Osteomalacia and rickets

Michael F. Holick

SECTION 16 METABOLIC BONE DISEASE

INTRODUCTION

Osteomalacia by definition means that osteoblasts have laid down a collagen matrix, but there is a defect in its ability to be mineralized. In children, a defect in the mineralization of the osteoid in the long bones and the failure or delay in the mineralization of endochondral new bone formation at the growth plate leads to the classic skeletal deformities of rickets. However, in adults, the mineralization defect takes on a different character due to the failure of mineralization of newly formed osteoid at sites of bone turnover of periosteal or endosteal apposition. Several causes of poor or absent skeletal mineralization can lead to both rickets and osteomalacia, which are reviewed in this chapter.

CALCIUM, PHOSPHORUS, AND VITAMIN D METABOLISM

The major components of skeletal mineral are calcium and phosphate. Thus any alteration in the calcium-phosphate product in the circulation can result in a mineralization defect of the skeleton. Vitamin D plays a critical role in maintaining both serum calcium and phosphate concentrations. Vitamin D is obtained by exposure of the skin to sunlight resulting in the conversion of 7-dehydrocholesterol to previtamin D3 (Fig. 199.1). Previtamin D3 being thermodynamically unstable is rapidly converted to vitamin D3. Once formed, vitamin D3 is ejected out of the epidermal cell into the extracellular space and, by diffusion, enters the circulation bound to the vitamin D binding protein (DBP). Vitamin D3 and vitamin D2 (D represents D2 or D3) in the diet are ingested, and the fat-soluble vitamins are incorporated into chylomicrons and absorbed into the lymphatics. The lymphatic drainage into the thoracic venous system permits the entrance of vitamin D into the circulation, where it is bound to the DBP and lipoproteins.

Vitamin D is converted in the liver by a vitamin D-25-hydroxylase (25-OHase) to form the major circulating form of vitamin D, 25-hydroxyvitamin D [25(OH)D]. There have been at least four different 25-OHases identified both in mitochondria and in microsomes. 1,2 25(OH)D is, however, biologically inert and requires hydroxylation in the kidneys on carbon 1 by the CYP27B mitochondrial enzyme 25-hydroxyvitamin D-1α-hydroxylase [1-OHase]. This results in the formation of 1α,25-dihydroxyvitamin D [1,25(OH)2D] which is the biologically active form of vitamin D responsible for regulating calcium and phosphorus homeostasis. 1,2 1,25(OH)2D enters the circulation and is bound to the DBP and travels to its target tissues. In the small intestine, 1,25(OH)2D interacts with its vitamin D nuclear receptor (VDR) that results in the expression of several gene products including the epithelial calcium channel, calbindin, and a calcium dependent ATPase (see Figure 199-1). 1,2,4 1,25(OH)2D increases the efficiency of intestinal calcium absorption. In a vitamin D deficient state, the small intestine is able to passively absorb about 10% to 15% of dietary calcium. Vitamin D sufficiency enhances the absorption of calcium in the small intestine to about 30% to 40%.1

1,25(OH)2D enhances the efficiency of intestinal calcium absorption principally in the duodenum and to a less of degree in the jejunum and ileum. 1,25(OH)2D also stimulates phosphate absorption in the jejunum and ileum. The small intestine passively absorbs about 60% of dietary phosphate. 1,25(OH)2D enhances the efficiency of phosphate absorption by an additional 20% to about 80%.1 When there is adequate calcium and phosphate in the diet and vitamin D sufficiency is present, the serum calcium normal range is approximately 8.6 to 10.2 mg/dL (mg%) and the serum phosphate level is approximately 2.5 to 4.5 mg/dL. It is the calcium × phosphate product in the circulation and in the extravascular space that plays a major role in the normal mineralization of osteoid laid down by osteoblasts.

