Tumor-Induced Osteomalacia

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1. Clinical description and evaluation

Disease phenotype

Tumor-induced osteomalacia (TIO) is a rare syndrome (about 350 such cases have been described), characterized by hypophosphatemia, increased urinary losses of phosphate as a result of reduced tubular phosphate reabsorption, reduced or inappropriately normal concentrations of 1,25-dihydroxyvitamin D, normal parathyroid hormone concentrations, rickets or osteomalacia which are caused by substances (generally, fibroblast growth factor-23, FGF-23, and more rarely other peptides) elaborated by mesenchymal tumors (1–8). Patients manifest symptoms of osteomalacia or rickets with bone pain and proximal muscle weakness. Sometimes the causal tumors are readily visible or palpable on physical examination, but more often the tumors are small and very difficult to detect. Removal of the tumor results in reversal of the biochemical abnormalities, thereby demonstrating that the tumors produce a substance which alters phosphate homeostasis.

Key biochemical abnormalities seen in the syndrome of TIO are shown in Table 1. As shown, these include hypophosphatemia, normal or low serum calcium concentrations, normal parathyroid hormone concentrations, normal 25-hydroxyvitamin D concentrations, inappropriately low 1,25-dihydroxyvitamin D concentrations, normal renal function, elevated fractional excretion of phosphorus or a low TMP/GFR and generally elevated serum FGF-23 concentrations. Most, but not all, patients with TIO have elevations in serum FGF-23 concentrations (9, 10). Patients generally have osteomalacia or rickets noted on skeletal radiography (Figure 1A) although the findings can often be quite subtle or absent.

Disclosures: Drs. Kumar, Folpe and Mullan have nothing to disclose.
Bisphosphonate technetium 99 scans reveal the presence of fractures in various bones in severe cases (Figure 1B). Bone biopsy followed by staining of the bone core with Goldner’s stain shows an increase in the amount of osteoid (osteoid stains orange whereas bone stains green) in a patient with osteomalacia (compare the left top panel of Figure 2 with the right top panel of Figure 2) (11). When bone is examined by fluorescence microscopy following the administration of two sequential tetracycline doses to label the mineralization front, normal bone exhibits two distinct fluorescent labels separated by unlabeled osteoid (bottom left panel of Figure 2) (11). In patients with osteomalacia or rickets in whom mineralization is impaired, sequentially administrated tetracycline labels are not separated from one another, or are separated by a smaller distance than normal, thus indicating a failure in mineralization (lower right panel Figure 2) (7, 11).

TIO can be distinguished from other forms of hypophosphatemia by a combination of clinical findings and biochemical investigations (Table 1). Obtaining a family history is important in making a diagnosis, since several inherited disorders are also associated with hypophosphatemia. Acquired disorders presenting with hypophosphatemia and osteomalacia or rickets include nutritional vitamin D deficiency, nutritional phosphorus deficiency or a severe Fanconi syndrome. Nutritional vitamin D deficiency can be readily distinguished from TIO by the presence of low serum calcium concentrations, low 25-hydroxyvitamin D concentrations (generally less than 10 ng/mL (25 nmol/L)), elevated parathyroid hormone concentrations and low urinary calcium excretion (12–14). There are no reports of FGF-23 concentrations in patients with pure nutritional vitamin D deficiency, although rickets secondary to calcium-deficiency in Gambia are associated with elevated FGF-23 concentrations (15). Patients with vitamin D deficiency are hypophosphatemic on account of secondary hyperparathyroidism and urinary phosphate wasting (the tubular maximum of phosphorus is increased and fractional excretion of phosphorus is elevated). In addition, these subjects have reduced absorption of phosphorus in the intestine. A nutritional history may reveal a very low vitamin D intake. More usually, these subjects have disorders of fat absorption seen in the context of various malabsorption syndromes. Nutritional phosphate deficiency is associated with elevated 1, 25-dihydroxyvitamin D concentrations, a low normal parathyroid hormone concentration, elevated urinary calcium excretion and low urinary phosphate excretion (a low fractional excretion of phosphorus or an elevated tubular maximum for phosphate per GFR) (12, 16). There are no reports of FGF-23 concentrations in patients with pure phosphate deficiency, although perhaps those administered a low phosphate diet can have low FGF-23 concentrations (17). The Fanconi syndrome associated with light chain deposition in the kidney can often manifest with laboratory findings similar to that of TIO (18). Anemia and the elevated excretion of light chains and amino acids differentiate the acquired Fanconi syndrome from TIO. In post-transplant hyperparathyroidism, serum calcium concentrations are generally elevated, as are concentrations of parathyroid hormone (19–28). 25-Hydroxyvitamin D is normal and 1,25-dihydroxyvitamin D is at the upper end of the normal range or frankly elevated. The fractional excretion of phosphorus is increased, and TMP/GFR is diminished. In some instances, FGF 23 concentrations are elevated in hypophosphatemic patient’s following renal transplantation (22, 24, 28).

