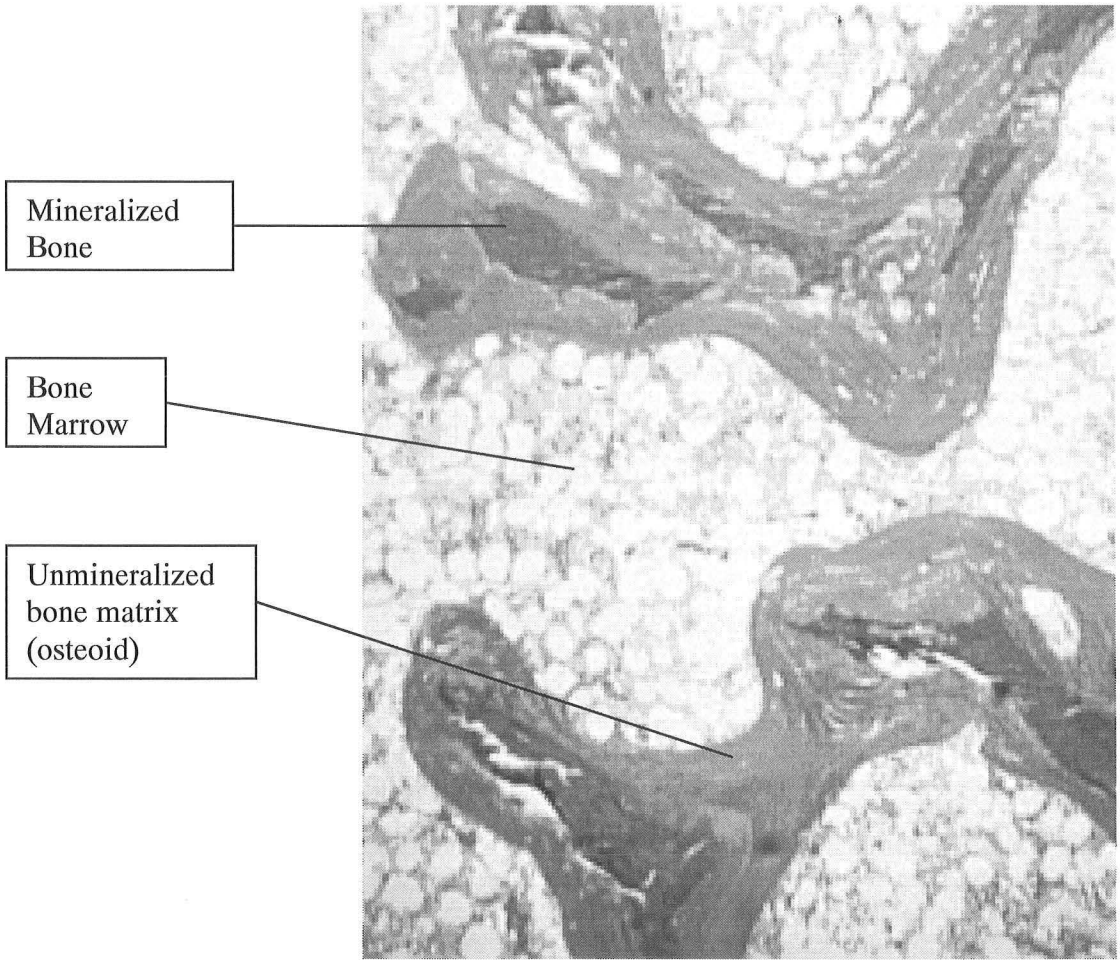
Osteomalacia: A Forgotten Cause of Low Bone Mineral Density



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Clinical and Research Interests: prevention of kidney stone recurrence, elucidation of low bone mass in stone-formers, metabolic bone disease, mineral disorders

OBJECTIVES

1. List 3 symptoms, 3 physical findings and 4 laboratories that distinguish osteomalacia from osteoporosis.
2. List four general etiologies for osteomalacia and describe why approved therapy for osteoporosis may be harmful for patients with osteomalacia.
3. Discuss the purported physiological actions of phosphatonins.
4. Discuss why patients many patients with renal phosphate wasting are at risk for secondary hyperparathyroidism.
5. Estimate the prevalence of vitamin D insufficiency in Dallas, and list four patient subgroups who are especially at risk.

INTRODUCTION

Over the last decade, the diagnosis and treatment of osteoporosis has flourished with the ready accessibility of bone mineral densitometry and the growing arsenal of approved drugs proven to prevent fracture. However, there is potential danger in equating low bone mineral density with osteoporosis. Today, we will focus on osteomalacia- a cause of low bone mineral density that requires discernment of the underlying cause to allow optimal management. We will also briefly discuss hereditary causes of rickets to highlight new discoveries with a focus on phosphatonins (circulating factor which induces renal phosphate wasting, hypophosphatemia and suppression of serum 1,25-dihydroxyvitamin D).

DEFINITIONS

Rickets- Defect in mineralization of the bone matrix (protein) occurring at the growth plate. The quantity of bone matrix or osteoid is normal or even increased. The resulting soft bone and excessive bone matrix results in bony deformities and fractures.

Osteomalacia (derivation: osteo= bone; malacia= soft)- Defect in mineralization of the bone matrix at the endosteal and periosteal surfaces of bone.

Osteoporosis- A state in which the bone is predisposed to fracture due to decrease in bone mass (protein and mineral are equally affected) and reduced quality of the bone. Previously, this was a clinical diagnosis in patients who suffered fracture with modest to no trauma. More recently, defined by the World Health Organization (WHO) as a loss in bone mass > 2.5 standard deviations below the expected peak as measured by bone mineral densitometry with or without fracture. This definition, though originally designed to facilitate epidemiologic and clinical studies in groups of subjects, has been increasingly applied to single individuals.

CHRONOLOGICAL HISTORY

Reviewing the discovery of the two most important causes of rickets (vitamin D deficiency and renal phosphate wasting) is useful to demonstrate the process of scientific inquiry as it overcomes seemingly insurmountable contradictions.

Historical Highlights of Nutritional Rickets

1645	first reported case by Whistler[1]
1800's	common disease and common cause of mortality in young children
1900's	rickets noted to occur in the north and in areas where individuals are deprived of sunlight
1919	Mellanby noted that cod liver oil, which was known to be a source of vitamin A, could cure or prevent rickets in dogs[2]
1919	Huldshinsky found that rickets in children could be prevented or cured with exposure to sunlight [3]
1922	McCollum destroyed vitamin A activity (ability to prevent xerophthalmia) with heating the cod liver oil. It still cured rickets, so he reasoned cod liver oil had a different required vitamin which he called vitamin D[4]
1923	Chick found that rickets in children could be prevented or cured with exposure to artificial ultraviolet light[5]
1925	Steenbock and Black induced vitamin D activity by irradiating animals or their diets. This was confirmed by Hess and Weinstock.[6,7]
1931	Askew isolated and determined the structure of ergocalciferol from irradiated plant sterols[8]
1968	25OHD isolated[9]
1970	1,25-D produced at kidney[10]
1971	1,25-D isolated[11]
1988	Cloning of human vitamin D receptor (VDR)[12]

Historical Highlights of Hypophosphatemic Rickets

1937	Rickets resistant to vitamin D[13]
1958	Noted X-linked transmission of hypophosphatemia[14]

CASE HISTORIES

It is useful to review case histories of osteomalacia to best illustrate the clinical manifestations, the typical course of the disease, and response to treatment.

Case 1. Osteomalacia due to vitamin D deficiency.