Vitamin D effect on bone metabolism

It is known that both in rodents and humans that vitamin D is not necessary for the mineralization of the osteoid matrix. 3,8 This was demonstrated when vitamin D-deficient rats were either infused with calcium and phosphorus to maintain a normal calcium-phosphate product in the circulation or when they received a high-calcium lactose, high-phosphorus diet that maintained a normal serum calcium-phosphate product. In both circumstances, bone histology revealed that the mineralization occurred normally without any significant unmineralized osteoid. Vitamin D-resistant rickets patients have a mutation of their VDR and have severe rickets and osteomalacia. When these patients were infused with calcium and phosphorus to maintain a normal calcium-phosphate product, the unmineralized osteoid was mineralized. 6

1,25(OH)2D interacts with its VDR in osteoblasts to increase the expression of alkaline phosphatase, osteocalcin, and receptor activator of NFκB ligand (RANKL). 7 Alkaline phosphatase produced by osteoblasts is important in bone mineralization because patients with a decrease in the bone-specific alkaline phosphatase known as hypophosphatasia suffer from a mineralization defect of the osteoid. 8,9 Osteocalcin is the major noncollagenous protein in the skeleton. Although its function is not well understood, it appears to have a role in osteoclastic activity. 10 RANKL, once expressed on the surface of an osteoblast, interacts with its receptor RANK on osteoclast precursors. This intimate interaction leads to signal transduction that results in the formation of multinucleated mature osteoclasts. 1,7,10 These osteoclasts under the direction of a variety of cytokines 11 increase the resorption of bone in the skeleton by releasing hydrochloric acid to dissolve the

*This work was supported in part by National Institutes of Health grant 1ULIR025771 and the UV Foundation.
25-hydroxyvitamin D-24-hydroxylase (24-OHase) to catabolize 1,25(OH)\textsubscript{2}D and maintain neuromuscular function. Calcium and phosphorus levels promote the mineralization of the skeleton and thus vitamin D's effect on bone metabolism is to maintain a normal serum calcium and phosphorus levels. It accomplishes this by increasing intestinal calcium and phosphorus absorption and by mobilizing calcium and phosphorus from the skeleton.

CAUSES OF OSTEOMALACIA/RICKETS

Consequences of vitamin D deficiency on bone mineralization

It is usually assumed that when vitamin D deficiency occurs, it leads to hypocalcemia, which is therefore responsible for causing rickets in children and osteomalacia in adults. When a child or adult becomes vitamin D deficient, there is a decrease in the efficiency of intestinal calcium absorption that causes a transient decrease in the ionized calcium. This is recognized by the calcium sensor in the parathyroid glands, resulting in an increase in the expression and production of parathyroid hormone (PTH) [see Fig. 199.1]. PTH conserves calcium by increasing tubular reabsorption of calcium throughout the proximal tubule and finely controls tubular reabsorption in the distal convoluted tubule. When these actions are inadequate to maintain the blood ionized calcium levels, the PTH and 1,25(OH)\textsubscript{2}D will interact with their receptors to increase the expression of RANKL. Once the RANK on the preosteoclast binds RANKL, signal transduction results in the formation of a mature osteoblast. (From Holick MF. Copyright 2007. Reproduced with permission.)
bone chemistries show a low serum 25(OH)D (<20 ng/mL), elevated PTH, elevated or normal alkaline phosphatase level, and normal or low-normal serum calcium and phosphate levels. In young children with rickets due to vitamin D deficiency, they have 25(OH)D less than 20 ng/mL, elevated PTH, and alkaline phosphatase levels with low-normal or low serum calcium and phosphate (Table 199.1).8,14

**Calcium deficiency**

It is well documented especially in Africa, where children are exposed to sunlight daily, that they develop rickets caused by calcium deficiency.15 A diet poor in calcium will result in an increase in PTH levels, which causes hyperphosphaturia. Thus children living in Africa, India, and Bangladesh who ingest approximately 200 mg of calcium daily and who have a diet high in phytates and oxalates, which irreversibly bind calcium in the gut, preventing its absorption, will develop rickets and osteomalacia.15-23 They are usually vitamin D sufficient due to adequate sun exposure.

**Phosphate deficiency, heritable and acquired disorders**

Nutritional phosphate deficiency is uncommon because our diet is rich in phosphate. Human breast milk, cow’s milk, and infant formulas have enough phosphate to satisfy an infant’s requirement. However, several acquired and inherited disorders cause phosphate wasting into the urine and can lead to severe hypophosphatemia resulting in rickets and osteomalacia.15

X-linked hypophosphatemic rickets and autosomal dominant phosphatic rickets are caused by either an increase in the production of fibroblast growth factor 23(FGF23) and other phosphatonin or a decrease in their catabolism resulting in severe phosphate wasting into the urine. FGF23 produced by osteocytes causes an internalization of the Na-Pi co-transporter and phosphaturia.14 In addition, the elevated blood level of FGF23/phosphatonin inhibits the renal production of 1,25(OH)2D, thus diminishing both the efficiency of intestinal calcium and phosphate absorption.13,14,24-27

