal serum phosphorus; prominent and progressive symptoms of pain, weakness, and fractures; absent family history of bone and mineral disorders; and the characteristic biochemical derangements (hypophosphatemia, hyperphosphaturia, low

calcitriol levels, and normal calcium and PTH levels).

Hereditary hypophosphatemic rickets with hypercalciuria, another inherited renal phosphate-wasting syndrome, is clinically similar to TIO, with bone pain, osteomalacia, and muscle weakness as prominent features, yet the distinction is easily made with biochemical testing. Both syndromes are characterized by hypophosphatemia secondary to impaired renal phosphorus reabsorption; however, patients with hereditary hypophosphatemic rickets with hypercalciuria exhibit elevated levels of calcitriol and hypercalciuria, which distinguish it from TIO, XLH, and ADHR.[13,14]

Recently, a new hypophosphatemic disorder was described in 2 individuals with mutations in the sodium-phosphate cotransporter gene (*NPT2*), which is the major sodium-phosphate cotransporter in the renal proximal tubule and is responsible for reabsorption of up to 85% of filtered phosphorus. The clinical consequences of these mutations are renal phosphate wasting, hypophosphatemia, and osteopenia or nephrolithiasis. The presence of hypercalciuria and elevated calcitriol make these patients easily distinguishable from patients with TIO.[15]

There are other disorders in which hypophosphatemia and renal phosphate wasting are part of a more global renal proximal tubular defect known as Fanconi syndrome. Global proximal tubular dysfunction is a manifestation of multiple myeloma, Wilson disease, and cystinosis.

## Pathophysiology

**Dual Defect: Renal Phosphate Wasting and Abnormal Vitamin D Metabolism.** The basic pathophysiology of TIO is hypophosphatemia secondary to inhibition of renal phosphorus reabsorption, which leads to hypophosphatemia compounded by a vitamin D synthetic defect that blocks the compensatory rise in calcitriol stimulated by the hypophosphatemia. Phosphate wasting and the defect in vitamin D synthesis in TIO are caused by a humoral-factor (or factors) produced by mesenchymal tumors, termed phosphatonin. Tumor extracts can inhibit phosphorus transport in vitro,[16-19] produce phosphaturia and hypophosphatemia in vivo,[20] and inhibit renal 25-hydroxyvitamin D–1α-hydroxylase activity in cultured kidney cells.[21] Further evidence that the tumor is the source of the humoral factor(s) that leads to the biochemical derangements is that complete surgical resection of tumor tissue results in normalization of serum phosphorus and calcitriol, reversal of renal phosphorus loss, and eventual remineralization of bone.[2,4]

***FGF-23*: Phosphatonin Front-Runner.** Initially, identifying phosphatonin was hampered by the slow growth of cultured tumor cells and the frequent loss of phosphate-inhibitory activity by tumor cells in culture. By adopting a new strategy of examining gene expression profiles of these tumors to identify highly and differentially expressed genes, I and other investigators[22-25] have identified several candidate genes for the phosphaturic substance produced by these tumors. Included among these genes is *FGF-23*, a member of the fibroblast growth factor family.

The *FGF-23* gene is expressed at very low levels in normal tissue but highly expressed in TIO tumors.[25-27] The FGF-23 protein can inhibit phosphorus transport in cultured renal proximal tubular epithelium[26,28] and reduces serum phosphorus and increases fractional excretion of phosphorus[25,29] when injected into mice. Mice chronically exposed to FGF-23 become hypophosphatemic with increased renal phosphorus clearance, demonstrate reduced bone mineralization, and have reduced expression of renal 25-hydroxyvitamin D–1α-hydroxylase with decreased circulating levels of calcitriol.[25] The biochemical and skeletal abnormalities of transgenic mice that overexpress FGF-23 mimic human TIO.[30,31] Conversely, FGF-23–deficient mice exhibit growth retardation and early death with biochemical abnormalities that include hyperphosphatemia, elevated calcitriol levels, and hypercalcemia.[32,33]

Circulating FGF-23 is detectable in human serum.[34,35] In most patients with TIO, serum levels of FGF-23 are elevated. In a few instances when both presurgical and postsurgical samples have been available, FGF-23 levels have plummeted after complete tumor resection. However, some individuals with TIO have normal levels or only mildly elevated levels, underscoring the heterogeneous composition of phosphatonin. Elevated serum FGF-23 levels are also observed in XLH, albeit to a more modest degree.[34,35]