A 52 year old Caucasian woman was referred for "osteoporosis." Four years prior to visit, she was active and healthy. She walked > 2 miles/day, > 2 flights/stairs. Thereafter, she noted a gradual decline. First, she had difficulty climbing stairs. This was followed in order by progressive difficulty walking long distances, standing, combing her hair and finally even feeding herself. She complained of progressive pain for several months at the hips, ribs, inner thigh, lower back and feet. During the same interval, she noted foot swelling. These difficulties confined her to the house (no sunlight). She lost 20-25 pounds over 2 years with decreased appetite. She denied diarrhea; yet, since vagotomy and antrectomy for peptic ulcers she had two or three bowel movements/day and > four bowel movements twice weekly. She did not complain of fever, chills, sweats, palpitations, tremulousness, cough, abdominal pain, change in stool caliber or consistency, or gastrointestinal or genitourinary bleed. Dietary calcium intake was < 400 mg/day. She had supplemented this over the prior year with calcium carbonate 1200

mg twice daily. PMH was notable for seizure disorder treated with phenobarbital for 20 years (stopped 3 mo prior).

On physical exam, she was cachectic, older than stated age, and sat in a wheel-chair. She was edentulous with perleche and tongue atrophy. Thyroid was normal. No lymphadenopathy or hepatosplenomegaly. She had bilateral edema at the feet with tenderness at the left 1st and 3rd metatarsals and right 1st and 4th metatarsals. Spine was straight. She was unable to stand from seated position without help. X-rays bilateral multiple metatarsal fractures, bilateral proximal femoral pseudofractures and pelvic pseudofractures.

Labs:

Date	Fasting Blood						Urine		BMD (SD from peak)		
	Ca	P	AP	PTH	25D	1,25D	Ca	P	Spine	Fn	DR
Baseline	7.8	2.1	298	124	10	50	13	223	-2.8	-5.4	-5.7
1 month	8.0	2.4	328	66							
4 months	8.7	2.8	469	19			53	1734			

Case 2. Tetany due to inappropriate treatment

A 75 year old woman was admitted acutely for tetany. Her pertinent history began in 1963, when she was diagnosed with Crohn's disease. She had been treated with Prednisone since that time at a dose usually ≥ 20 mg/day. She had 4 intestinal resections (for strictures?) resulting in short bowel syndrome and 5 to 10 bowel movements per day. She noted poor calcium intake lifelong and did not take calcium supplements. She had been treated with estrogen since hysterectomy in 1963. Other key medications included phenytoin and prednisone.

About 1 month ago, she was admitted in Mississippi for severe bronchitis; at that time, they discontinued her vitamin D supplement for unclear reasons. On discharge, she was prescribed an oral bisphosphonate for osteoporosis which had been noted on x-ray. Over the next three weeks, while visiting relatives in Dallas, she noted increasing fatigue, weakness, diffuse musculoskeletal cramping and tingling. She was admitted to the DVAMC when she was unable to stand. Labs: Serum calcium 5.2 mg/dl, phosphorus 1.8 mg/dl, magnesium 0.6 mg/dl, alkaline phosphatase 267, albumin 3.6 with normal GGT. PTH was elevated and 25-D was deficient at 3 ng/dl.

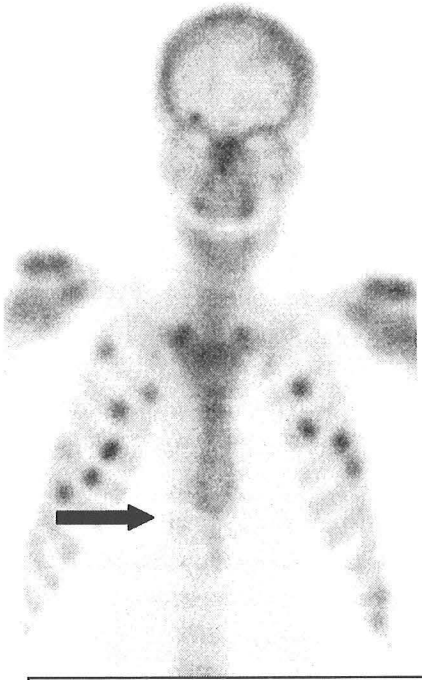


Figure 1: Bone Scan- Case 3

Case 3. Oncogenic osteomalacia

58 year old Caucasian man noted pain at the left lower ribcage 3 years prior to evaluation. Alkaline phosphatase was elevated > 300. Bone scan revealed increased uptake at the left 11th rib and one other rib, and metastatic cancer was considered. One rib was resected and the pathology was "benign" per M.D. Anderson. Bone scan was repeated in 9 months later (Figure 1), and uptake was increased at 10 or 11 areas in the ribcage. 9 months prior to evaluation, he developed right hip pain and lower back pain. He was diagnosed with a right hip stress fracture in Waco. Low serum phosphate and 1,25-dihydroxyvitamin D were discovered, and he was started on Rocaltrol. Pain improved slightly but alkaline phosphatase remained elevated and he developed great difficulty walking. He was referred to our center. He had poor dairy intake, but sun

exposure was several hours/day. He denied diarrhea or treatment with antacids, glucocorticoids or etidronate.

Inpatient GCRC evaluation:

Blood: Ca 8.7 to 9.3 mg/dl, P 2.1 mg/dl, alkaline phosphatase 420, intact PTH 30 to 36 pg/ml (normal 10-65), 25-D normal at 33 ng/ml, 1,25-D 9 pg/ml (nl 18-52).

Urine: Ca 85to 102 mg/d, P 700, Uric acid 315 to 344. Negative urinalysis for glucose, protein.

Fractional calcium absorption: 28.3% (normal 40-60%).

Bone biopsy: Severe osteomalacia (see front of protocol). Mineralization lag time was considerably delayed, and huge collections of unmineralized osteoid were found upon every bony surface.

Follow-up: His pain had almost completely improved (only mild residual hip pain and limp) over several months treatment with phosphate and higher doses of calcitriol, and he went back to work again. He was scheduled for octreotide scan through his main doctor, but it was reportedly negative. Old bone scans were received in Dallas, and he was noted to have a persistent small area of uptake in the right skull (arrow in Figure 1). Plain films of the skull were negative, but CT scan revealed a 2.8 cm mass at the right inferotemporal/middle fossa with destruction of the greater wing of the sphenoid bone. Five years after the onset of symptoms, he was surgically cured by Dr. Caetano Coimbra at UT Southwestern with complete resolution of symptoms and normalization of labs. Pathology: "hemangiopericytoma-like" tumor.

Date	Fasting Blood			Urine			BMD (SD from peak)		
	Ca	P	AP	Ca	P	DPD	Spine	Fn	DR
Baseline	9.0	2.1	420	102	700	18.2	+0.8	-1.1	-2.1
3 mo	9.1	1.5	322	67	1810	28.2			
10 mo	9.0	1.5	250	82	2853	11.1	+2.8	+0.2	-3.0
19 mo	9.2	1.3	131	206	1732	4.6			
23 mo (2 mo post-op)	9.5	3.6	104	283	924	6.8			
48 mo	9.5	2.8	99	230	625	4.8	+4.6	+0.7	-3.6

EPIDEMIOLOGY

The epidemiology of rickets and osteomalacia has markedly changed over time. In the 1800's, rickets was a disease of the inner city poor in northern Europe and carried high mortality. In the early part of the 20th century, the advent of effective prevention and treatment (with cod liver oil, sunlight, indoor ultraviolet (UV) light and UV-radiated foods) seemed to conquer the nutritional rickets (vitamin D deficiency). With the resolution of nutritional rickets, hypophosphatemic rickets became apparent by the 1950's.[13-15] Over the last 10 years, nutritional rickets/osteomalacia is reemerging in the U.S. with a different epidemiologic pattern. Now, there is a shift in representation by breast-fed babies, subjects consuming vegan diets, subjects with poor sunlight exposure (less time enjoying outside activities, more use of sunscreen), subjects with pigmented skin and immigrants.[16,17] In the last five years, 97% of cases have been in African-American children.[16]

