

Osteomalacia as a Result of Vitamin D Deficiency

Arti Bhan, MBBS^a, Ajay D. Rao, MD^b, D. Sudhaker Rao, MBBS^{c,*}

KEYWORDS

- Osteomalacia • Vitamin D deficiency
- Secondary hyperparathyroidism • Treatment

Among the metabolic bone diseases with known pathogenic mechanisms, osteoporosis is the most common and osteomalacia is the least common disorder. Nevertheless, osteomalacia occurs with regular frequency such that it may escape recognition especially in its early stages because of the often indefinite symptoms such as vague bone pain and muscle weakness. In reality, however, osteomalacia is an end-stage bone disease of severe vitamin D or phosphate depletion of any cause with characteristic biochemical, radiological, and bone histologic features. The descriptive term osteomalacia originally referred to a generalized softening of bone leading to crippling deformities, and is almost always caused by vitamin D deficiency, and rarely by phosphate and calcium depletion.¹ The cardinal histologic bone feature of osteomalacia is an excessive accumulation of unmineralized or poorly mineralized bone matrix.¹ In contrast, rickets (see the article by Thandrayen and Pettifor elsewhere in this issue for further exploration of this topic) is a disease of impaired mineralization of cartilage resulting in defective enchondral bone formation. By definition, therefore, rickets occurs only in children and adolescents before epiphyseal fusion, whereas osteomalacia occurs in children and in adults. Although this is an important clinical distinction, the pathogenesis of rickets and osteomalacia is similar.

HISTORICAL PERSPECTIVE AND SCOPE OF THE PROBLEM

The first description of osteomalacia was by Gustav Pommer, a German pathologist, in the late nineteenth century who discussed the histologic differences between osteomalacia, osteoporosis, and osteitis fibrosa.¹ One of the earliest reports of osteomalacia studied by tetracycline-based bone histomorphometry of the ribs was reported from Henry Ford Hospital in 1966.² Based on current concepts of bone

^a Division of Endocrinology, Diabetes and Bone & Mineral Disorders, Henry Ford Hospital, Detroit, MI 48202, USA

^b Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, USA

^c Bone & Mineral Research Laboratory, Henry Ford Hospital, E&R Building 7th Floor, 2799 West Grand Boulevard, Detroit, MI 48202, USA

* Corresponding author.

E-mail address: srao1@hfhs.org

remodeling, Pommer's observations can be restated as replacement of resorbed bone by the same amount of bone in healthy adults, by a lesser amount of bone in age-related osteoporosis, and by unmineralized bone matrix (or osteoid) in osteomalacia. With the realization of the critical role of vitamin D in bone and mineral metabolism in general and bone mineralization in particular, it became apparent that almost all cases of bone softening were the result of vitamin D deficiency, and osteomalacia was synonymous with bone disease that could be cured by vitamin D repletion. However, it is now clear that not all cases of osteomalacia are cured by vitamin D therapy and similarly not all individuals with vitamin D depletion develop osteomalacia. Nevertheless, it is important to bear in mind that almost all individuals with prolonged severe vitamin D depletion will eventually develop osteomalacia with irreversible cortical bone loss and increased risk of fractures for the rest of their lives.³ Osteomalacia manifests as a distinct metabolic bone disease with its characteristic clinical, biochemical, radiographic, and histologic bone features,⁴ that can be distinguished unambiguously from osteoporosis or any other metabolic bone disease.

Because of the lack of any systematic studies on osteomalacia it is difficult to estimate the precise prevalence of osteomalacia. A MEDLINE search from 1950 to 2009 using the MeSH term "osteomalacia" reveals several articles, but all are concerned with individual case reports or case series. Nevertheless, vitamin D deficiency is the most common cause of osteomalacia worldwide, but in the United States, gastrointestinal disorders causing vitamin D deficiency and hypophosphatemic osteomalacia are the most common. Gastric bypass surgery for morbid obesity is now emerging as the leading cause of vitamin D deficiency osteomalacia in this country. Other uncommon causes of vitamin D deficiency osteomalacia are summarized in **Box 1**.