Oncogenic osteomalacia is due to a benign or malignant tumor production of FGF23/phosphatonin.28 The result is increased phosphate wasting into the urine causing severe hypophosphatemia. Because this disease is often seen in adults, no overt clinical skeletal manifestations of the osteomalacia occur other than the complaint of aches and pains in the bones and muscles and clinical observation of periosteal discomfort by applying pressure on the periosteum of sternum, radius, ulna, and anterior tibia. An x-ray of the skeleton may show osteopenia, and low bone mineral density is often detected by bone densitometry.29

**Fanconi syndrome and renal tubular acidosis**

Fanconi syndrome is a disorder of the renal proximal tubules resulting in decreased reabsorption of phosphorus, glucose, and amino acids.30 These findings are accompanied by metabolic acidosis secondary to proximal tubular bicarbonate wasting (type II renal tubular acidosis).31 Typically these patients have hypophosphatemia, hyperphosphaturia, and a low tubular maximum for inorganic phosphate. In addition, they have glycosuria and generalized amino aciduria, hypobicarbonatemia, and excessive bicarbonate excretion in the urine. The serum calcium is usually normal with an elevated alkaline phosphatase and a normal PTH and 25(OH)D but an inappropriately low or low-normal serum 1,25(OH)2D (see Table 199.1).32,33-35 Children with Fanconi syndrome have classic x-ray evidence of rickets, whereas adults have radiographic changes consistent with osteomalacia.33 As noted in Box 199.1, a multitude of acquired and heritable disorders can cause Fanconi syndrome.30 Patients who have hypophosphatemia in a fasting blood specimen should be evaluated for Fanconi syndrome and the underlying cause identified and either appropriately treated or the offending agent removed.30

**Aluminum**

Aluminum-containing antacids were routinely used to prevent phosphate absorption in patients with chronic kidney disease. It was
## TABLE 199.1 BIOCHEMISTRIES OF OSTEOMALACIA/RICKETS

<table>
<thead>
<tr>
<th>Deficiencies</th>
<th>Ca</th>
<th>PO₄</th>
<th>25(OH)D</th>
<th>1,25(OH)₂D</th>
<th>PTH</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>vitamin D deficiency</td>
<td>≈↓</td>
<td>or N</td>
<td>↓ or N</td>
<td>↑ or N</td>
<td>↑</td>
<td>Alk Phos</td>
</tr>
<tr>
<td>Calcium-deficiency diet</td>
<td>↓</td>
<td>or N</td>
<td>↓ or N</td>
<td>↑ or N</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>Kidney disease</td>
<td>↓</td>
<td>or N</td>
<td>N or ↓</td>
<td>↓ or N</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>1α hydroxylase deficiency pseudo vitamin D deficiency rickets</td>
<td>↓</td>
<td>or N</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td></td>
</tr>
<tr>
<td>VDR defect vitamin D resistant rickets</td>
<td>↓</td>
<td>or N</td>
<td>N</td>
<td>↑↑↑</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

### Hypophosphatemia

<table>
<thead>
<tr>
<th>Deficiencies</th>
<th>Ca</th>
<th>PO₄</th>
<th>25(OH)D</th>
<th>1,25(OH)₂D</th>
<th>PTH</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-linked hypophosphatemic rickets</td>
<td>N</td>
<td>↓↓</td>
<td>N</td>
<td>or low N</td>
<td>N</td>
<td>↑FGF23/phosphatonin</td>
</tr>
<tr>
<td>Autosomal-dominant hypophosphatemic rickets</td>
<td>N</td>
<td>↓↓</td>
<td>N</td>
<td>or low N</td>
<td>N</td>
<td>↑FGF23/phosphatonin</td>
</tr>
<tr>
<td>Autosomal-recessive hypophosphatemic rickets</td>
<td>N</td>
<td>↓↓</td>
<td>N</td>
<td>or low N</td>
<td>N</td>
<td>↑FGF23/phosphatonin</td>
</tr>
<tr>
<td>Oncogenic osteomalacia</td>
<td>N</td>
<td>↓↓</td>
<td>N</td>
<td>or low N</td>
<td>N</td>
<td>↑FGF23/phosphatonin</td>
</tr>
<tr>
<td>“Hereditary hypophosphatemic rickets with hypercalcioria,” NaPi2c mutation</td>
<td>N</td>
<td>↓↓</td>
<td>N</td>
<td>↑ or N</td>
<td>N</td>
<td>↑Urinary calcium</td>
</tr>
<tr>
<td>Renal phosphate loss (including Fanconi syndrome, Dent disease, cadmium toxicity, heavy metal poisoning)</td>
<td>N</td>
<td>↓↓</td>
<td>N</td>
<td>N or low N</td>
<td>N</td>
<td>↑Urinary phosphate</td>
</tr>
</tbody>
</table>