Transl Endocrinol Metab. Author manuscript; available in PMC 2015 October 14.
Amongst the inherited disorders associated with hypophosphatemia, X-linked hypophosphatemic rickets (XLH), autosomal dominant hypophosphatemic rickets (ADHR), and autosomal recessive hypophosphatemic rickets (ARHR) (Table 2), have a biochemical phenotype identical to that of TIO. A positive family history differentiates affected subjects from those with TIO. FGF-23 concentrations are generally elevated to a variable degree in patients with XLH and ARHR (10, 29, 30). Patients with vitamin D hydroxylation-deficient rickets, type 1A (also known as vitamin D-dependency rickets type 1A), vitamin D hydroxylation-deficient rickets, type 1B (also known as vitamin D-dependency rickets type 1B), and vitamin D-dependency rickets, type 2A, manifest hypophosphatemia (Table 2). These patients have secondary hyperparathyroidism and renal phosphate wasting due to increases in parathyroid hormone and a lack of vitamin D function resulting in reduced phosphate uptake from the intestine. Patients with VDDR 1A have undetectable 1,25-dihydroxyvitamin D concentrations whereas patients with VDDR 1B have diminished concentrations of 25-hydroxyvitamin D. Patients with VDDR 2A and mutations in the vitamin D receptor, have elevated concentrations of 1,25-dihydroxyvitamin D. FGF-23 concentrations have not been measured in these conditions.

Tumor pathology

McCance first described TIO, although he did not appreciate that the material removed from his patient’s femur was a neoplasm (1). Prader and colleagues were the first to recognize a neoplasm as the cause of osteomalacia in their 1957 report of what they considered to be a giant cell reparative granuloma of the rib (2). During the subsequent two decades a modest numbers of TIO-associated mesenchymal tumors were reported, either as “garden variety” soft tissue and bone tumors of various types (e.g., hemangiopericytoma, hemangioma, giant cell tumor, osteoblastoma, etc) or in a simply descriptive fashion. In 1972 it began to be appreciated by certain investigators, most notably Evans and Azzopardi (4) and Olefsky et al (5) that TIO-associated mesenchymal tumors were quite distinctive, likely comprising an unrecognized histopathological entity. Weidner and Santa Cruz introduced the term “phosphaturic mesenchymal tumor, mixed connective tissue variant” (PMTMCT) for these morphologically unique lesions (31). Folpe and co-workers firmly established that over 90% of TIO-associated mesenchymal tumors represent a single histopathological entity, PMTMCT (32). PMTMCT are extremely rare tumors, which most often occur in middle-aged adults, in soft tissue, bone and sinonasal locations (32, 33). Extremely rare PMTMCT have been reported in infants (34). Most PMTMCT present as non-specific soft tissue or bone masses. Some tumors are highly calcified. Histologically, PMTMCT are characterized by a highly vascular proliferation of bland, spindled to stellate cells, which produce an unusual “smudgy” matrix (Figure 3). The vasculature of PMTMCT may be hemangiopericytoma-like, or may consist simply of numerous arborizing capillaries. The matrix of PMTMCT calcifies in a distinctive “grungy” or flocculent fashion, and may resemble primitive cartilage or osteoid (31–33). This calcification in turn appears to serve as a stimulus for the recruitment of osteoclasts, occasionally provokes a fibrohistiocytic reaction and/or aneurysmal bone cyst-like changes, and may undergo osseous metaplasia. A variable component of mature adipose tissue is also frequently present. Lesions occurring in the craniofacial sinuses are less likely to contain calcified matrix for unknown reasons (32), although typical PMTMCT may occur in these locations (35). Malignant PMTMCT show
frankly sarcomatous features, such as high nuclear grade, high cellularity, necrosis and elevated mitotic activity, resembling undifferentiated pleomorphic sarcoma (so-called “malignant fibrous histiocytoma”) in most instances (32). Although it is now clear that the overwhelming majority of cases of mesenchymal tumor-associated TIO are caused by PMTMCT, there are well-documented instances of TIO in patients with neurofibromatosis types 1 and 2 (36–38). Similarly, patients with polyostotic fibrous dysplasia of bone/McCune Albright syndrome may suffer from TIO (38–42). The risk of TIO rises in such patients with increasing tumor burden (41).