The precise incidence of rickets and osteomalacia in the U.S. are unknown. However, acquired vitamin D deficiency appears to be the most common cause. In one series of postmenopausal women with vertebral compression fracture and clinical diagnosis of osteoporosis, 8% had evidence on bone biopsy of osteomalacia.[18] In ambulatory outpatients,

vitamin D deficiency severe enough to cause osteomalacia is occurs in approximately 4%,[19] but in selected inpatient populations that figure may exceed 50%.[20] Of the inherited causes of rickets, x-linked hypophosphatemic rickets, estimated at 1 per 20,000 births, is the most common etiology.[21]

BACKGROUND

BONE PHYSIOLOGY

Bone is critical for both architectural support and for the regulation of mineral homeostasis. The bone mass is primarily made up of minerals (especially calcium and phosphorus in the form of hydroxyapatite) and a protein matrix which is 90% collagen type I.[22,23] Understanding the anatomy and function of the growth plate is necessary to comprehend the pathological characteristics of rickets. The three main zones of the growth plate from the epiphyseal side to the metaphyseal side are the reserve zone, the proliferative zone, and the hypertrophic zone.[24] The **reserve zone** is made up of spherical chondrocytes sparsely populating an extracellular matrix. The function of this zone is unknown, however the cells are active and store glycogen, synthesized proteins and lipids. The **proliferative zone** contains flattened chondrocytes aligned in columns parallel to the long axis of the growing bone. The tops of these columns have a rich blood supply originating from the epiphyseal artery, and the delivered nutrients and oxygen facilitate chondrocyte division. This is the only region of the growth plate where significant cellular proliferation transpires. The **hypertrophic zone**, which is avascular, can be further subdivided into the zone of maturation, zone of degeneration, and the zone of provisional calcification. In this region, the chondrocytes gradually become spherical and enlarge eventually achieving five times their original size prior to undergoing apoptosis with calcification. In rickets, the reserve and proliferating zones are relatively normal, but in the hypertrophic zone, there is disorganization of the usual columnar pattern with an expanded number of chondrocytes leading to an increase in the length and width of the growth plate.

REGULATION OF CALCIUM AND PHOSPHATE

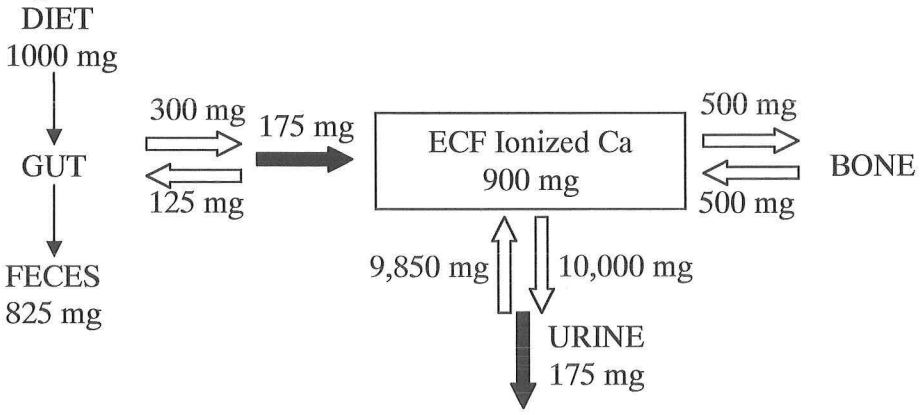
Model of calcium homeostasis

There are three organ systems that primarily regulate ionized calcium in the extracellular fluid, the intestine, the bone and the kidney (Figure 2). At steady state, an excess amount of calcium is absorbed from the intestine. The amount of calcium entering the bone is equal to that released by bone resorption. The excess calcium is excreted into the urine. At a hormonal level, parathyroid hormone (PTH), calcitonin and 1,25-dihydroxyvitamin D regulate the system (Table 1). A new level of control that has recently been elucidated is the calcium-sensing receptor[25] which is located on the cell surface of the parathyroid and the C-cells of the thyroid (which secrete calcitonin).

Table 1: Hormonal Regulation of calcium and phosphate

Hormone	Stimulated by:	Suppressed by:	Primary Actions
PTH	↓Ca, ↑P	↑1,25-$(OH)_2$ D	↑bone resorption, renal calcium reabsorption, intestinal calcium absorption (indirectly); ↓renal phosphate reabsorption
Calcitonin	↑Ca, Gastrin	↓Ca	↓bone resorption
1,25-$(OH)_2$ D	↓P, ↑PTH	↑P, 1,25-$(OH)_2$ D	↑intestinal absorption of calcium and phosphate, bone resorption, ↑renal phosphate reabsorption

Figure 2: Homeostatic model of calcium

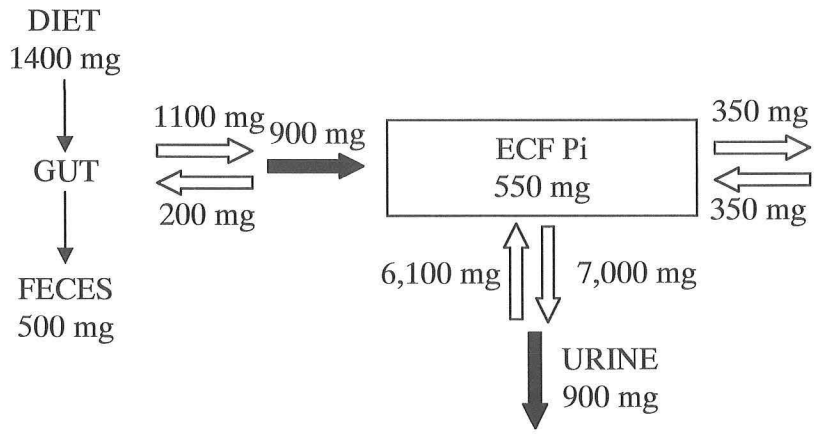


Adapted from ref 26

Integration of the response to hypocalcemia

The body readily adapts to hypocalcemic stressors. One example is inadequate intake or malabsorption of calcium. The fall in ionized calcium is sensed by the calcium-sensing receptor on the parathyroid gland, and this stimulates production and release of PTH. Increased serum PTH mobilizes calcium from the bone and reduces loss of calcium into the urine. Calcium sensor in the kidney further enhances renal calcium reabsorption. Intestinal calcium absorption improves due to enhanced production of 1,25-$(OH)_2$ D. The calcium-sensing receptor on the C-cells of the thyroid suppress release of calcitonin, so mobilization of calcium from the bone is further accentuated. This combination of changes results in restoration of ionized calcium but with the cost of bone loss.

Figure 3: Homeostatic model of phosphate



Adapted from ref 26

Model of phosphate homeostasis

Similar to the calcium homeostasis model, the triangle of organ systems regulating phosphate in the extracellular fluid include the intestine, the bone and the kidney (Figure 3) and the triad of hormones include PTH, calcitonin and 1,25-dihydroxyvitamin D (Table 1). At steady state, an excess amount of phosphate is absorbed from the intestine. The amount of phosphate entering the bone is equal to that released by bone resorption. Phosphatonins,

substances that induce phosphaturia, have recently been described that may add a new tier to the regulation of phosphate and mineralization of the bone. However, they have not yet been clearly proven to play a role in normal homeostasis.

Integration of the response to hypophosphatemia

Hypophosphatemia potently stimulates production of 1,25-$(OH)_2$ D which modestly increases phosphate mobilization from the bone, intestinal phosphate absorption and renal phosphate reabsorption. In addition, 1,25-$(OH)_2$ D further decreases renal phosphate excretion by directly suppressing PTH. The balance rise in serum 1,25-$(OH)_2$ D and fall in serum PTH generally cancels out any effect on serum calcium.

ETIOLOGY (TABLE 3)

REDUCED VITAMIN D STORES OR ACTION

Vitamin D may be absorbed from the diet (vitamin D_3 from animal sources and vitamin D_2 from plant sources). Yet, it is not truly a nutritional disease since it may also be made in the skin with adequate ultraviolet light exposure. Vitamin D binding protein (VDBP) then transports vitamin D_3 to the liver where it is hydroxylated. 25-hydroxyvitamin D (25OHD) is then transported by VDBP to the kidney where it may be activated to 1,25-dihydroxyvitamin D or inactivated by 24-hydroxylase. Vitamin D action may be reduced by decreased production or resistance to its action.

