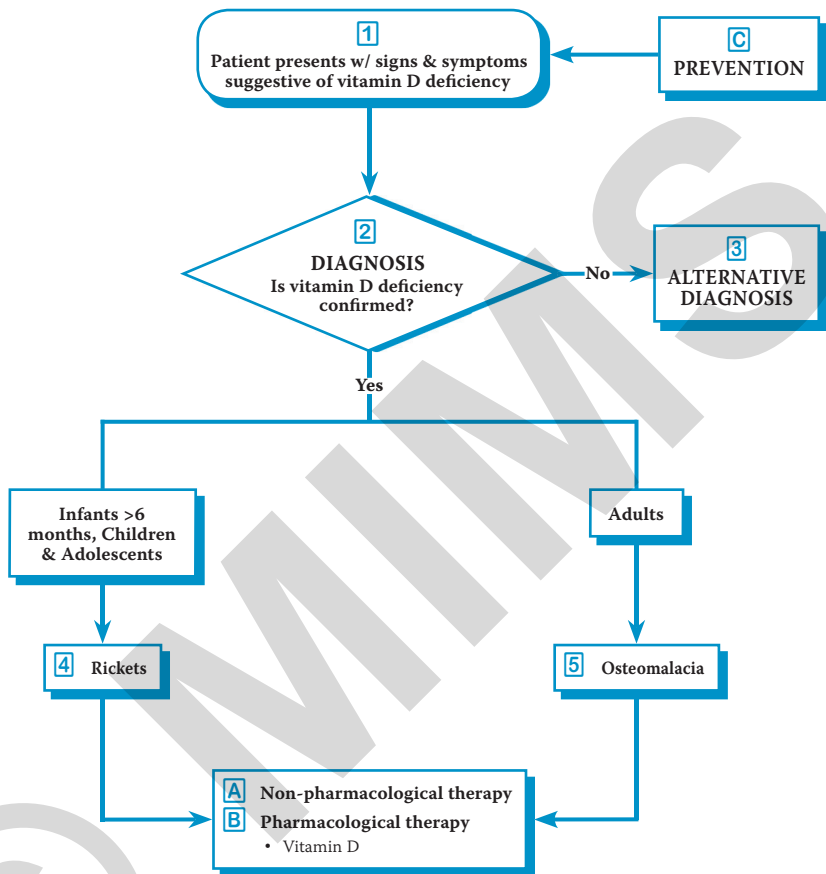


Vitamin D Deficiency (1 of 8)



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Specific prescribing information may be found in the latest MIMS.*

1 Vitamin D Deficiency

- A condition wherein there is low circulating levels of vitamin D
- Vitamin D is an essential steroid hormone found in the body
- Low vitamin D levels are more common in the Middle Eastern & South Asian regions
- Common in the elderly, medical & institutionalized patients, people living at higher latitudes, during winter & those w/ low sun exposure

Vitamin D Insufficiency

- Less severe state of calcidiol-deficiency
- Common among older adults & hospitalized & institutionalized individuals
- Occurs in 40-50% pre-adolescent Caucasian girls & in 17% of chronic kidney disease patients
- Typical calcidiol range is 21-29 ng/mL (525 to 725 nmol/L)
- Associated w/ increased parathyroid hormones (PTH) & osteoporosis