Evolution of Hypovitaminosis D Osteopathy and Osteomalacia

In its early stages, vitamin D deficiency is associated with increased serum alkaline phosphatase and parathyroid hormone (PTH) levels, increased bone turnover without mineralization defect, and irreversible cortical bone loss, which the authors defined as hypovitaminosis D osteopathy stage I (HVO-I) or preosteomalacia.⁴ Recognition of this preclinical stage is important to prevent PTH-mediated cortical bone loss and progression to frank osteomalacia.³ In the next stage, hypovitaminosis D osteopathy stage II (HVO-II), there is progressive accumulation of unmineralized matrix (or osteoid) with some preservation of mineralization. In the last stage, hypovitaminosis D osteopathy stage III (HVO-III), there is complete cessation of mineralization with no tetracycline uptake, conforming to the traditional descriptions of osteomalacia.⁴ The distinguishing histologic bone features of osteomalacia and osteoporosis along with reference ranges are summarized in **Table 1**. Osteoporosis is characterized by a quantum decrease in bone volume without mineralization defect, whereas osteomalacia is associated with a decrease in bone volume and excess osteoid accumulation.⁵ The extent of bone mineralization is either near normal or slightly reduced in osteoporosis, whereas it is always absent in osteomalacia. Secondary hyperparathyroidism, an inevitable consequence of chronic vitamin D deficiency, in rare cases is associated with bone marrow fibrosis, similar to that found in primary hyperparathyroidism. In osteomalacia, osteoid volume, thickness, and surface are all increased, whereas in osteitis fibrosa, only the osteoid volume and surface but not the thickness are increased and usually not to the same extent as in osteomalacia (see **Table 1**). A mineralization lag time (MLT) of more than 100 days separates osteomalacia unambiguously from all other conditions with increased osteoid indices as a result of increased bone turnover, such as

Box 1**Common causes of vitamin D deficiency osteomalacia***Extrinsic*

- Decreased exposure to sunlight
- Use of sunscreens (especially >8 SPF)
- Use of a veil (or hijab)
- Increased or dark skin pigmentation
- Inadequate dietary intake
- Morbid obesity

Intrinsic

- Advancing age with decreased cutaneous production of vitamin D
- Malabsorption caused by various gastrointestinal disorders
 - Gastrectomy (partial, total, or bypass procedure)
 - Small intestinal disease, resection, or bypass
 - Gluten enteropathy (celiac sprue)
 - Biliary cirrhosis (uncommon)
 - Pancreatic insufficiency including cystic fibrosis (uncommon)
- Acquired vitamin D deficiency
 - (as a result of increased catabolism or metabolic clearance)
 - Anticonvulsants
 - Calcium deficiency with secondary hyperparathyroidism
 - Primary hyperparathyroidism
 - Paget's disease of bone (depletion caused by excess consumption)

hyperparathyroidism, hyperthyroidism, and Paget disease of bone (see **Table 1**). Thus a combination of increased osteoid thickness greater than 15 μm and an MLT more than 100 days should be used as diagnostic criteria for osteomalacia of any cause including vitamin D deficiency osteomalacia.^{1,4}

CLINICAL MANIFESTATIONS OF OSTEOMALACIA

Osteomalacia in its classic form manifests with a constellation of symptoms and signs that can be collectively referred to as osteomalacic syndrome. Some symptoms are vague and nonspecific and can easily escape the attention of the clinician, whereas others are highly specific and often diagnostic. Between these 2 extremes a patient may present with a combination of symptoms and signs. Therefore, a high degree of suspicion in the right clinical context is necessary to diagnose osteomalacia especially in the early stages. Because of the increase in serum alkaline phosphatase levels and dramatic appearance on bone scans, metastatic disease is often suspected leading to exhaustive, expensive, and often unnecessary testing. A recent case seen by the senior author illustrates the problem. A 59-year-old white woman with no previous history of cancer or gastrointestinal surgery was seen for a high serum alkaline phosphatase level (890–950 IU/L) that had progressively increased over