With decreased vitamin D action, intestinal calcium absorption decreases. The resulting secondary hyperparathyroidism, restores intestinal calcium absorption but causes bone loss-primarily in the cortical skeleton. Due to diminished repression of PTH by decreased vitamin D action, the increment in serum PTH may be accentuated with hypocalcemia and serum PTH may remain elevated even with normocalcemia. With severe vitamin D deficiency, serum calcium falls because intestinal calcium absorption cannot be corrected even by high elevations in serum PTH. Moreover, serum phosphate falls due primarily due to the phosphaturic action of PTH, but also due to the loss of vitamin D action on phosphate homeostasis. The combination of low serum calcium and phosphate results in a defect in bone mineralization.

1. ↓ Vitamin D

In the absence of ultraviolet B light (UVB), many experts recommend daily intake of vitamin D of 600 to 800 IU/day based on studies in subjects deprived of UVB light (residency in extreme northern latitudes, or submarines)[27]; yet, U.S. dietary reference intake remains lower (Table 2). Since average intake is only 100 IU/day, vitamin D sufficiency must rely on synthesis of the vitamin in the skin by adequate sunlight exposure. In the southern latitudes, it is estimated that only 15 minutes thrice weekly will provide sufficient sunlight exposure to maintain vitamin D sufficiency. During winter in the northern latitudes (at 42 degrees northern latitude, such as Boston, or further north), vitamin D synthesis by the skin is not possible because UVB radiation is filtered by the longer pathway through atmosphere of the tilted earth's axis.[28]

Table 2: Dietary reference intake for vitamin D

Age	Recommended intake
0-50 years	200 IU
51–70 years	400 IU
>71 years	600 IU

Standing Committee on the Scientific Evaluation of Dietary Reference Intakes, Food and Nutrition Board, Institute of Medicine 1997 Vitamin D. In: Dietary Reference Intakes for Calcium, Phosphorus, Magnesium, Vitamin D, and Fluoride. National Academy Press, Washington, DC, USA, pp. 250–281.

The lower limit of serum 25OHD by different labs is 20 ng/ml or much lower, but recent data suggests that this level is too low. Serum 25OHD correlates with intestinal calcium absorption, serum PTH and bone turnover markers and bone mineral density is lower in patients with vitamin D deficiency. As serum 25OHD rises from 20 to 35 ng/ml, intestinal calcium absorption increases by 65%.[29] Further increases in serum 25OHD from 30 to 49 ng/ml was not associated with any significant increase in calcium absorption.[30] As serum 25OHD falls from > 20 ng/ml to between 10 and 20, serum PTH rises 17%, and treatment with calcium and vitamin D corrects this change[31] Finally, bone turnover rises[32] and femoral trochanter bone mass falls with decreased serum 25OHD.[31]

2. ↓ 25OHD

There are several mechanisms for reduced production or increased losses of 25-hydroxyvitamin D. Since 25-D and parent vitamin D are transported by vitamin D binding protein, it is not surprising that **nephrotic syndrome** may be result in vitamin D deficiency.[33] Megalin, an clearance receptor for circulating proteins highly expressed in the proximal renal tubule, is known to recycle filtered vitamin D binding protein. Most mice lacking megalin die prenatally, but the few that survive to adulthood had severe rickets due to vitamin D deficiency.[34] Rapid intestinal transit will impair absorption of vitamin D. Small quantities of Vitamin D is excreted with the bile and reabsorbed in the ileum. This enterohepatic loop may contribute to vitamin D deficiency, but the quantities are so small that the contribution is believed to be minimal.[35] Severe liver disease may result in poor 25-hydroxylation of vitamin D, but bone disease in these patients is usually multifactorial. Finally, a few case reports suggest that rare inherited defects in the liver 25-hydroxylase may exist.[36,37]

3. ↓ 1,25-$(OH)_2$ D- Vitamin D dependent rickets type I (VDDRI)

VDDRI is caused by a deficiency in the renal 25-hydroxyvitamin D-1-α-hydroxylase.[38,39] Labs usually reveal low serum calcium and phosphate, high serum PTH, normal serum 25-D and low (or inappropriately low normal) serum 1,25-(OH)2 D. Treatment of high doses of vitamin D_3 or 25OHD are ineffective. Treatment with normal doses of 1,25-(OH)2 D completely correct the disease. Although 1,25-D is low in renal failure, phosphate is high and renal calcium loss is eliminated. Thus, lack of 1,25-$(OH)_2$ D is not a common cause of osteomalacia in patients with renal failure.

4. Resistance- Vitamin D dependent rickets type II (VDDRII)

VDDRII is caused by a mutation in the vitamin D receptor (VDR).[40] Clinical manifestations are variable. Patients often have baldness (sometimes alopecia totalis) probably due to the presence of mutated VDR in hair follicles. Labs demonstrate low serum calcium and

phosphate, elevated serum PTH, normal serum 25-D and high 1,25-D. Some patients respond to supraphysiologic doses of 1,25-D.[41] In those with severe resistance, intravenous infusions of calcium may cure rickets.[42] This syndrome may be renamed in the future to better reflect resistance to vitamin D.

PHOSPHATE DEFICIENCY

1. Poor Intake plus binding

Except with severe malnutrition, it is extremely difficult to achieve deficient intake of this common mineral. Phosphate binders (especially aluminum) in addition to low phosphate intake is usually necessary to achieve deficiency.[43,44] Typically, urinary phosphate is very low due to a compensatory increase in renal phosphate reabsorption. The hypophosphatemia-induced production of 1,25-$(OH)_2$ D may cause kidney stones by increasing urinary calcium.[45,46]

2. Renal Loss

The kidney is the most important organ to maintain phosphorus balance. In each of the following rare syndromes, renal phosphate wasting causes hypophosphatemia.

a. X-linked hypophosphatemic rickets (XLHR)- This is the most common cause of inherited rickets with a prevalence of 1/20,000,[21,47] and XLHR comprises 80% of familial phosphate wasting.[48] Despite clinical evidence for a causative humoral factor, XLHR is instead caused by inactivating mutations in the PHEX gene (phosphate-regulating gene with homologies to endopeptidase on the X chromosome).[49] The current paradigm suggests that PHEX normally cleaves phosphaturic factors, and these phosphatonins accumulate in the absence PHEX function. Usually hypophosphatemia is present at birth, but it may not become apparent for > 1 year.[50] . The defect is usually less severe in female heterozygotes than in male hemizygotes.[51]

b. Autosomal dominant hypophosphatemic rickets- a rare condition characterized by dominant transmission, hypophosphatemia and inappropriately normal 1,25-D production with normal urine calcium.[52] Clinical manifestations of rickets and hypophosphatemia are variable or even absent. In a few patients with childhood rickets, the disease resolved in adulthood. In contrast, the disease may present clinically after puberty. ADHR is caused by a mutation in the gene coding for (fibroblast growth factor 23) FGF-23 that increases the half life of the protein by impairing its cleavage into inactive fragments.[53]

c. Oncogenic osteomalacia (also termed tumor-induced rickets/osteomalacia, tumor rickets)- A rare acquired disorder in which a benign mesenchymal tumor causes osteomalacia by the elaboration of a factor (termed phosphatonin) which causes renal phosphate wasting and reduced 1,25-$(OH)_2$ D production.[54,55] Resection of the tumor cures the disease. These patients tend to be severely symptomatic. Yet, the interval between onset of symptoms and diagnosis is several years. It is unclear whether a single phosphatonin or a concert of phosphatonins is culpable, but the most likely factors include fibroblast growth factor-23, MEPE (matrix extracellular phosphoglycoprotein) and FRP-4 (frizzled related protein 4) which are further discussed below.