Vitamin D Deficiency

- Results from inadequate sunlight exposure, malabsorptions &/or inadequate nutrition
- Classified as serum 25-hydroxyvitamin D(25-[OH]D) levels of <20 ng/mL (50 nmol/L)
- Common in 40-50% of Hispanic & African American adolescents & 29% of chronic kidney disease patients
- Affects 40-100% of elderly & 60% of nursing home residents
- Vitamin D deficiency rickets is most prevalent in children <2 years old w/ peak incidence between 3-18 months
- Osteomalacia due to vitamin D deficiency may be found in 30% of gastric surgery or bypass for obese patients
- Adolescents w/ low serum vitamin D levels are associated w/ increased risk of hyperglycemia, hypertension & metabolic syndrome
- Pregnant & lactating women taking prenatal vitamins & calcium supplements w/ vitamin D remains at risk for vitamin D deficiency
- Associated w/ increased risk of gestational diabetes mellitus, pre-eclampsia, pre-term birth, small-for-gestational age (SGA) infants, impaired fetal skeletal formation leading to infant rickets & reduction in bone mass
- Mothers who are vitamin D deficient will have infants w/ rickets & no vitamin D stores at birth
- Important etiologic factors:
 - Autoimmune diseases (eg multiple sclerosis, diabetes mellitus type 1)
 - Cancer (eg colon cancer, breast cancer, non-Hodgkin's lymphoma)
 - Cardiovascular diseases (eg hypertension, heart failure, sudden cardiac death)
 - Inflammatory bowel disease (eg Crohn's disease)
 - Infections
 - Immune deficiency
 - Neurocognitive disorders (eg Alzheimer's disease)
- Stages of vitamin D deficiency:
 - Stage 1 presents as decreased 25-OH-D levels, unchanged or increased 1,25-OH₂-D leading to hypocalcemia & euphosphatemia
 - Stage 2 presents w/ continued decreased 25-OH-D levels, slight increased in skeletal alkaline phosphatase levels, eucalcemia, hypophosphatemia & PTH maintains calcium through bone demineralization
 - Stage 3 manifests as severe 25-OH-D deficiency w/ increased alkaline phosphatase, hypocalcemia, decreased bone mass & increased fracture risk
- Complications:
 - Bone disease (eg rickets, osteoporosis, low bone mass)
 - Decreased immunity to fight of infection (eg tuberculosis, influenza, viral infection)
 - Increased incidence of death caused by cancer (eg breast, colon, prostate), fracture, heart disease, inflammatory bowel disease, & respiratory diseases
 - May affect reproductive success

1 Vitamin D Deficiency (CONT'D)

Risk Factors:

- Age
- Dark-skinned individuals (eg African Americans)
- Drugs [eg anticonvulsants (eg Phenobarbital, Phenytoin), antiretrovirals, Cholestyramine, Rifampicin]
- Exclusively breastfed infants & children who have limited sunlight exposure
- Genetic disorders [eg 25-hydroxylase deficiency, 1 α -hydroxylase deficiency, hereditary resistance to vitamin D (Vitamin D-dependent rickets type 2)]
- Geographic location (eg sunshine-deficient areas, higher latitude living, people living in northern climates)
- Kidney disease (eg nephritic syndrome)
- Institutionalized individuals (eg hospitalized patients, nursing home residents)
- Intestinal malabsorption disease (eg biliary obstruction, celiac sprue, cystic fibrosis, gastric resection, pancreatic insufficiency, or Whipple's disease)
- Intestinal resection
- Liver disease (eg liver cirrhosis)
- Obese individuals
- Multiple, short interval pregnancies & lactating women
- Sarcoidosis & lymphomas - increases metabolism of 25[OH]D to 1,25[OH]D
- Strict sunscreen & skin concealing garments use
- Severe chronic liver diseases (eg cirrhosis)
- Vegetarians, high phytate consumption (eg chapatis) & other unusual diets

2 DIAGNOSIS

Clinical Presentation:

- Fracture w/ minimal trauma
- Hypophosphatemia
- Muscle cramps
- Neuromuscular
- Paresthesia
- Severe hypocalcemia - seen in later stages of vitamin D deficiency causing seizure tetany

Laboratory Tests:

Serum 25(OH)D

- Good indicator of vitamin D status & stores
- Used to evaluate vitamin D status in patients at risk for deficiency
- Normal value: 30-40 ng/mL (75-100 nmol/L) in adults
- Indications for screening:
 - African-American & Hispanic adults & children
 - Chronic kidney disease
 - Granuloma-forming disorders (eg berylliosis, coccidiomycosis, histoplasmosis, sarcoidosis, tuberculosis)
 - Hepatic failure
 - Hyperparathyroidism
 - Malabsorption syndromes - eg bariatric surgery, Crohn's disease, cystic fibrosis, inflammatory bowel disease, radiation enteritis
 - Medications (eg anticonvulsants, antifungals, antiretrovirals, cholestyramine, glucocorticoids)
 - Obese adults & children (BMI >30 kg/m²)
 - Older adults w/ history of falls &/or nontraumatic fractures
 - Osteomalacia
 - Osteoporosis
 - Pregnant & lactating women

Serum 1,25-dihydroxyvitamin D

- Elevated in cases of concomitant hyperparathyroidism
- Significant in cases of vitamin D resistance or defective 1-hydroxylation which appears in low levels

Parathyroid Hormone (PTH)

- Marker of vitamin D insufficiency
- Elevated in vitamin D insufficiency

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2 DIAGNOSIS (CONT'D)

Laboratory Tests: (cont'd)