Measurement	Normal Postmenopausal White Women ^a	Osteoporosis (With Fractures) ^a	Osteomalacia
Bone Histomorphometry			
Osteoid surface/bone surface (%)	20.3 (4.35–39.7)	15.7 (2.78–34.5)	69 ± 13
Osteoid thickness (μm)	8.49 (5.75–12.2)	7.63 (4.74–11.5)	27 ± 9
Mineralization lag time (MLT; days)	71.2 (18.6–158)	73.8 (17.1–132)	>100
Bone formation rate/bone surface (μm ³ /μm ² /y)	15.9 (1.00–33.9)	13.0 (0.436–33.7)	0
Bone Mineral Density			
Spine T-score	Referrent	−2.3 ± 1.8	−3.0 ± 1.6
Spine Z-score	Referrent	−1.2 ± 0.8	−2.0 ± 1.4
Femoral neck T-score	Referrent	−2.1 ± 1.6	−4.1 ± 1.0
Femoral neck Z-score	Referrent	−1.1 ± 0.6	−2.7 ± 0.7
Forearm Z-score	Referrent	−1.1 ± 1.0	−6.0 ± 2.3
Forearm T-score	Referrent	−0.85 ± 0.5	−3.8 ± 0.8

Note the magnitude and pattern of bone mineral deficits with more trabecular bone deficit (spine and hip) in postmenopausal osteoporosis and predominant cortical bone deficit (forearm bone mineral density) in osteomalacia.

^a Representative data from the authors' laboratory (published and unpublished).

Data from Basha B, Rao DS, Han Z-H, Parfitt AM. Osteomalacia due to vitamin D depletion in the US. *Am J Med* 2000;108:296–300.

a period of 1 to 2 years during which she developed vague musculoskeletal symptoms, which she described as aches and pains of getting old. A whole body bone scan showed multiple bilateral rib fractures without increased uptake elsewhere in the skeleton (**Fig. 1**), an unusual finding in malignancy, but nevertheless referred to an oncologist for further evaluation. She underwent an exhaustive investigation for cancer and myeloproliferative diseases including a bone marrow examination that was normal. Only when a house officer ordered measurement of serum PTH, because that was the only test that had not yet been performed, and found to be 879 pg/mL was the patient referred to a bone and mineral specialist. The house officer did not consider measurement of 25-hydroxyvitamin D. She had profound proximal myopathy, diffuse bone pain, and an undetectable level of serum 25-hydroxyvitamin D (<4 ng/mL). Bone biopsy confirmed severe osteomalacia (**Fig. 2**) and all her symptoms improved dramatically within 3 to 4 months of vitamin repletion. This case illustrates the problems with diagnosis of osteomalacia even though much has been written on vitamin D deficiency recently.

Clinical manifestations of osteomalacia are primarily related to a variety of underlying pathogenetic mechanisms that are poorly understood. The classic symptoms are bone pain and tenderness, muscle weakness, and difficulty in walking, all of which can often be vague and unremitting but less in severity during the summer months. Consequently patients are labeled with varied diagnoses ranging from fibromyalgia, severe myopathy,⁶ unusual pain syndrome,⁷ or neurologic disorders of unknown cause. In patients with the genetic forms of osteomalacia and those with childhood