### Toxicities

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>Ca</th>
<th>PO₄</th>
<th>25(OH)D</th>
<th>1,25(OH)₂D</th>
<th>PTH</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoride</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↑Fluoride bone bx</td>
</tr>
<tr>
<td>Etidronate</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>or low N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Parenteral aluminum</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>or ↓</td>
<td>N or ↑</td>
<td>Aluminum staining bone box</td>
</tr>
<tr>
<td>Hypophosphatia</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓Alk phos</td>
</tr>
<tr>
<td>Acidosis</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N or low N</td>
<td>N</td>
<td>Low N</td>
</tr>
</tbody>
</table>

## BOX 199.1 DISORDERS ASSOCIATED WITH FANCONI SYNDROME

### Acquired
- Vitamin D deficiency
- Multiple myeloma
- Lymphoma
- Light chain nephropathy
- Amyloidosis
- Sjögren syndrome
- Neprotic syndrome
- Renal transplantation
- Balkan nephropathy
- Paroxysmal nocturnal hemoglobinuria
- Interstitial nephritis/uveitis syndrome
- Renal vein thrombosis

### Heritable
- X-linked hypophosphatemic rickets
- Autosomal dominant hypophosphatemic rickets
- Cystinosis
- Lowe syndrome
- Hereditary fructose intolerance
- Tyrosinemia
- Galactosemia
- Glycogen storage disease
- Wilson disease
- Cytochrome oxidase deficiency
- Subacute necrotizing encephalomyelopathy
- Alport syndrome
- Leigh syndrome
- Franconi-Bickel syndrome
- Dent disease
- GRACILE syndrome
- Rod-cone dystrophy, sensorineural deafness, and renal dysfunction
- Pearson syndrome

### Drugs
- Ifosfamide
- Methy-3-chromone
- 6-Mercaptopurine
- Gentamicin
- Valproic acid
- Streptozocin
- Isophthalanilide
- Cephalothin
- Outdated tetracycline

### Heavy Metals
- Cadmium
- Lead
- Mercury
- Uranium
- Platinum
- Copper
- Bismuth

### Other
- Paraquat
- Lysol
- Toluene inhalation
observed in patients who were taking aluminum antacids or who were being dialyzed with water containing a high aluminum content that they developed osteomalacia.\textsuperscript{1,34} Aluminum is a trivalent cation that in low concentrations stimulates osteoblastic activity. However, at higher concentrations, it will inhibit PTH release and 1-OHase activity. It also inhibits osteoblastic activity at high concentrations and is deposited on the mineralizing surface of the skeleton, preventing further mineralization of osteoid. These patients often have little osteoblastic or osteoclastic activity resulting in inactive bone remodeling or complete absence of bone remodeling known as \textit{adynamic bone disease} (see Chapter 201). A bone biopsy that demonstrates stainable aluminum on the mineralization surface helps to make the diagnosis of aluminum-induced osteomalacia.\textsuperscript{1,34}

Patients who are on total parenteral nutrition (TPN) or hemodialysis where the water is not monitored for aluminum content are at high risk for this aluminum metabolic bone disease. In addition, patients on TPN have been exposed to high aluminum from casein hydrolysate solutions. As a result, hemodialysis baths are now free of aluminum contamination, as are TPN solutions. Aluminum-based phosphate binding agents for patients with chronic kidney disease have been replaced with either calcium carbonate or resins that bind phosphate.\textsuperscript{1,34}

### Heavy metals

Several heavy metals can cause phosphaturia.\textsuperscript{1,8,15,35,36} Cadmium exposure causes Itai-Itai disease (see \url{http://www.kanazawa-med.ac.jp/~pubhealt/cadmium2/itaiitai-e/itai01.html} accessed October 2, 2009). High cadmium exposure has wide-ranging pathologic effects on the body including the damage of the glomerulus and renal tubular function. Besides leading to renal failure, it initially causes proteinuria and phosphaturia.\textsuperscript{15}