d. Hypophopshatemic nonrachitic bone disease- This entitiy may represent ADHR but no defect in FGF23 gene.[56] Patients have hypophosphatemia, bowing, but no rickets.[57] Reported male-male transmission rules out X-linked transmission.

e. Hereditary hypophosphatemic rickets with hypercalciuria- Rare recessive disorder in which hypophosphatemic rickets is accompanied by excess 1,25-$(OH)_2$ D production and hypercalciuria.[58] Carriers of this mutation may have hypercalciuria, high normal to increased 1,25-$(OH)_2$ D and kidney stones.[59] PTH is usually suppressed. The cause is unknown.

f. Renal tubular acidosis (RTA)- Osteomalacia is most common in proximal RTA

(type II) due to the increased propensity to waste phosphate, but it may occur in severe distal RTA (type I). In proximal RTA, phosphate is lost due to generalized proximal tubule defect. Additional findings with proximal RTA include glycosuria, aminoaciduria, hyperuricosuria and bicarbonaturia. Causes of proximal RTA include Cystinosis, Tyrosinemia, Wilson's disease, multiple myeloma, poisoning with cadmium or lead.[60] Acidosis may contribute by enhancing renal phosphate wasting and by impairing bone mineralization.

g. **Fibrous dysplasia-** Condition caused by a somatic activating mutation of GNAS1 gene, which codes for the α subunit of the stimulatory G protein.[61] Fibrous dysplasia is associated with variable clinical manifestations including single or multiple bone lesions (fibrous lesions that may appear by x-ray to be lytic, sclerotic or mixed), café-au-lait macules and endocrine hyperfunction (premature puberty, acromegaly, hyperprolactinemia, etc.). This triad is referred to as McCune Albright syndrome. Up to half of patients exhibit renal phosphate wasting, and rarely this is severe enough to result in hypophosphatemic osteomalacia likely related to elaboration of phosphatonin(s) by the bony lesions.[62-65]

MEDICATION-INDUCED

Several medications have been associated with osteomalacia and rickets.

1. **Aluminum** (Antacids, Pica)- May directly block mineralization by deposition at the mineralization front.[66] As noted above, aluminum may also cause hypophosphatemia by binding phosphate in the intestinal lumen and preventing its absorption.
2. **Anticonvulsants**- Phenobarbital and phenytoin are believed to increase the catabolism of 25-D by upregulating the degrading p450 enzymes. Phenytoin may also directly diminish intestinal calcium absorption.
3. **Heavy Metals**- Cadmium, lead and mercury may induce Fanconi's syndrome and renal phosphate wasting.[60]
4. **Bisphosphonates**- Etidronate is the only bisphosphonate well-reported to induced osteomalacia, and this generally occurred with prolonged treatment at high dose (20 mg/kg).[67]
5. **Fluoride**- Fluoride induces bone formation, so toxic doses with insufficient calcium absorption may result in inadequately mineralized new bone formation.[68,69]

OTHER

1. **Collagen disorder- Fibrogenesis imperfecta ossium (FIO)**, a rare disease with < 20 cases reported, is characterized by progressive bone pain and fractures with no known cause or effective treatment.[70,71] It seems to be an acquired disease given that the onset is usually after the age of 50, but one man and his 12 year-old daughter have been reported.[72] X-rays reveal thickened trabeculae and coarsening- may be confused with Paget's disease (osteitis deformans). Bone histology reveals osteomalacic features combined with a loss of normal birefringence of collagen under polarized light. It is associated with monoclonal gammopathy, and the bone disease of one patient reversed with treatment of the gammopathy with prednisone and melphalan,[73] but this was ineffective in another patient.[74] Bisphosphonates are not effective.
2. **Endogenous mineral inhibitors-** Approximately 300 cases or hypophosphatasia have been reported. It is caused by inactivating mutations in the tissue-nonspecific (bone/liver/kidney) isoenzyme) of alkaline phosphatase (TNSAP).[75] The full role of TNSAP is unclear, but it cleaves pyrophosphate, a mineral inhibitor, into two phosphate molecules. Hypophosphatasia is characterized biochemically by subnormal activity of the alkaline phosphatase (usually < 20). Clinically, manifestations range complete lack of mineralization with death to no symptoms.[76]
3. **Axial osteomalacia-** In this rare entity (< 20 cases reported), x-ray reveal axial

hyperostosis (spine, ribs and pelvis) with coarsened sponge-like features and thickened cortex that particularly involves the cervical spine.[77-79] These x-ray changes are stable for up to 18 years of follow-up. Patients, usually middle-aged, may complain of pain at the spine. Despite biopsy-proven osteomalacia, biochemical evaluation is usually normal. The histological features are different from typical osteomalacia in that the cortical thickness is increased and the mineralization defect may be heterogeneous. In a few reports, axial osteomalacia was associated with anklylosing spondylitis or polycystic kidney disease. All cases, except for a report in a mother and son have been sporadic.

4. **Calcium deficiency-** Since calcium and phosphate compose the mineral content of bone, intuitive reasoning would suggest that inadequate intake of calcium or phosphate may cause rickets. In fact, only a few well-documented cases of rickets induced by dietary calcium deficiency have been reported.[80] In each case, mostly from South Africa, dietary calcium intake was < 200 mg/day. The rarity of rickets caused by dietary calcium deficiency in the setting of vitamin D sufficiency is because compensatory hyperparathyroidism usually yields equal loss of mineral and bone matrix so a mineral defect is not found.

Table 3: Summary Table of Etiologies of Rickets/Osteomalacia

Cause	Details
A. ↓ Vitamin D Effect	Plain D- **lack of sunlight**, poor dietary intake (need 600-800 IU/day) 25-D- **diarrhea**, nephrotic syndrome 1,25-D- enzyme defect (VDDR I- vitamin D dependent rickets type I), most renal phosphate wasting disorders Resistance- (inactivating VDR mutation- VDDRII)
B. Hypophosphatemia	Poor GI intake- Almost always requires concomitant phosphate binder Renal phosphate wasting- **XLHP (x-linked hypophosphatemic rickets),** ADHR (autosomal dominant hypophosphatemic rickets), TIO (tumor-induced osteomalacia, oncogenic osteomalacia) HHRH (hereditary hypophosphatemic rickets with hypercalciuria) RTA- type II and probably type I Fibrous dysplasia
D. Drug	Blocking mineralization front- aluminum, Etidronate Enhanced vitamin D catabolism- phenytoin, phenobarbital Induced renal tubular acidosis- cadmium, lead and mercury Excessive bone formation- toxic doses of fluoride
E. Other	Hypophosphatasia Fibrogenesis imperfectum ossium Axial osteomalacia Severe calcium deficiency

NEW BREAKTHROUGHS

Over the last half decade, multiple discoveries have been made relating to phosphate metabolism and bone mineralization.

PHEX AND PHOSPHATONINS

Accumulating data suggests that the hormonal calcitropic triangle is incomplete. Hypophosphatemia should stimulate elevated production of 1,25-$(OH)_2$ D; yet, in several

hypophosphatemic states, the hormone is low or normal. Evidence for phosphatonin, a factor causing renal phosphate wasting and hypophosphatemia, was first observed in patients with oncogenic osteomalacia. This entity is characterized by acquired hypophosphatemic osteomalacia associated with low or inappropropriately normal 1,25-$(OH)_2$ D that completely reverses after resection of the causative tumor.

PHEX

A series of experiments on the HYP mouse, a model of X-linked hypophosphatemic rickets characterized by blood findings of low phosphate and low to normal 1,25-$(OH)_2$ D, initially suggested a similar humoral factor. In parabiosis experiments, the blood from the HYP mouse caused renal phosphate wasting and hypophosphatemia in the wild type mouse.[81] The factor was not PTH because parathyroidectomy did not abolish the hypophosphatemic response.[82] Nesbitt et al. found that the HYP kidneys did not harbor a structural defect. Kidneys transplanted from HYP mice into wild type mice excreted phosphate normally, and the transplantation of wild type kidneys into HYP mice did not correct renal phosphate wasting.[83] However, the causative mutation was instead found to be an endopeptidase.[49] The cleavage site of PHEX is very small, so it cannot cleave any of the suspected intact phosphatonins but it may active fragments. Further research is needed to understand how PHEX mutations cause rickets.