By immunohistochemistry, the cells of PMTMCT typically express FGF-23 and vimentin, in the absence of other markers (32). Unfortunately, at the present time commercially available FGF-23 antibodies applicable to formalin-fixed, paraffin-embedded (FFPE) tissues are not widely available. FGF-23 expression can be demonstrated by RT-PCR in FFPE tissues, both in PMTMCT with and without a clinical history of TIO (33). It must be recognized, however, that molecular methods for the detection of FGF-23 expression, such as RT-PCR and in situ hybridization, are exquisitely sensitive, and capable of detecting very low levels of FGF-23 mRNA present in non-PMTMCT, including occasional cases of fibrous dysplasia (41), aneurysmal bone cyst and chondromyxoid fibroma of bone (43). The absence of FGF-23 mRNA in a tumor indicates that other phosphaturic factors are the proximate cause of clinical hypophosphatemia. The presence of FGF-23 mRNA in mesenchymal tumors without overt clinical hypophosphatemia is difficult to interpret. In such instances, if serum FGF-23 concentrations are normal and there is no overt hypophosphatemia, it would be safe to assume that the tumor was producing insufficient FGF-23 to cause changes in serum phosphate. To date, a specific genetic mutation has not been identified in PMTMCT.

2. Investigations for diagnosis

Physical examination

Physical examination is generally not helpful unless profound osteomalacia is present in which case proximal muscle weakness may be noted. The tumors are generally small and difficult to identify on examination. Nevertheless, a diligent physical examination for small growths is useful, and in interrogation of the patient relative to the occurrence of new lumps or bumps is of value.

Laboratory investigations

Table 1 shows the essential biochemical features of TIO. Many of the laboratory investigations noted below are required to arrive at the correct diagnosis and localize the tumor. Localization is required for successful resection. Key measurements are determination of serum inorganic phosphorus, calcium, 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, parathyroid hormone, FGF-23, alkaline phosphatase, bone alkaline phosphatase, creatinine, sodium, potassium, chloride, bicarbonate, serum protein electrophoresis, and immunofixation for monoclonal proteins. Intact (whole molecule) or carboxyl-terminal fragments of FGF-23 can be measured in serum and tests for these forms of FGF-23 are available from commercial vendors. A comparison of intact and carboxyl-terminal assays shows that the intact assay has greater sensitivity in the hypophosphatemia
Serum carboxyl-terminal fragment FGF-23 measurements are commercially available through Mayo Medical Laboratories. In the urine, a urinalysis, urine microscopy, and a 24-hour urine collection for calcium, inorganic phosphorus and creatinine are required. The tubular maximum for phosphate/glomerular filtration rate should be estimated. Additionally, the urine should be tested for monoclonal proteins, and κ and λ light chains which are the most frequent cause of an acquired Fanconi-like syndrome. From the serum and urine phosphorus and creatinine determinations, the fractional excretion of phosphorus and the tubular reabsorption of phosphorus can be readily calculated (the fractional excretion of phosphorus, % = [urine phosphorus concentration in mg/dL x serum creatinine concentration in mg/dL] ÷ [plasma inorganic phosphorus concentration in mg/dL x urinary creatinine concentration in mg/dL] x 100). TMP/GFR can be calculated using nomograms (44). In a typical patient with TIO, low serum phosphate, normal to low calcium, normal PTH, low or inappropriately normal 1, 25-dihydroxyvitamin D, normal 25-hydroxyvitamin D, normal creatinine, normal electrolyte, elevated alkaline phosphatase (bone alkaline phosphatase), and elevated FGF-23 concentrations will be seen. There will be evidence of phosphate wasting in the form of increased urinary phosphate excretion per 24 hours, increased fractional excretion of phosphorus and a reduced tubular maximum for phosphate/glomerular filtration rate (TMP/GFR) (44–47). Bone biopsy (11) performed after tetracycline labeling of bone will show increased osteoid relative to mineralized bone and a reduced mineral appositional rate (Figure 2) (7).