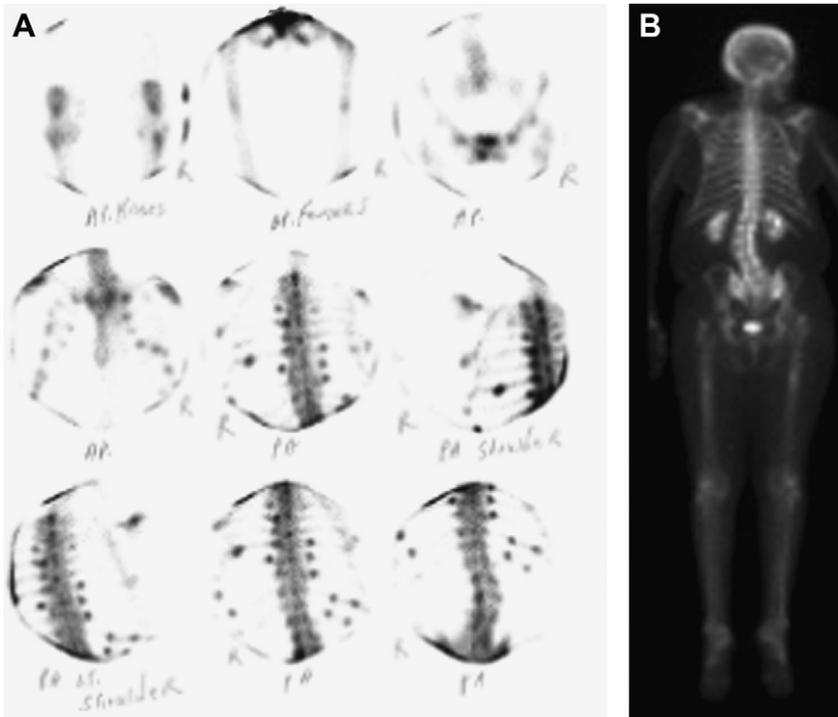


Fig. 1. A whole body bone scan before (A) and after (B) vitamin D therapy in the patient described in the text. Complete and thorough evaluation did not reveal any cause for vitamin D deficiency other than nutritional deficiency. Note multiple bilateral hot spots in the ribs without any other discrete foci elsewhere in the body, characteristic of osteomalacia, but not of metastatic disease as was thought initially in this patient. Also, note a decreased uptake in the kidney in the absence of renal insufficiency suggesting an avid uptake and retention in the skeleton.

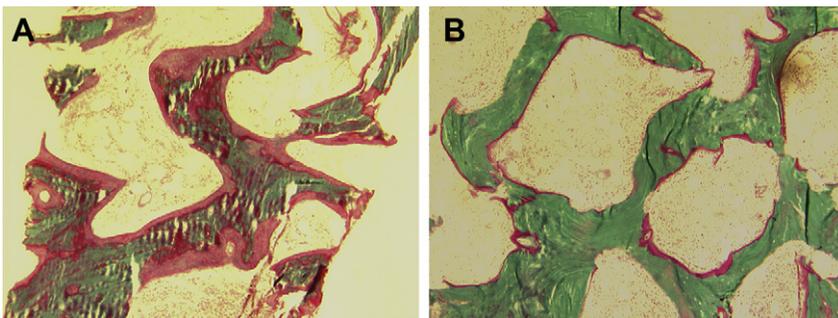


Fig. 2. Composite photomicrograph of bone biopsy from the patient with vitamin D deficiency osteomalacia. (A) Low-power view showing increased osteoid (magenta or red color) surface covering the entire bone surfaces with poorly mineralized trabecular bone (green with red areas within), thick osteoid seams, and relatively well-preserved trabecular architecture. (B) After vitamin D repletion there was complete healing of osteomalacia with substantial decrease in osteoid surface and thickness.

celiac disease, residual deformities of rickets with associated short stature may be seen, but are not usually seen in patients with nutritional rickets. Deformities related to the softening of the adult skeleton include kyphosis, coxa vara, pigeon breast, protrusio acetabuli, and triradiate pelvis with a narrow pubic arch; the latter can lead to difficulty in labor and vaginal delivery. However, such extreme skeletal abnormalities are uncommon in contemporary practice in the United States,⁸ but are not uncommon in parts of the world where vitamin D depletion is endemic.⁹