FGF-23 is also central in the pathogenesis of an inherited renal phosphate wasting syndrome, ADHR. Missense mutations in 1 of 2 arginine residues at positions 176 or 179 have been identified in affected members of ADHR families.[36] These mutated arginine residues prevent the degradation of FGF-23, resulting in prolonged and/or enhanced FGF-23 action.[26,29,37-39]

Additional evidence suggests that FGF-23 may also be key in the pathogenesis of XLH. X-linked hypophosphatemia is caused by mutations in the *PHEX* gene,[40] which encodes an endopeptidase. Speculation about how loss of endopeptidase activity results in phosphate wasting has led to the hypothesis that FGF-23 is a substrate for *PHEX* and that failure to cleave FGF-23 prolongs or enhances its activity. Although there is disagreement in the literature, *PHEX* is thought to either directly[26,41] or indirectly[42,43] regulate FGF-23.

FGF-23 plays a central role in 4 distinct disorders of renal phosphate wasting (FIGURE 3). In TIO, tumors produce FGF-23, which then exerts its activity at the proximal renal tubule to inhibit tubular reabsorption of phosphorus and down-regulate 25-hydroxyvitamin D–1α-hydroxlase, resulting in hypophosphatemia and osteomalacia. In ADHR, *FGF-23* bears mutations that enhance its biological activity and render it resistant to proteolytic cleavage and, again, the result is hypophosphatemia, phosphaturia, bone deformity, and rickets. In XLH, mutated *PHEX* directly or indirectly leads to the accumulation of FGF-23 in the circulation and exerts its phospha-

turic activity at the renal proximal tubule. In some patients with polyostotic fibrous dysplasia who exhibit renal phosphate wasting, serum FGF-23 is elevated and correlates with the severity fibrous dysplastic skeletal involvement.[44] FGF-23 is not the only factor secreted by tumors in TIO that affects renal phosphate handling and bone mineralization.[45-48] Other compelling phosphatonin candidates have been identified and are the subject of ongoing research.

## Treatment

The definitive treatment for TIO is complete tumor resection. This results in rapid correction of the biochemical derangements and remineralization of bone.[49] As in the present patient, often the tumor remains obscure or incompletely resected and medical management becomes necessary.

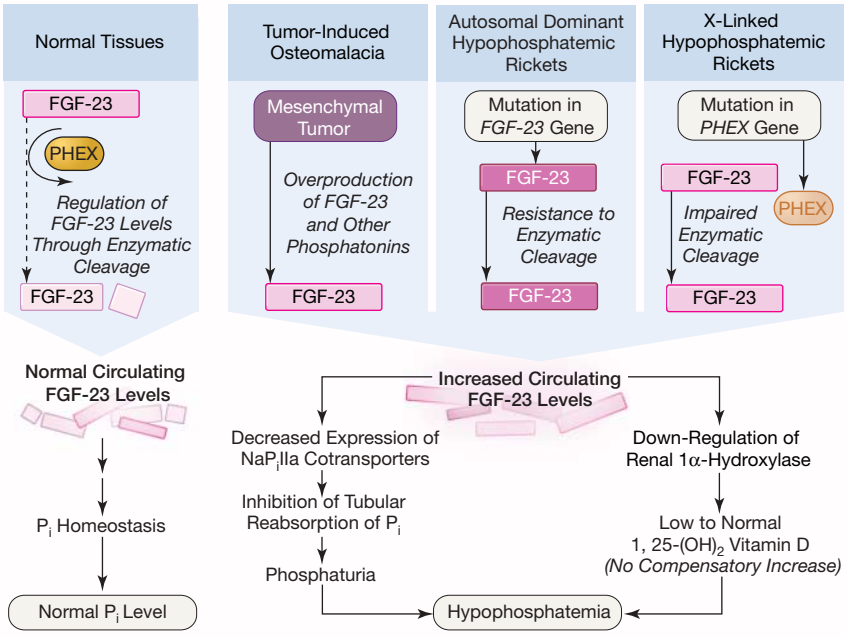
As demonstrated by Ms R, TIO is treated with phosphorus supplementation in combination with calcitriol. The phosphorus supplementation serves to replace ongoing renal phosphorus loss and the calcitriol supplements insufficient renal production of 1,25-dihydroxyvitamin D and enhances renal and gastrointestinal phosphorus reabsorption. Generally, patients are treated with phosphorus, 1 to 4 g/d, in divided doses and calcitriol, 1 to 3 µg/d.[2] In some cases, administration of calcitriol alone may improve the biochemical abnormalities seen in TIO and heal the osteomalacia.[50] Therapy and dosing should be tailored to improve symptoms, maintain fasting phosphorus in the low normal range, normalize alkaline phosphatase, and maintain PTH in the normal range without inducing hypercalcemia or hypercalciuria. Phosphorus supplementation should be accompanied by calcitriol treatment to avoid the development of secondary hyperparathyroidism. Although the mechanism is not well understood, it is thought that multiple doses of oral phosphate binds and transiently lowers serum calcium, leading to intermittent stimulation of the parathyroid glands. Prolonged stimulation of the parathyroid glands with unopposed phosphorus supplementation may ultimately lead to parathyroid autonomy and tertiary hyperparathyroidism. As in Ms R's case, appropriate treatment results in reduced muscle and bone pain and healing of the osteomalacia within several months.