**Radiological investigations**

Skeletal x-rays will demonstrate (in severe cases) evidence of osteomalacia and adults and rickets in children (Figure 1A). Since many tumors causing osteomalacia are small and difficult to locate, radiologic methods are often employed to localize the tumors. Several different methods have been used including magnetic resonance imaging (48–50), technetium 99m sestamibi scintigraphy (51–55), radiolabeled octreotide scanning (8, 56–61), and F-18 fluorodeoxyglucose positron emission tomography with computed tomography (8, 62–67). In some small series, authors have claimed sensitivities of 60–80% with radiolabeled octreotide scanning and PET/CT scanning. To our knowledge, no direct comparisons between the various techniques have been performed, and therefore, it is difficult to recommend one technique over another. In large part, the method used for detection of the tumor will depend upon methods available for imaging at a particular institution. However, in our hands whole-body magnetic resonance imaging (Figure 4A) together with technetium 99m sestamibi scintigraphy (Figure 4B) has proved successful in identifying many tumors. Furthermore, an advantage of these techniques is that they are relatively inexpensive and available in most medical centers.

**Venous sampling**

Venous sampling has been proposed as a method to localize a tumor secreting FGF 23 (68–71). While a gradient for FGF 23 is demonstrable in individuals who have known tumors that have been localized by other means, random venous sampling of different areas has not been successful in localizing tumors (68). Because of the attendant morbidity associated central venous sampling, this method cannot be recommended for purposes of detecting and localizing tumors.
In summary, a diagnosis of TIO should be considered in patients presenting with hypophosphatemia and excessive losses of phosphate in the urine. Following a careful history to assess the presence or absence of vitamin D or mineral deficiencies and malabsorption syndromes, a detailed family history is obtained. A careful physical examination is conducted to look for the presence of tumors in various regions. Biochemical testing noted in Table 1 is carried out. Radiological identification of the tumor with magnetic resonance scanning and technetium 99m sestamibi scanning is performed. Consideration should be given to using radiolabeled octreotide scanning or F-18 fluorodeoxyglucose/CT scanning in the event that magnetic resonance scanning and technetium 99m sestamibi scanning is unsuccessful.

3. Pathogenesis, including genetics, molecular, cellular, physiology and pathophysiological Mechanisms; animal models

A brief review of phosphorus homeostasis will be useful to appreciate abnormalities seen in the syndrome of tumor induced osteomalacia (TIO) and related hypophosphatemic disorders. It is important to appreciate that the intestine and kidney play key roles in the maintenance of phosphate homeostasis (Figure 5) (17, 72–74). In states of neutral phosphorus balance, the amount of phosphorus absorbed in the intestine equals the amount excreted in the urine. In states of phosphorus demand, such as occur following dietary phosphate restriction, a series of physiological adaptations shown in Figure 6, help bring concentrations of phosphorus and overall phosphorus homeostasis back to normal. In states of dietary phosphorus excess, a series of events occur that are the converse of those seen in phosphorus depletion. In addition, in states of dietary phosphate excess, physiological adaptations involving the release of substances from the intestine rapidly occur to inhibit renal phosphorus reabsorption (73, 74).