FGF 23 (fibroblast growth factor 23)

The gene FGF 23, which codes for the protein FGF-23, was first identified by linkage studies in ADHR.[56] Later, mutations in FGF 23 were noted to impair inactivating cleavage of the peptide.[53] The current tissue source of circulating FGF-23 is unclear, but it is expressed at very low levels in the heart, liver, thyroid and parathyroid. FGF 23 is highly expressed in tumors causing oncogenic osteomalacia.[84] The physiological relevance of FGF-23 is underlined by the physiologic findings of a knock model including ↑serum phosphate and 1,25-$(OH)_2$ D.[85]

FGF-23 is measurable in normal humans.[86] In oncogenic osteomalacia, serum FGF-23 is usually highly elevated and falls with surgical cure. In XLHR, serum FGF-23 tends to be high, but there is much overlap with the normal range. Administration or targeted production of FGF-23 in animal models or in vitro results in phosphaturia, hypophosphatemia and reduction in 1,25-$(OH)_2$ D.[87-88] Interestingly, 1,25-$(OH)_2$ D is suppressed long before phosphate falls.

sFRP-4 (secreted frizzled related protein 4)

sFRP-4 is a circulating factor that blocks renal Wnt-signaling. Several factors suggest that sFRP-4 may act as a phosphatonin.[89] Serial analysis of gene expression (SAGE) of four tumors responsible for oncogenic osteomalacia identified sFRP-4 was highly expressed in tumors. In vitro, it inhibited sodium-dependent phosphate transport. Finally, sFRP-4 infusions in rats over 2 hours increased renal fractional excretion of phosphate from 14 to 34%. Even in parathyroidectomized rats, sFRP-4 infusion increased renal fractional excretion of phosphate from 0.7 to 3.8%. Serum phosphate fell at 8 hours, but serum 1,25-$(OH)_2$ D did not change.

MEPE (matrix extracellular phosphoglycoprotein)

MEPE, also known as OF45, osteoblast/osteocyte factor 45 in rats, was originally cloned "from a cDNA library of" oncogenic osteomalacia.[90] MEPE expression is localized in osteoblasts, osteocytes and odontoblasts inferring a role in tissue mineralization.[91] The effect of MEPE effect on phosphate transport has been inconsistent between studies. "Recombinant MEPE" from mammalian cells "failed to inhibit phosphate transport in vitro" or to cause

phosphaturia in mice. However, insect-derived human MEPE decreased decreased phosphate uptake on cultures of renal proximal tubular cells and diminished BMP2-induced mineralization in cultured osteoblasts. In vivo studies, showed dose-dependent increases in urinary phosphate (best at 400 mcg/kg/30h and decreases in serum phosphate in mice after intraperitoneal administration. In contrast, MEPE knockout mice have increased bone mineralization and no defect in phosphate metabolism. The most recent studies with MEPE have found a potential new mechanism of osteomalacia. A short C-terminal fragment of MEPE contains an ASARM (acidic serine-aspartate-rich motif) peptide which seems to block BMP2-mediated mineralization.[91,92] There is evidence that PHEX blocks cathepsin-mediated cleavage of MEPE, which may prevent release of ASARM peptide.

CLINICAL MANIFESTATIONS AND DIAGNOSIS

Osteomalacia presents primarily with progressive diffuse bone and muscle pain that is improved when sitting or supine.[93-95] Patients may develop muscular weakness particularly proximally. The first manifestation of weakness is difficulty climbing stairs or standing from a sitting position, but later, patients may develop difficulty combing their hair or ultimately even feeding themselves. They may develop fractures with increased localized pain (most commonly in the ribs, pelvis, hips and metatarsals) and with time many develop diffuse bony pain. Since osteomalacia is uncommon, patients are often symptomatic > 2 years prior to diagnosis. They may be referred to a Rheumatologist to rule out connective tissue disease or to manage fibromyalgia, to an Oncologist to rule out malignancy or to an Orthopedist to treat fractures. The finding of lower extremity deformities should raise suspicion for childhood rickets as this does not generally occur in adults. Osteoporosis, in contrast, is usually asymptomatic until fracture occurs. The gait is a characteristic walking waddling as the pelvis dips with each step.

Rickets presents with many clinical findings. The enlarged growth plate translates clinically into swollen wrists, knees, ankles and beading of the costochondral junctions (**rachitic rosary**). Bowing occurs in the weight-bearing bones (arms when crawling and legs when walking). The ulna is characteristically more involved than radius because it grows faster.[94] Other skeletal findings include **craniotabes** (softening of the skull leading to squaring of the skull, flattening of the parietal and occipital bones, and frontal bossing), widening of the skull bone sutures, **Harrison's groove** (indentation of the lower ribs at the site of attachment of the diaphragm), dwarfism, scoliosis, and fractures/pseudofractures (described further in the x-ray section). Delayed tooth eruption and enamel hypoplasia have been described with vitamin D related rickets. Patients with vitamin D rickets are more likely to suffer symptoms of hypocalcemia including muscle weakness, muscle cramps and acral paresthesisas. A few clinical findings are most consistent with XLHR. Another clinical sign is the appearance of the teeth. Unlike nutritional rickets, patients with XLHR get dentin defects causing dental abcesses rather than enamel hypoplasia. Calcification or bone formation at the entheses, sites of muscle insertions in the bone, is another characteristic of XLHR. This complication may cause significant morbidly by pain and limitation of motion. Hypotonia and muscle weakness does not occur with XLHR.

DIAGNOSIS (TABLE 4)

Osteomalacia is a clinical diagnosis strongly dependent on the astute clinician. Obvious osteomalacia is characterized by progressive proximal weakness, diffuse pain centered in the skeleton rather than the joints, and fractures especially when occurring in uncommon locations including the ribs, metatarsals and sternum. It is likely that obvious osteomalacia only represents the tip of the iceberg. Therefore, the possibility of subtle osteomalacia should be recognized in

patients with risk factors for vitamin D deficiency (elderly, highly pigmented skin, poor sunlight exposure, poor intake of dairy, inadequate supplementation with vitamin D or calcium). Rickets should be highly suspected in the same subgroups or any child with impaired growth. The history and physical are also useful to narrow the etiology- particularly the chronological aspects, muscle weakness and family history.

The diagnosis is only confidently made by bone biopsy after tetracycline labeling, but a combination of noninvasive tests may be very suggestive. The suspected diagnosis is confirmed by the histomorphometrical combination of widened osteoid seams with prolonged mineralization lag time. Bingham et al. found that all patients had at least two of: low Ca, low P, elevated alkaline phosphatase or radiographic finding suggestive of osteomalacia.[96] The most useful noninvasive test is alkaline phosphatase which is elevated in almost all patients. It the rare case that alkaline phosphatase is not elevated, it should be high normal. In contrast, it should be low in patients with hypophosphatasia.

Other tests help diagnose the underlying cause of osteomalacia. Low serum Ca in combination with phosphate is suggestive of a vitaminD-mediated cause. However, vitamin D deficient osteomalacia may occur with low normal blood calcium and high normal alkaline phosphatase. Secondary hyperparathyroidism and low urinary calcium are also expected with vitamin D deficiency and the range of labs roughly corresponds with the severity of disease. Serum PTH > 46 should be considered elevated on the "intact" assay, since the upper limit of 65 falls to 46 after exclusion of patients with vitamin D insufficiency.[97] We consider urinary calcium < 100 mg/day to be low. Urinary phosphate may be useful. While it may be high in both renal phosphate wasting disorderes and vitamin D deficiency, urinary phosphate is low with inadequate gastrointestinal phosphate absorption. In patients with low calcium and phosphate, 25OHD, the best marker of vitamin D deficiency, should be measured. If normal, 1,25-dihydroxyvitamin D should be measured. Suggestive histological findings of hypophophatemic rickets are hypomineralized periosteocytic lesions. They never completely disappear although they will diminish with active treatment.