### Fluoride

Fluoride is well known to stimulate osteoblastic activity in low concentrations. Fluoride has been effective in preventing dental caries in part because the fluoride is incorporated into the dentin, reducing dental caries activity.\textsuperscript{15} At high concentrations, however, fluoride not only stimulates osteoblastic activity but gets incorporated into the skeleton as a calcium fluoride hydroxyapatite crystal. Because fluoride has a larger atomic weight than the OH that it replaces, the skeleton appears on x-ray to be hyperdense and there is a substantial increase in bone mineral density on bone densitometry. It is well documented that ingestion of food and water with a high fluoride content between 3 and 16 ppm is associated with increased bone mineral density that leads to stiffness, rigidity, and limitation of movement at the spine and can also lead to skeletal deformities and fractures (Fig. 199.4).\textsuperscript{1,8,15,37-39}

Certain populations including children in India who are exposed to high dietary fluoride and are on a low-calcium diet can develop severe skeletal deformities.\textsuperscript{15,40-42} These children have classic features of rickets at their epiphyseal plates and osteomalacia with Looser zones. Histologically, the bone biopsy shows widened osteoid seams, poorly mineralized new bone formation, and areas of hypermineralization.\textsuperscript{15}

### Drugs

A wide variety of drugs can cause rickets and osteomalacia.\textsuperscript{1,8,15} Children and adults who are institutionalized and on several antiseizure medications often develop rickets/osteomalacia.\textsuperscript{1,14,15,43-44} It is now recognized that not only antiseizure medications but glucocorticoids, medications used to treat infection with human immunodeficiency virus (HIV), and even St. John’s Wort can cause vitamin D deficiency and resulting rickets and osteomalacia. It has been demonstrated that antiseizure medications, HIV medications, glucocorticoids, and other drugs interact with the steroid xenobiotic receptor, which binds to retinoic acid X receptor. This complex is recognized by the vitamin D responsive element for the 25-hydroxyvitamin D-24 hydroxylase [24-OHase]. The 24-OHase introduces a hydroxyl group on carbons 23 and 24, resulting in cleavage at carbon 23 to form a water-soluble inactive vitamin D metabolite for both 25(OH)D and 1,25(OH)\textsubscript{2}D.\textsuperscript{1,14,45}

Thus antiseizure medications, glucocorticoids, and other medications will enhance the destruction of 25(OH)D and 1,25(OH)\textsubscript{2}D, resulting in vitamin D deficiency and its consequences on skeletal mineralization.

Patients with Paget disease have an increase in bone remodeling activity (see Chapter 202). In the 1970s, a new class of drugs known as bisphosphonates were introduced as an effective treatment for Paget’s disease. The first bisphosphonate that was used was etidronate. The drug was typically given at a dose of 400 mg/day. Within a few months, there was a marked reduction in Pagetic bone activity, suggesting that this would be a safe and effective method for treating this metabolic bone disease. However, many patients who were on the medication for more than 6 months began developing bone pain. Bone biopsies revealed that they were suffering from osteomalacia.\textsuperscript{1,8,15,46} To prevent this complication, patients with Paget disease took the medication for several months and then stopped the medication for several months and restarted it again to control the Paget’s disease but prevent the side effect of osteomalacia.\textsuperscript{1,15}

When it was realized that bisphosphonates inhibited bone resorption, several pharmaceutical companies began developing bisphosphonate analogs that had much higher potency in inhibiting osteoclastic activity while having minimum negative effects on skeletal mineralization. As a result, the new class of bisphosphonates was effective in treating Paget’s disease when given either daily, weekly, or monthly without any evidence of osteomalacia on the basis of bone biopsies. These potent bisphosphonates are also used for the prevention and treatment of osteoporosis and do not cause osteomalacia.

Ifofamide, a drug used to treat solid tumors, has been associated with renal Fanconi syndrome and hyperphosphaturia.\textsuperscript{15,30,47,48} Saccharated ferric oxide used intravenously can cause transient proximal renal tubular damage leading to phosphaturia.\textsuperscript{15,30,49} A wide variety of other drugs have been associated with hypophosphatemia, osteomalacia, and rickets (Boxes 199.1 and 199.2).\textsuperscript{5,12}
X-RAY AND BIOCHEMICAL MANIFESTATIONS OF OSTEOMALACIA AND RICKETS