Serum or Bone Alkaline Phosphatase

- Increased activity is associated w/ osteomalacia due to vitamin D deficiency
- May present as normal or borderline in some patients

24-hour Urine Calcium

- Not indicated in patients taking thiazides

Radiologic Findings:

- In children w/ rickets, epiphyseal growth plate appears widened in the context of cupped metaphysis & an ill-defined diaphyseal border caused by decreased mineralization
- Stage I rickets presents as demineralization of the calvarium & loss of definition of skull sutures
- Poorly defined trabecular pattern of the metaphyses w/ bowed & thinned cortices of diaphyses
- In osteomalacia, absence or blurred margins w/ thin cortices may be noted on cancellous bones
- Looser's zones
 - Also known as Milkman's fractures or pseudofractures
 - Pathognomonic of osteomalacia
 - Bilateral, thin (2-3 mm), radioluscent bands
 - Perpendicular to periosteal surface in femoral neck, ribs, ischial & pubic rami, metatarsals & below the glenoid fossa on the outer border of the scapula
 - Appears as increased uptake on bone scans which may lead to search for primary malignancies
- In secondary hyperparathyroidism, subperiosteal erosions along the cortices may be seen
- Sacroiliac joint pseudowidening or widening w/ hazy margins have been observed
- Bone mineral density T-scores between -3 & -4 w/ radial diaphyseal density lower than the lumbar spine or total proximal femur

Quantitative Histologic Findings:

- Examination of undecalcified bone is required in order to establish unequivocal presence of osteomalacia
- Trabeculae covered w/ abnormally thickened osteoid seams
- Findings in osteomalacia:
 - Osteoid width augmentation of $>15 \mu\text{m}$ (normal value = $4-12 \mu\text{m}$)
 - $>10\%$ osteoid area of cancellous bone area (normal value = $<4\%$)
 - >100 days of mineralization lag time (normal value = $9-20$ days)
 - Determined by osteoid width divided by distance between & linear extent of double tetracycline labels observed in bones after 2 time-spaced oral tetracycline course
- 2 time-spaced course of Tetracycline
 - Deposited Tetracycline in the hydroxyapatite crystal formation early in the course generates bright stripes at the mineralized bone & osteoid interface when viewed w/ fluorescent microscopy
 - Courses of Tetracycline 1g/day for 3 days are given on a 14-day interval
 - Mineralization rate ($\mu\text{m/day}$) = average distance between double labels / number of days between 2 courses
 - Results:
 - Increased bone turnover when numerous & widely spaced double labels w/ intact mineralizations & excess osteoid
 - Delayed or ceased mineralization of osteomalacia once paucity of tetracycline labels are narrowly spaced in the presence of excessive osteoid

3 ALTERNATIVE DIAGNOSIS

- Arthritis
- Fibromyalgia
- Hyperparathyroidism
- Paget's disease
- Thyrotoxicosis

4 RICKETS

- Seen in children
- Due to defective mineralization of cartilaginous growth plate & endochondral bone formation
- Stages of rickets:
 - Stage 1 - early clinical manifestations of vitamin D deficiency related to hypocalcemia w/ clinical signs of hypocalcemia which is commonly seen in infants <6 months old
 - Presents w/ apneic episodes, convulsions or tetany w/ no clinical signs of rickets
 - Stage 2 - impaired bone mineralization is apparent
 - Stage 3 - presents w/ signs of hypocalcemia & severe rickets
- Manifestation:
 - Bowing of the legs - genu varum (bowed legs) or genu valgum ("knock knees")
 - Craniotabes - highly suggestive in the absence of hydrocephalus & osteogenesis imperfecta
 - Delayed tooth eruption
 - Teeth enamel hypoplasia
 - "Hot-cross bun appearance" - delayed fontanelles closure & growth w/ frontal & parietal bossing
 - Harrison's groove/sulcus - lower anterior thoracic wall indentation
 - Hypocalcemia-induced seizure - observed only in severe vitamin D deficiency
 - Increased susceptibility to infections
 - Leg bone pain
 - Metaphyseal flaring/widening
 - Motor delays
 - Poor growth
 - Rachitic rosary - costochondral junction prominence influenced by difference in individual bone growth rates
 - Violin vase deformity - narrowing of lateral diameter of the chest due to negative intrapleural pressure associated w/ breathing
- Presents as border-normal or low total calcium levels, low phosphate levels, elevated alkaline phosphatase activity & PTH concentrations
- May also occur in severe recessive form of osteopetrosis