X-rays may be very useful.[98] **Pseudofractures** (Looser's zones, Milkman fractures), which are focal accumulations of unmineralized osteoid found in cortical bone perpendicular to the long axis, are characteristic of osteomalacia. They are generally bilateral and symmetrical. Common locations include the ribs, pelvis, medial aspect of the femur, lateral aspect of the scapulae and metatarsals. In XLHR and hypophosphatasia, Looser's zones tend to occur on the outer cortex of the femur unlike nutritional rickets in which the pseudofractures tend to be on the medial cortex.[99] Pseudofractures may progress to fracture (Figure 4). Insufficiency fractures occur at the same sites and may therefore be confused with pseudofractures. Features that strongly suggest pseudofractures include ≥ 3 broad lucent bands; absent or minimal callus; symmetry; at least one lucency at the rib, pubis or femur; and biochemical features suggestive of osteomalacia (low blood calcium or phosphate, elevated alkaline phosphatase). Other findings common in osteomalacia include osteopenia (reduction of mineralized bone), trabeculae that are coarsened and indistinct, biconcave vertebral bodies. Cortical thinning and subperiosteal resorption is common with secondary hyperparathyroidism resulting from lack of vitamin D action.

Several x-ray findings are characteristic of rickets.[98] An early sign is widening of the space between the end of the metaphysis and epiphysis. It is best seen and the proximal tibia. **Fraying** is a specific sign for rickets in which threadlike shadows of calcified fibers extend from the end of the shaft into the transparent cartilage. Early on, they impart a "fuzzy" outline to the end of the shaft, and in advanced cases the threads become long and coarse. **Cupping**, a concavity in the end of the shaft, is best seen at the distal ulna or either end of the fibula. **Spreading** of the shaft is

sometimes seen as well. In rickets and osteomalacia, the cortices are usually thin, but some forms including hypophosphatemic rickets may present with hypertrophic cortices. Calcified enthuses are most consistent with XLHR.

Bone mineral density is poorly studied in osteomalacia. It tends to be low tends to be low particularly in cortical bone except in x-linked hypophosphatemic rickets, in which bone mineral density may be above average. Since bone mineral density primarily represents mineral, bone density increases tremendously and rapidly with effective treatment. So while calcium and vitamin D treatment increase the bone density minimally, if at all, in osteoporosis; in osteomalacia, density may increase 30% in one year with only calcium and vitamin D treatment.

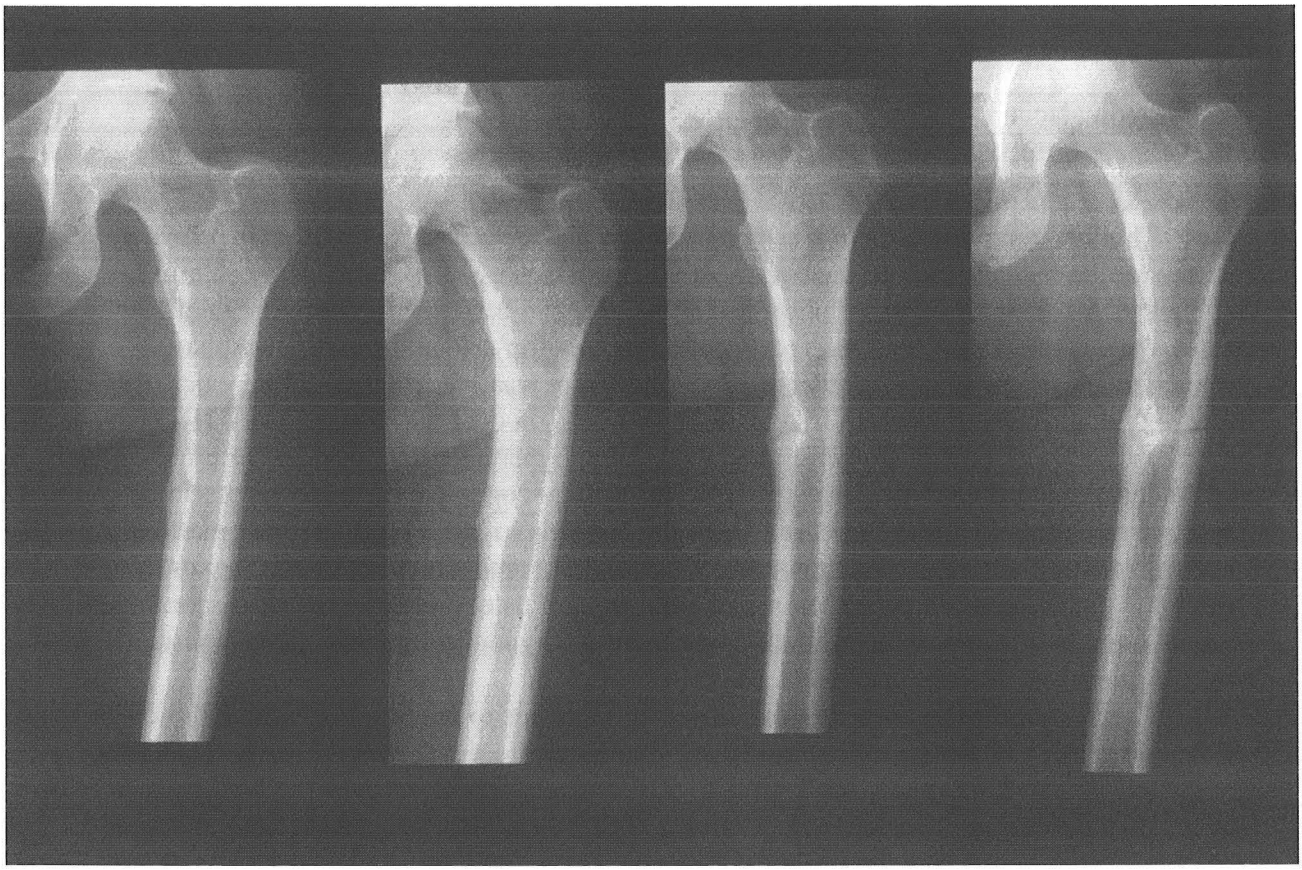


Figure 4: Progression from pseudofracture to complete fracture in a patient with oncogenic osteomalacia despite maximal medical therapy. Courtesy of Dr. Neil Breslau

Table 4: Laboratory findings with different causes of rickets/osteomalacia

Disorder	SCa	SP	AP	PTH	1,25-$(OH)_2$ D
↓Vit. D, ↓25OHD	N or ↓	N or ↓	↑	↑	N, ↑, or ↓
VDDR I	↓	↓	↑	↑	↓
VDDR II	↓	↓	↑	↑	↑↑
Most Renal P wasting disorders	N	↓	↑	N or ↑	↓ (or inappropriately normal)
HHRH	N	↓	↑	N	↑
Hypophosphatasia	N or ↑	N or ↑	↓	N	N
Fibrogenesis imperfecta ossium	N	N	N to ↑	N	N
Axial osteomalacia	N	N	N	N	N

MANAGEMENT

Therapy is based on the underlying etiology and severity. This section is primarily focused on the management of the two most common causes of osteomalacia- vitamin D deficiency and disorders of renal phosphate wasting. In a basic sense, vitamin D deficiency is treated with calcium and vitamin D (or a potent metabolite). In addition to phosphate supplements, patients with disorders of renal phosphate wasting usually require calcitriol (1,25-dihydroxyvitamin D_3) to prevent hyperparathyroidism. In contrast, patients with HHRH should only be treated with phosphate given their associated hypercalciuria, elevated serum calcitriol and tendency toward nephrolithiasis. In patients with oncogenic osteomalacia, resection of the causative tumor abolishes the disease. Until the tumor is found, symptoms may markedly improve with aggressive management (see Case 3), but some patients progess inexorably (see Figure 4). When possible, drugs known to contribute to osteomalacia must be discontinued. At present, there is no consistently effective treatment for hypophosphatasia, fibrogenesis imperfecta ossium or axial osteomalacia.