It is not possible to distinguish osteomalacia from osteopenia and osteoporosis either by x-ray examination or by bone densitometry. The only exception is if the x-ray examination reveals Looser zones (Fig. 199.5). These are radiolucent lines that are often penetrating through the cortex perpendicular to the shaft and are most often seen in the medial cortices of the femurs and in the pelvis and ribs. In children, rickets/osteomalacia is easily detected because the epiphyseal plates have not closed. There is widening of the physis with fraying, cupping, and splaying of the metaphases (Fig. 199.6). The diaphyses of the long bones often appear to be less dense (i.e., osteopenic and show thinning of the cortices with periosteal new bone formation).8,15

Rickets and osteomalacia are associated with a variety of abnormalities on blood biochemistries. However, it is often the presenting symptoms or manifestations of osteomalacia that will prompt the diagnosis before the biochemical abnormalities are appreciated. The reason for this is that depending on the cause, the abnormal biochemistries can vary. For example, in children with severe vitamin D deficiency, there will be a low-normal or low serum calcium with a low-normal or low fasting serum phosphorus with an elevated alkaline phosphatase and a 25(OH)D less than 15 ng/mL. If the child has been vitamin D deficient for a prolonged period of time or there is little calcium intake, then the biochemical presentation is often hypocalcemia associated with all of the other biochemical abnormalities. An adult with vitamin D deficiency will present with a normal or low-normal serum calcium, a low-normal or low serum fasting phosphorus, a normal alkaline phosphatase, an elevated PTH, and a 25(OH)D less than 20 ng/mL. However, if the cause is due to an acquired disorder that causes severe

---

**BOX 199.2 CAUSES OF OSTEOMALACIA/RICKETS**

- Vitamin D deficiency
- Calcium deficiency
- Hypophosphatemia
- Fanconi syndrome
- Pseudovitamin D–deficiency rickets, vitamin D–dependent rickets type 1
- Vitamin D–resistant rickets, vitamin D–dependent rickets type 2
- X-linked hypophosphatemic rickets
- Autosomal dominant hypophosphatemic rickets
- Oncogenic osteomalacia
- Hypophosphatasia
- Malabsorption syndrome
- Hypokalemic distal renal tubular acidosis
- Wilson disease
- Renal failure, chronic
- Cystinosis
- Phenytoin
- Glucocorticoids
- HAART
- Etidronate
- Glutethimide
- Heavy metals
- Cancer drugs

---

Fig. 199.5 Radiograph of the femur demonstrating a radiolucent line perpendicular to the shaft known as a Looser zone.

Fig. 199.6 Radiographs of a child with vitamin D deficiency rickets demonstrating bowing of the femurs and tibias (a) and widened, frayed, demineralized epiphyseal plates (b and c).
phosphate wasting in the urine, these patients present with a normal or low-normal serum calcium, elevated PTH, low serum phosphorus, elevated alkaline phosphatase, and a normal 25(OH)D. The distinguishing features of the various causes of osteomalacia based on biochemistries are summarized in Table 199.1.1,8,15

Clinical findings
Children with rickets often have skeletal abnormalities including a rachitic rosary, bowed or knocked knees, frontal bossing, soft fontanels, delayed tooth eruption, dental caries, and severe muscle weakness (Fig. 199.7). The more serious consequences include grand mal seizures, carpal pedal spasms (Fig. 199.8), and upper respiratory tract infections.14 Often children with rickets have other subtle symptoms as noted in Box 199.3.

In adults, osteomalacia does not present with any overt skeletal signs. However, patients with osteomalacia complain of throbbing, aching bone discomfort. They often note that the bone discomfort is worse when sitting or lying in bed. They also have proximal muscle weakness and aching in their muscles.1,8,15,29,50 To make the diagnosis, pressing with thumb or forefinger with some force on the sternum, radius, ulna, or anterior tibia will often result in wincing bone discomfort. Often physicians conclude that pressing on the skeleton resulting in discomfort is consistent with a trigger point leading to the diagnosis of fibromyalgia. In many cases these patients are suffering from periosteal bone discomfort consistent with osteomalacia.50