Patients with TIO have excessive renal losses of phosphate as a result of the production of factors by the tumor (the so-called “phosphatonin(s)” (7, 75). These factors not only directly inhibit the renal reabsorption of phosphate, but also inhibit the production of 1, 25-dihydroxyvitamin D thereby preventing the vitamin D-mediated up-regulation of intestinal phosphate absorption (76–83). Using a variety of methods, three phosphaturic substances specifically generated by tumors associated with TIO have been identified (77–81, 84–89). These are: Fibroblast growth factor-23 (FGF 23), secreted frizzled related protein-4 (sFRP-4) and matrix extracellular phosphoglycoprotein (MEPE). Infusions of these substances intravenously in rats increase urinary phosphate losses and cause hypophosphatemia (77, 78, 80, 85). Transgenic mice over-expressing FGF-23 are hypophosphatemic and mice in which the FGF 23 gene has been deleted manifest hyperphosphatemia (87, 89, 90). Renal phosphate losses occur as a result of the redistribution of the sodium-phosphate co-transporters in the proximal tubule. Additionally, at least two of these substances, namely, FGF 23 and sFRP-4, reduce 25-hydroxyvitamin D 1-hydroxylase activity (76, 87, 89, 90). FGF 23 appears to function in renal cells by binding to FGF receptors and a co-receptor molecule, klotho (91–93). Additional information from the examination of individuals with inherited rickets (XLH, ADHR and ARHR) establish a role for FGF-23 in the pathogenesis of hypophosphatemia, renal phosphate wasting, the
regulation of the 25-hydroxyvitamin D 1-hydroxylase, and in the causation of a mineralization defect (Figure 7).

4. Clinical management and current treatments

Resection of the tumor

Resection of the tumor (if it can be localized) with wide margins to ensure complete removal, is the most appropriate treatment. If successful, removal of the tumor is associated with a rapid return of serum phosphorus concentrations to normal, and a return of the elevated renal phosphorus excretion to normal (7). Elevated FGF 23 concentrations also return to normal (10, 94). Serum 1, 25-dihydroxyvitamin D concentrations also return to normal after successful removal of the tumor (7). It is therefore important to measure these variables prior to surgical resection and 24 and 48 hours following resection.

In some instances, the tumor recurs locally (7) and in other, rare instances, tumors metastasize (8, 32, 95).

Medical treatment

When the tumor cannot be localized, or when it is not amenable to complete resection, treatment with oral phosphate supplements and 1α, 25-dihydroxyvitamin D (calcitriol) or 1α-hydroxyvitamin D (alphacalcidol) is required. Phosphate supplements replace phosphorus lost in the urine. Generally, in our clinical care, we administer 1–3 g of elemental phosphorus per day. Four to six divided doses per day are recommended. It is generally prudent to start with 1 g of elemental phosphorus per day and build up the dose to 2–3 g per day because phosphate supplements often cause gastrointestinal distress and diarrhea. The addition of calcitriol (0.5–2 μg per day) is often necessary to increase the absorption of phosphorus in the intestine. With the combination of phosphorus and calcitriol, generally, serum phosphorus concentrations are normalized. However, hypercalcemia associated with calcitriol therapy can and does occur, and on occasion, is associated with untoward consequences such as a reduction in glomerular filtration rate. Therapy should be monitored by measuring serum phosphorus, calcium, parathyroid hormone and creatinine concentrations. Urinary calcium should also be monitored to forestall calcitriol toxicity. Skeletal x-rays and bone density measurements are useful to demonstrate healing of osteomalacia.

Octreotide therapy was reported to correct hypophosphatemia in one patient with TIO (96). Octreotide was administered subcutaneously at a dose of 50 μg three times a day for five days and then at a dose of 100 μg three times a day for eight days. Serum phosphorus concentrations rose and tubular wasting of phosphorus was ameliorated.