The key goal of treatment in patients with rickets is to maximize height and prevent bone deformities.[100,101] If treatment is started early, bone deformities usually resolve. However, treatment in the asymptomatic adult with XLRH is controversial because the key goals have been met and the patients are usually asymptomatic. There is no data suggesting that treatment prevents fracture, enthesopathy or dental abcesses. Moreover, there are risks of treatment including nephrocalcinosis and hypercalcemia. However, one study in 18 symptomatic adults with XLHR found treatment improved symptoms and histomorphometry, so treatment should be considered in symptomatic adults.[102]

Considering the number of years most patients have suffered osteomalacia prior to treatment, recovery is quite rapid. Within two to three weeks, much of the pain will resolve. Muscle weakness generally requires months correct. To avoid complications of treatment, it is imperative to follow laboratories carefully.

Urinary calcium is the most useful marker to follow during the treatment with vitamin D derivatives. Urinary calcium stays low as mineral is rapidly deposited into osteoid, and its rise toward or above 100 mg/day is a signal that recovery is nearing completion and that the doses of vitamin D, if large, should be lowered. Urinary calcium exceeding 250 mg/day should be avoided. Serum calcium should be followed to avoid hypercalcemia, but hypercalcemia only occurs when very high calcium loads or due to some impairment in the kidneys ability to excrete

excess calcium. Although high normal serum calcium suggests that the dose of vitamin D should be diminished, the same dose should instead be continued if the low urinary calcium has not risen. Alkaline phosphatase, the most sensitive marker of osteomalacia, is also useful to follow during treatment. It initially increases with treatment because of the robust recovery of bone formation and mineralization. Then, alkaline phosphatase slowly declines over months. If serum PTH was elevated at baseline, one should document its normalization.

In disorders of renal phosphate wasting, alkaline phosphatase is the best indicator of recovery although it should initially increase during recovery. Fasting serum phosphate will remain low and may actually be lower than baseline because overnight renal phosphate excretion is enhanced with high phosphate intake. Serum phosphate exhibits a circadian rhythm with gradually increasing concentrations later in the day. Moreover, it may fall with carbohydrate load since insulin drives phosphate into cells. Therefore, one should check serum phosphate toward the afternoon. Although the development of nephrocalcinosis is common with treatment, it is unclear whether excessive treatment with phosphate of calcitriol is more culpable. However, one should monitor urinary calcium and phosphate carefully to avoid this complication. Serum PTH should be followed in any patient treated with phosphate. Tertiary hyperparathyroidism complicates 10-15% cases with oncogenic osteomalacia possibly related to the loss of the repressive actions of 1,25-$(OH)_2$ D on PTH production.

Calcium- Since calcium absorption plateaus at about 500 mg, optimal absorption requires divided doses. Calcium should be given separate from food in a hypophosphatemic patient because it will bind phosphate. Patients should be given approximately 1500 mg of elemental calcium. Dairy is a good source of calcium and phosphate.

Vitamin D- There are several forms of vitamin D. Vitamin D3 is available in multiple vitamins (400 units) and in calcium supplements (usually 100-200 IU/pill). A liquid form with 8000 units/ml is also available. Ergocalciferol (vitamin D_2) is available in 50,000 units pills. Vitamin D_3 is believed to raised serum 25OHD approximately 70% than the same dose of ergocalciferol.[103] Calcitriol is approximately 5000 times more potent than vitamin D_3. It works much more quickly (days vs. weeks to months) and its effect resolves much more quickly when discontinued.(days vs. weeks).

The dosing and formulation used depends on the severity and etiology of disease. In patients who have malabsorption or who use anticonvulsants, the needed dose will be higher.[104] One may use serum 25OHD to estimate the necessary treatment dose (1000 units/day will raise it approximately 7 ng/ml.[105] The goal serum 25OHD should be > 30 ng/ml and some suggest > 40 ng/ml. In my experience, each patient has markedly different needs for vitamin D that diminish as the bone heals. My general approach for severe vitamin D deficiency is to start at 50,000 units twice per week with close follow-up of labs. Less symptomatic patients should be treated with 1000 to 1500 units of vitamin D_3. Patients with a defect in the synthesis of 1,25-hydroxyvitamin D are best managed with calcitriol. The dose of calcitriol in osteomalacia is usually 0.25 to 1.5 mcg/day in divided doses, but some patients may need more.

Phosphate- As a good source of dietary phosphate, a high dairy diet is recommended. Additionally, most patients will require 1 to 3 grams/day in divided doses (usually three to five times daily). Phosphate must be given separately from calcium or dairy to avoid binding. Common side effects of phosphate treatment include bloating, abdominal cramping and diarrhea.

OSTEOPOROSIS VS. OSTEOMALACIA

Although osteomalacia is less common than osteoporosis, it is critical to recognize. Table 5 summarizes several differentiating features between the two diagnoses. BMD, which is low by definition in osteoporosis, may also be low in osteomalacia- particularly in states of vitamin D deficiency. With vitamin D deficiency, intestinal calcium absorption is impaired. The resulting secondary hyperparathyroidism maintains blood calcium by mobilizing calcium from the bone. By blocking bone resorption, potent antiresorptive therapy initiated due to the misdiagnosis of osteoporosis may instigate hypocalcemic tetany. Vitamin D insufficiency also results in compensatory secondary hyperparathyroidism, but presents most commonly with PTH-mediated bone loss rather than obvious osteomalacia. Although vitamin D insufficiency is particularly common in populations who are elderly, institutionalized, highly pigmented or anticonvulsant-treated, it is common worldwide (25%) even in sunny populations. Treatment with appropriate doses of calcium and vitamin D decreases fracture risk and improves the bone density response to approved antiosteoporotic agents.

Table 5: Summary comparison of osteomalacia and osteoporosis

Category	Osteomalacia	Osteoporosis
Prevalence	Uncommon, but more prevalent than realized	Common
Distribution	Men = Women	Women > Men
Symptoms	Diffuse pain and weakness	Asymptomatic prior to fracture
Fractures	Spine, hips and in unusual locations- ribs, scapula, pelvis and metatarsals. Also, pseudofractures	Fractures tend to occur and lower spine, hip, proximal humerus and distal radius
Blood and Urine Tests	Multiple lab abnormalities- ↓ serum Ca, P and urine calcium; ↑ serum alkaline phosphatase and PTH	Labs are normal in the majority
BMD	Low, normal or high	Low density
Response to treatment	Treatment with calcium and vitamin D may result in huge increase (>20%/1 year). Potent antiresorptive therapy may result in hypocalcemia and tetany.	Treatment with calcium and vitamin D increase bone density < 2%. Improvement with approved therapy is generally < 10%/3 years.

SUMMARY

Osteomalacia, though rare, is more common than currently recognized. When treated effectively, symptoms gratifyingly resolve within weeks to months and bone mineral density may increase tremendously. Alternatively, inappropriate treatment with potent antiresorptives may result in tetany in patients with vitamin D deficient osteomalacia. Preceding clinical osteomalacia patients may have undiagnosed vitamin D insufficiency for many years. It is now recognized that vitamin D insufficiency with compensatory hyperparathyroidism leads to bone loss and is common even in sunny populations (25% worldwide) and the prevalence is much higher in at-risk populations such as the elderly. This may explain why treatment of the elderly with calcium and vitamin D is so effective at preventing fractures. The discovery of potential phosphatonins and endogenous inhibitors of bone mineralization promise new avenues to increase bone mass and prevent fracture.

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