Bone Pain and Tenderness

Pain in osteomalacia is dull and poorly localized but clearly felt in the bones rather than in the joints and is distinct from muscle pain. The pain is believed to be caused by hydration of the unmineralized bone matrix underneath the periosteum that stretches causing throbbing pain.¹⁰ Patients are often able to distinguish between muscle and bone pain on carefully directed questioning. The bone pain is usually persistent, made worse by weight-bearing or contraction of the muscles during locomotion, and is rarely relieved completely by rest. Pain is usually symmetric and diffuse, beginning in the lower back, later spreading to the pelvic girdle, hips and upper thighs, and ribs. It is almost never of a radicular nature and in the absence of fracture there is tenderness on percussion of bones, especially over the tibial shins. Lateral compression of the ribs or of the pelvic girdle and compression of the sternum are useful clinical maneuvers to elicit pain in mild to moderate cases. The anatomic location of the pain to the axial rather than appendicular skeleton is most likely as a result of a higher proportion of cancellous bone in the spine, which accumulates relatively more osteoid than the cortical bones in the long bones of the extremities. A few patients are completely asymptomatic despite severe hypocalcemia,¹¹ whereas others suffer from excruciating pain with the least movement; the reasons for such dichotomy are not clear.

Muscle Weakness

Proximal limb muscle weakness is characteristic of osteomalacia. The severity varies from a subtle abnormality detectable only on careful physical examination to severe disability verging on complete paralysis.¹² Muscle atrophy is mild in relation to the severity of weakness, tone is reduced, and fasciculation is absent, but deep tendon reflexes are preserved or increased. In mild cases, true weakness must be distinguished from unwillingness to tense the muscle because of pain. Specific symptoms include difficulty in rising from a chair, walking up or down stairs, and the characteristic gait described as waddling gait caused by inability to lift the leg off the ground because of quadriceps weakness or flex the hip or the knee joints. A more recent meta-analysis suggests a close relationship between muscle strength and serum 25-hydroxyvitamin D level particularly when the serum levels decrease to less than 20 ng/mL.¹³

Difficulty in Walking

Abnormal gait can be the result of either pain or weakness, but usually both contribute to the problem. A change in gait discriminates more reliably between young adults with and without osteomalacia than any other symptoms. Many patients feel pain only when walking, which they consequently avoid. Because of weakness, the legs may feel heavy and the patient tires easily, walks more slowly with flatfooted springless gait, and is more likely to stumble. A waddling gait is characteristic of osteomalacia.

RADIOLOGICAL FEATURES OF OSTEOMALACIA

Many structural and pathologic changes in bone can be detected on radiograph examination and are the result of increased PTH secretion or of impaired matrix mineralization (**Figs. 3–6**). Secondary hyperparathyroidism, an inevitable consequence of vitamin D depletion, leads to thinning of cortical bone. Increased cortical porosity is manifested as cortical striations in the metacarpals and phalanges on high-resolution radiographs of the hands. Rarely, generalized osteitis fibrosa cystica may be present.¹⁴ The most common radiographic manifestation of impaired mineralization in cancellous bone is osteopenia. Changes in bone shape such as protrusio acetabuli (see **Fig. 6**) can be seen, although rare in this country.

The best known and the characteristic radiographic feature of osteomalacia is the Looser's zone (see **Figs. 3–6**), a lucent band adjacent to the periosteum that represents an unhealed insufficiency-type stress fracture. Stress fractures are incomplete fissures without displacement that occur as a result of repetitive trauma. Looser's zones occur most commonly in ribs, pubic rami, and outer borders of scapulae (see **Figs. 3–6**), and less commonly on the inferior aspect of the femoral necks, medial aspect of proximal femur, metatarsals, and medial aspect of the shafts of long bones. This is in contrast to the fissure fractures that occur on the outer convex border of the long bones in Paget disease of bone. Occasionally pseudofractures can occur without osteomalacia.^{15,16}