Although the exact cause of the muscle weakness and bone discomfort is not fully understood, it is believed that because the major cause of osteomalacia is vitamin D deficiency and because skeletal muscle has a VDR, the lack of 1,25(OH)2D interacting with the skeletal muscle VDR increases muscle weakness.1,2 Osteoblasts laying down the collagen matrix on the periosteal surface with no mineralization provides little structural support for the periosteal covering that is heavily innervated with sensory fibers. Thus pressing on the periosteal covering causing deformation leads to immediate bone discomfort. In addition, the collagen matrix acts like JELL-O and, once hydrated, expands. As a result, the outward pressure on the periosteal covering gives the sensation of throbbing, aching bone discomfort.50
To treat vitamin D deficiency, 50,000 IU of vitamin D3 once a week for 8 weeks will often fill the empty vitamin D tank and raise the blood level above 30 ng/mL. Patients who are severely vitamin D deficient with a 25(OH)D less than 10 ng/mL or who are on medications that would enhance vitamin D destruction or obese may require an additional 8 weeks of therapy with 50,000 IU of vitamin D3. Once the blood level of 25(OH)D is above 30 ng/mL, vitamin D3 sufficiency can be maintained by giving patients 50,000 IU of vitamin D3 once every 2 weeks. In our clinic, we have found over a 5-year period that the blood levels are sustained between 40 and 50 ng/mL on this regimen. Alternatively, to treat vitamin D deficiency with vitamin D supplementation, 5000 IU of vitamin D daily for 2 months followed by 2000 IU of vitamin D daily will treat vitamin D deficiency and maintain vitamin D sufficiency in most adults.

The American Academy of Pediatrics recommends that all infants and children receive 400 IU of vitamin D per day. This will prevent rickets in children.

Children and adults who have calcium-induced rickets/osteomalacia should be treated with the adequate intake recommendation for calcium, which is 800 milligrams per day for children younger than the age of 12 years, 1300 milligrams per day for teenagers, 1000 milligrams for adults aged 19 to 50 years, and 1200 milligrams per day for adults older than the age of 50. They should also be taking an adequate amount of vitamin D to maximize the benefit of the calcium.

Patients with phosphate wasting need to take either Neutra-Phos or sodium phosphate in amounts of 250 mg to 500 mg 3 to 5 times a day along with 1,25(OH)2D3 (calcitriol) 0.5 to 1.0 mg twice a day. It should be noted that the more frequent dosing of phosphate at lower doses to help maintain the serum levels of phosphate is desirable for two reasons. The first is that maintaining a more normal calcium-phosphate product will help in the mineralization of osteoid. Secondly, taking large amounts of phosphate orally results in a transient decrease in serum ionized calcium, which stimulates the parathyroid glands to produce and secret PTH. The chronic stimulation of the parathyroid glands by transient hypocalcemia can result in tertiary hyperparathyroidism.

**KEY REFERENCES**


13. Balasubramanian K, Rajeswari J, Gulab, et al. Varying serum calcium and phosphorus on skeletal mineralization over time after oral administration of vitamin D2 and/or vitamin D3. Healthy adults recruited at the end of the winter received either placebo (n = 14; □), 1000 IU of vitamin D2 (D2, n = 20; ●), 1000 IU of vitamin D3 (D3, n = 16; ▪), or 500 IU of vitamin D2 and 500 IU of vitamin D3 (D2/D3, n = 18; ★) daily for 11 weeks. The total 25-hydroxyvitamin D levels are demonstrated over time. P = 0.037 comparing 25(OH)D over time between vitamin D2 and placebo. P = 0.041 comparing 25(OH)D over time between 500 IU vitamin D3 + 500 IU vitamin D2 and placebo. P = 0.023 comparing 25(OH)D over time between vitamin D2 and placebo. (From Holick MF. Copyright 2008. Reproduced with permission.)

14. Fig. 199.9 Mean ± SEM serum 25-hydroxyvitamin D levels after oral administration of vitamin D2 or vitamin D3. Healthy adults recruited at the end of the winter received either placebo (n = 14; □), 1000 IU of vitamin D2 (D2, n = 20; ●), 1000 IU of vitamin D3 (D3, n = 16; ▪), or 500 IU of vitamin D2 and 500 IU of vitamin D3 (D2/D3, n = 18; ★) daily for 11 weeks. The total 25-hydroxyvitamin D levels are demonstrated over time. P = 0.037 comparing 25(OH)D over time between vitamin D2 and placebo. P = 0.041 comparing 25(OH)D over time between 500 IU vitamin D3 + 500 IU vitamin D2 and placebo. P = 0.023 comparing 25(OH)D over time between vitamin D2 and placebo. (From Holick MF. Copyright 2008. Reproduced with permission.)
REFERENCES

Full references for this chapter can be found on www.expertconsult.com.