In an attempt to induce medical hypoparathyroidism, the calcium sensing receptor agonist, cinacalcet (Sensipar), has been recently used to treat two patients with TIO already on treatment with phosphorus and calcitriol (97). Following treatment, the tubular reabsorption of phosphorus increased along with serum phosphorus concentrations. A reduction in the requirement for phosphorus was noted.
5. Patient case histories to illustrate principles noted in 1–4

A 47-year-old male presented for evaluation of bone pain and recurrent fractures. Eight years prior to evaluation at the Mayo Clinic, he developed pain in the right knee. An x-ray and magnetic resonance evaluation found a ganglion cyst in the right leg. This was not removed surgically. Four years prior to evaluation, he spontaneously developed pain in the left ribs. There was no history of trauma at the time. A CT scan of the chest and abdomen performed elsewhere was negative. The pain diminished in six months. Three years prior to evaluation the patient developed right rib pain. The pain worsened. He also developed pain in the left hip. Two years prior to evaluation, a whole body radionuclide scan found four healing rib fractures and arthritis of the left ankle. Magnetic resonance imaging of the hips, pelvis, and ribs was not revealing of any specific lesion. Magnetic resonance imaging of the brain with and without contrast and a brain SPECT scan were all negative. Eighteen months prior to evaluation the patient had constant pain in the mid back, feet, ankles, and ribs. He could not walk or run without feeling pain. Sneezing caused severe rib pain. One year prior to evaluation the patient was noted to be hypophosphatemic. A PET scan was performed and was unrevealing. The patient was placed on calcitriol 0.25 mcg per day. He was started on Boniva once per month. Serum 25-hydroxyvitamin D levels were found to be low. The patient was given vitamin D 50,000 units once per week and was advised to stop the calcitriol. Evaluation for parathyroid disease was negative. A sestamibi parathyroid scan was negative. 24-hour urine tests were performed which suggested that the patient had a renal phosphate leak. He was restarted on calcitriol 0.5 mcg per day and calcium. With the calcitriol and subsequent institution of Neutra-Phos (2 g per day), the patient felt that his bone pain improved.

Examination of the patient was normal

Laboratory evaluation showed a normal hemoglobin, leukocyte count and platelet count. Serum sodium, potassium, chloride and bicarbonate were normal. Serum calcium was normal at 9.4 mg/dL (2.35 mmol/L) and phosphorus was low at 1.2 mg/dL (0.387 mmol/L). Serum albumin was 3.0 g/dL. Alkaline phosphatase was slightly elevated at 125 IU/L. Serum creatinine was 1.3 mg/dL (114.9 μmol/L). Parathyroid hormone concentration was 64 pg/mL (6.8 pmol/L) (normal 15–65 pg/mL; 1.6–6.9 pmol/L). Serum total 25-hydroxyvitamin D was 30 ng/mL (75 nmol/L) and 1, 25-dihydroxyvitamin D was inappropriately low at 22 pg/mL (52.9 pmol/L). Tubular reabsorption for phosphate was 46% (normal greater than 80%) and TMP/GFR was 0.6 (normal 2.6–4.5). Serum FGF-23 concentrations were elevated at 950 RU/mL (upper limit of normal 180 RU/mL).