Radionuclide bone scans are most useful in evaluating patients with suspected osteomalacia. This imaging method can present in many different ways ranging

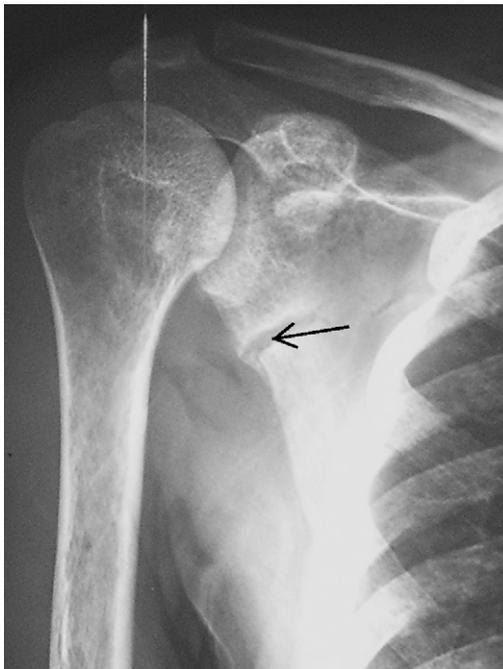


Fig. 3. Looser's zone (pseudofracture) in scapula (arrow). (Courtesy of Dr Sanjay K. Bhadada, Post Graduate Institute of Medical Education and Research, Chandigarh, India.)



Fig. 4. Looser zone (pseudofracture) in superior pubic rami (*arrows*). (Courtesy of Dr Sanjay K. Bhadada, Post Graduate Institute of Medical Education and Research, Chandigarh, India.)

from the so-called super scan, in which no discrete focal abnormalities are seen, to many discrete foci of increased radionuclide uptake mimicking metastatic cancer.¹

Bone mineral density as assessed by dual-energy x-ray absorptiometry (DXA) is always reduced at all relevant skeletal sites (spine, hip, and forearm) with the greatest deficits at the cortical-rich bone in the forearms.^{1,8,17} The contrasting features of the pattern of bone mineral deficits in osteoporosis and osteomalacia are summarized in **Table 1**.

SKELETAL FRACTURES

Several types of fractures occur in patients with osteomalacia with the pseudofractures that can progress to a complete fracture, usually in the subtrochanteric region of the femur or metatarsals, the greatest load-bearing bones. Rib fractures also occur commonly. When osteomalacia begins in childhood, the adult bones tend to be soft rather than brittle. Conversely, when osteomalacia begins later in adult life, the usual type fractures are more common. Spontaneous fractures of the sternum in the absence of trauma are almost always a result of adult onset osteomalacia.



Fig. 5. Late effects of osteomalacia leading to triradiate pelvis. (Courtesy of Dr Sanjay K. Bhadada, Post Graduate Institute of Medical Education and Research, Chandigarh, India.)



Fig. 6. Advanced osteomalacia with protrusioacetabuli and triradiate pelvis. (Courtesy of Dr Sanjay K. Bhadada, Post Graduate Institute of Medical Education and Research, Chandigarh, India.)

BIOCHEMICAL CHANGES IN OSTEOMALACIA

In its classic presentation, hypocalcemia, hypophosphatemia, and increased serum alkaline phosphatase level are the classic biochemical triad of osteomalacia,^{1,8} but increased serum alkaline phosphatase level is the most frequent and the earliest biochemical manifestation.⁸ As the vitamin D depletion advances, so does PTH hypersecretion leading to increased bone remodeling, endocortical bone resorption, and cortical thinning, which collectively results in irreversible cortical bone loss and increased fracture risk.³ Most patients at this earliest stage of hypovitaminosis D osteopathy are asymptomatic and recognition at this stage is of paramount importance to prevent fractures and progression of preosteomalacia to frank osteomalacia.^{3,4,8} Because of the associated secondary hyperparathyroidism, biochemical markers of bone turnover are increased.¹