Monitoring for therapeutic complications of high doses of calcitriol and phosphorus is important to prevent unintended hypercalcemia, nephrocalcinosis, and nephrolithiasis. To assess safety and efficacy of therapy, monitoring of serum calcium and phosphorus, urine calcium, renal function, serum alkaline phosphatase, and PTH is recommended at least every 3 months.

Unfortunately, Ms R has experienced a number of complications related to long-term therapy for TIO. She developed hypercalcemia and nephrolithiasis with transiently impaired renal function in the setting of escalating doses of calcitriol therapy. As a result of previous unopposed phosphorus supplementation, Ms R developed tertiary hyperparathyroidism that required subtotal parathyroidectomy.

Octreotide in vitro and in vivo has been shown to inhibit secretion of hormones by many neuroendocrine tumors. Some mesenchymal tumors express SSTRs that bind octreotide; this has provided the rationale for a therapeutic trial of octreotide in several patients with TIO and residual tumor. In 1 case, treatment with subcutaneous octreotide, 50 to 100 µg 3 times a day, resulted in correction of hypophosphatemia, improvement in phosphaturia, and reduction of alkaline phosphatase.[7] However, in 2 other patients, despite 8 weeks of treatment with subcutaneous octreotide, up to 200 µg 3 times daily, serum levels of phosphorus and calcitriol failed to increase serum phosphorus, and tubular reabsorption of phosphate remained depressed.[3] Given the limited and mixed experience with octreotide treatment in TIO, this therapy should be reserved for the most

**Figure 3.** Mechanisms of FGF-23 Excess in Renal Phosphate-Wasting Syndromes




In tumor-induced osteomalacia, fibroblast growth factor 23 (FGF-23) and other phosphatonins ectopically produced by a mesenchymal tumor lead to excess circulating FGF-23 levels. In autosomal dominant hypophosphatemic rickets, FGF-23 excess results from mutations in the *FGF-23* gene that render the protein resistant to cleavage and inactivation. In X-linked hypophosphatemia, the mechanism of FGF-23 excess is more speculative; mutations in the *PHEX* endopeptidase (presumably located on osteoblasts or osteocytes), are thought to either directly or indirectly result in FGF-23 excess by interfering with processing and inactivation of FGF-23.

severe cases that are refractory to current medical therapy.

## CONCLUSION

In conclusion, TIO is a rare disorder that presents with muscle weakness, bone pain, and osteomalacia (and ultimately, if left untreated, fractures). Because the symptoms are often nonspecific and because phosphorus measurement is no longer on routine chemistry panels, astute physicians must consider measuring serum phosphorus in patients with enigmatic bone pain, muscle weakness, and fractures. Tumor-induced osteomalacia is usually caused by benign mesenchymal tumors and cure can be achieved by complete resection of these tumors; therefore, localizing the tumor is of paramount importance.

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