The following laboratory examination was performed. Skeletal x-rays showed old fracture of the C7 and T1 spinous processes. Mild anterior wedging of multiple mid- and lower thoracic and L1 vertebral bodies, with reactive sclerosis adjacent to several vertebral endplates was observed. Healing bilateral rib fractures were present. Generalized osteopenia was noted. Stress fractures in the ilia near the lower SI joints could not be excluded. A whole body sestamibi scan demonstrated no evidence of abnormal radiotracer uptake. Magnetic resonance scanning of the head showed a 5 mm asymmetric focus of diminished enhancement within the left side of the pituitary gland compatible with a micro-adenoma.
disc extrusion at the C5 interspace indenting the right side of the cervical spinal cord was seen. MRI of the chest, abdomen and pelvis revealed a 3.2cm × 2.1cm × 3.8cm focal mass in the suprascapular notch of the right shoulder lying deep to the supraspinatus displacing it superiorly. This mass demonstrated a considerable amount of T1 signal but was not composed of fat; rather there was some enhancement with areas of non-enhancement similar to fluid. A small tract of nonenhancing fluid which dissects along the deep portion of the infraspinatus was also observed and considered likely to represent an intramuscular ganglion. Benign cystic change in the humeral head, compression of multiple thoracic vertebral bodies, and multiple left-sided rib fractures were seen. An old stress fracture of the left innominate bone extending into the inferior aspect of the SI joint and an acute or subacute stress fracture involving the right innominate bone extending to the right SI joint were also seen.

The right shoulder mass was biopsied using CT-guided techniques. Microscopic evaluation of tissue showed a mesenchymal tumor similar to those associated with phosphaturia. The mass was surgically excised one week later. 24 hours following surgery serum FGF-23 concentrations had returned to 80 RU/mL and serum phosphorus was 2.7 mg/dL (0.87 mmol/L).

The patient’s bone pain rapidly diminished and subsequently disappeared. The patient required continued therapy with phosphorus in diminishing amounts over the next two years. Calcitriol was continued at 1 μg/day for the next one year but then was decreased to 0.5 μg/day. Skeletal x-rays showed healing of fractures.

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Transl Endocrinol Metab. Author manuscript; available in PMC 2015 October 14.
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Figure 1.

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Figure 1A. Skeletal radiograph of the patient with nutritional osteomalacia. Note the presence of pseudofractures of the metatarsals (arrows).

Figure 1B. Technetium-99m methylene diphosphonate (Tc-99m MDP) bone scan of patient with osteomalacia. Note uptake over the ribs and sacro-iliac region.
Figure 2.
Photomicrograph of bone (Goldner's stain) showing normal bone (top left panel) and osteomalacic bone (top right panel) and normal mineralization (bottom left panel) and a mineralization defect (bottom right panel) after the administration of tetracycline labels.
Figure 3.
Low power photomicrograph (10x) of a phosphaturic mesenchymal tumor, showing the characteristic admixture of bland spindled cells, small blood vessels, adipocytes and calcified matrix.
High power photomicrograph (40x:) of a phosphaturic mesenchymal tumor, with an osteoclastic reaction to the distinctive calcified matrix produced by the lesional cells.
Figure 4A. Magnetic resonance scan of a patient with TIO. The arrow points to the tumor.

Figure 4B. Technetium 99m sestamibi scans of a patient with TIO (same patient as in figure 4B). Arrow and arrow head point to tumor.
Figure 5.
Phosphorus homeostasis in humans.
Figure 6.
Adaptations to changes in dietary phosphate intake.
Figure 7.
Mechanisms of hypophosphatemia in TIO and the inherited rickets
Table 1

Laboratory Evaluation and Outcomes in Patients with Hypophosphatemia.