DIAGNOSTIC APPROACH TO OSTEOMALACIA

In the right clinical setting, a careful history and physical examination and a high degree of suspicion should facilitate the diagnosis of osteomalacia. However, despite many advances in biochemical measurements none of them are specific and most have moderate to low sensitivity. A reduced serum calcium \times phosphate product and high alkaline phosphatase level in the presence of low 25-hydroxyvitamin D and high PTH makes the diagnosis of osteomalacia highly likely. On the other hand, a low serum 25-hydroxyvitamin D level is a poor predictor of osteomalacia, just as a low serum vitamin B₁₂ level is a poor predictor of bone marrow findings. Skeletal radiographs and bone scans might reveal pseudofractures and the bone scan might suggest only a super scan. An *in vivo* tetracycline-labeled transiliac bone biopsy may help to diagnose osteomalacia in challenging cases.^{2,4}

The authors routinely recommend *in vivo* tetracycline-labeled bone biopsy in all patients with gastrointestinal-related vitamin D depletion with increased alkaline phosphatase and PTH levels.⁸ A bone biopsy for detailed bone histomorphometry can be accomplished with a simple 11G or 8G Jamshidi needle using the same approach as

transiliac trephine biopsy used in the evaluation of bone quality measurements in patients with osteoporosis. The small Jamshidi needle biopsy provides an adequate quantity of cancellous bone sample for diagnostic purposes. The procedure can be performed in less than 30 minutes in the outpatient setting under local anesthesia with minimal discomfort to the patient and practically no morbidity.¹⁸ The undecalcified bone biopsy specimen should be preserved in 70% alcohol (not formalin) and can be sent to one of several specialized laboratories for detailed bone histomorphometry.

TREATMENT OF OSTEOMALACIA

Depending on the urgency with which vitamin D replenishment is needed, several dose regimens can be used.¹⁹ Although each has some advantages the authors routinely prescribe ergocalciferol (vitamin D₂) or cholecalciferol (vitamin D₃) 50,000 IU (1.25 mg) once a week for 8 weeks followed by dose adjustments based on serum 25-hydroxyvitamin D and PTH levels. In our experience, there are no distinct differences between the vitamin D preparations except perhaps a shorter half-life of vitamin D₂ and consequently the need for more frequent dosing during the maintenance phase. Most patients need longer duration of the weekly doses and many with intestinal disorders need daily doses as high as 150,000 IU/d in the first 1 to 3 months with dose reduction based on biochemical responses. Bone biopsy findings often help to decide on the dose and duration of high-dose therapy if the osteoid indices are high and if marrow fibrosis is also present. This is somewhat analogous to hungry-bone syndrome following parathyroidectomy in patients with severe primary or secondary hyperparathyroidism.

Careful and close follow-up is necessary during the first few months (1–3 months) of therapy to avoid therapy-related problems, although it is extremely uncommon to see hypercalcemia or renal dysfunction. More problematic is the risk of long-bone and hip fractures as the patient's muscle weakness improves and bone pain remits before bone mass and strength is restored. Long-term maintenance therapy is largely dictated by clinical and biochemical responses; the latter might take months and at times years to resolve. The authors routinely repeat Jamshidi needle biopsy to document healing of osteomalacia before recommending antiresorptive or anabolic therapy for the associated residual osteoporosis. Almost all patients with gastrointestinal-related vitamin D deficiency osteomalacia require life-long follow-up to avoid recurrence of osteomalacia caused by lapses in therapy, treatment of associated osteoporosis, and for the rare development of hypercalcemic autonomous secondary hyperparathyroidism. Despite these demanding needs, treatment of osteomalacia is most gratifying to the patient and the clinician, similar to that of myxedema or pernicious anemia.

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