| Clinical Condition                          | Serum or Urine Analyte or Test | Urine |
|--------------------------------------------|--------------------------------|-------|
|                                           | Pi    | Ca   | PTH | 25(OH)D | 1,25(OH)\(_2\)D | Cr | FGF-23 | Pi    | TmP/GFR | AA   |
| TIO (tumor induced osteomalacia)           | L     | N/L  | N   | L/N     | N               | N  | H/N    | N     | H       | L/V  |
| XLH (X-linked hypophosphatemic rickets)    | L     | N/L  | N   | L/N     | N               | N  | H/N    | H     | H       | L/V  |
| ADHR (autosomal dominant hypophosphatemic rickets) | L     | N/L  | N   | L/N     | N               | N  | H/N    | N     | H       | L/V  |
| ARHR (autosomal recessive hypophosphatemic rickets) | L     | N/L  | N   | L/N     | N               | N  | H/N    | N     | H       | L/V  |
| VDDR 1A (vitamin D dependency rickets, 1A) | L     | L    | H   | N      | L               | N  | ?      | L     | V       | L/V  |
| VDDR 1B (vitamin D dependency rickets, 1B) | L     | L    | H   | L      | N               | N  | ?      | L     | V       | L/V  |
| VDDR 2A (vitamin D dependency rickets, 2A) | L     | L    | H   | N      | H               | N  | ?      | L     | V       | L/V  |
| Dent's disease                            | L     | N/L  | N   | L/N     | N               | N  | ?      | V     | H       | L/V  |
| Nutritional Vitamin D Deficiency           | L     | L    | H   | L      | L/N             | N  | N      | L     | V       | L/V  |
| Nutritional Pi Deficiency                  | L     | N/L  | L   | N      | H               | N  | L/N    | H     | H       | N    |
| T\(^1\) HPT (primary hyperparathyroidism)  | L     | H    | H   | N      | H               | N  | H      | H     | L       | V    |
| Fanconi syndrome                          | L     | N/L  | N   | N      | L/N             | N  | ?      | V     | H       | L/V  |
| Post-transplant hyperparathyroidism        | L     | H    | H   | N/N    | N               | N  | occ    | H     | V       | L/V  |

Abbreviations: Ca = calcium; Pi = inorganic phosphorus; PTH = parathyroid hormone; 25(OH)D = 25-hydroxyvitamin D; 1,25(OH)\(_2\)D = 1, 25-dihydroxy vitamin D; FGF23 = fibroblast growth factor 23; TmP/GFR = tubular maximum for phosphorus/glomerular filtration rate; AA = urinary amino acids. H = high; L = low; N = normal.
Nomenclature and underlying pathophysiology of inherited rickets.

| Name                                           | Abbreviation | Name of mutated gene                                                                 | Mendelian Inheritance in Man (MIM), Online MIM link                                      |
|------------------------------------------------|--------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| X- linked hypophosphatemic rickets              | XLH          | PHEX, a phosphate regulating endopeptidase homologue located on the X chromosome. Mutations associated with elevated FGF-23, MEPE and sFRP-4. | MIM #307800, [http://www.ncbi.nlm.nih.gov/omim/307800](http://www.ncbi.nlm.nih.gov/omim/307800) |
| Autosomal dominant hypophosphatemic rickets     | ADHR         | FGF-23, fibroblast growth factor 23; mutant gene encodes protein that is proteolytically more stable than the native protein. | MIM #193100, [http://www.ncbi.nlm.nih.gov/omim/193100](http://www.ncbi.nlm.nih.gov/omim/193100) |
| Autosomal recessive hypophosphatemic rickets    | ARHR         | DMP1, dentin matrix protein 1. Mutations associated with elevated FGF-23.            | MIM #600980, [http://www.ncbi.nlm.nih.gov/omim/600980](http://www.ncbi.nlm.nih.gov/omim/600980) |
| Vitamin D hydroxylation deficient rickets 1A    | VDDR 1A      | CYP27B1, encodes the 25-hydroxyvitamin D 1-hydroxylase. Mutations associated with failure to form 1,25-dihydroxyvitamin D. | MIM #264700, [http://www.ncbi.nlm.nih.gov/omim/264700](http://www.ncbi.nlm.nih.gov/omim/264700) |
| Vitamin D hydroxylation deficient rickets 1B    | VDDR 1B      | CYP2A, encodes the vitamin D-25-hydroxylase. Mutations associated with failure to form 25-hydroxyvitamin D. | MIM #600081, [http://www.ncbi.nlm.nih.gov/omim/600081](http://www.ncbi.nlm.nih.gov/omim/600081) |
| Vitamin D dependency rickets 2A                 | VDDR2A       | VDR, encodes the vitamin D receptor. Mutations in the VDR are associated with resistance to 1,25-dihydroxyvitamin D. | MIM #277440, [http://www.ncbi.nlm.nih.gov/omim/277440](http://www.ncbi.nlm.nih.gov/omim/277440) |