5 OSTEOMALACIA

- Seen in adults or adolescents after epiphyseal closure
- Softening of bones referring to defective or delayed mineralization disorder of formed bones
- Depends on overlapping manifestation:
 - Due to underlying disorder such as gastrointestinal disease or surgery (eg troublesome gastric resection, stapling or bypass for obesity, & intestinal malabsorption)
 - Hypocalcemia or hypophosphatemia
 - Directly due to bone disease
- Manifestation:
 - Bone tenderness
 - Elicited by pressing on tibia, wrist, pubic rami or iliac crests or rib cage compression
 - Chronic muscle pain
 - May be worse at night & after sudden movements
 - Hypocalcemia
 - Severe cases presents w/ muscle cramps, paresthesias, positive Chvostek's sign, & seizures
 - Periosteal bone pain
 - Detected by putting firm pressure on the tibia or sternal bones
 - Usually nonspecific & poorly localized
 - Proximal muscle weakness
 - Patients usually complain of difficulty in climbing stairs or rising from sitting in a chair or on toilet
 - Absent in patients w/ X-linked hypophosphatemia
 - Often occurring in the lower back, pelvis & legs
 - Worse on weight bearing leading to characteristic flat-footed, spring-less, waddling gait
 - Pseudofractures - often seen where major arteries cross bones
 - Milkman's syndrome - multiple symmetric pseudofractures in osteomalacia patients
- Osteoblasts are usually flattened & sparse

A NON-PHARMACOLOGICAL THERAPY

Sunlight exposure

- Mild sunburn is equivalent to 10,000 to 25,000 IU dietary vitamin D
- Infants <6 months should be kept out of direct sunlight
- Full-body exposure in summer months for light pigmented skinned adults should be for 10-15 minutes to generate between 10,000-20,000 IU vitamin D₃ within 24 hours
- For individuals w/ darker pigmented skin 5-10 times more exposure will generate 10,000-20,000 IU vitamin D₃

Diet

- Rich in vitamin D sources (eg cod, mackerel & salmon)
- Fortified food products (eg dairy products, orange juices)

B PHARMACOLOGICAL THERAPY

Vitamin D

- Fat-soluble vitamin which acts as a hormone & steroid
- A prohormone synthesized in the skin after ultraviolet radiation exposure or absorbed from food sources
- Provides adequate levels of calcium & phosphorus via increased intestinal absorption
- Normal values: 20-100 ng/mL (50-250 nmol/L)
- Forms of vitamin D:
 - Ergocalciferol (Vitamin D₂)
 - Found in some plant foods & most vitamin D supplements
 - Formed upon exposure of ergosterol to irradiation
 - Cholecalciferol (Vitamin D₃)
 - Produced in sunlight exposed skin
 - Found in animal products
 - Formed when ultraviolet-B (UV-B) radiation converts 7-dehydrocholesterol in epidermal keratinocytes & dermal fibroblasts to pre-vitamin D which isomerizes to vitamin D₃
 - Calcidiol (25-hydroxyvitamin D or 25[OH]D)
 - Storage form of vitamin D
 - Formed in the liver after vitamin D bound to vitamin-D-binding protein (DBP)
 - Transported to the liver to undergo 25-hydroxylation to 25(OH)D
 - Major circulating form of vitamin D
 - Preferred monitoring indicator for vitamin D status due to its long circulating half-life of 2-3 weeks
 - Calcitriol (1,25-hydroxyvitamin D or 1,25[OH]₂D)
 - Active form of vitamin D
 - Formed in the kidney after 25(OH)D undergoes 1 α -hydroxylation to form 1,25(OH)₂ vitamin D
 - Circulating half-life: Approximately 4 hours
 - Regulated by calcium, PTH & phosphate serum levels
 - Used in cases of acquired & inherited metabolic disorders of 25(OH)D & phosphate including chronic kidney disease, chronic granuloma-forming disorders, hereditary phosphate-losing disorders, oncogenic osteomalacia, pseudovitamin D-deficiency rickets & vitamin D-resistant rickets
 - Appears normal or elevated in cases of vitamin D deficiency due to secondary hyperparathyroidism
- Sources:
 - Skin exposure to sunlight
 - May require at least 3-5 times longer exposure to make the same amount of vitamin D w/ naturally dark skin toned people
 - Food sources: Eggs, meat, mushrooms, oily fish (eg mackerel, salmon, sardines), cod liver oil & other fish oils
 - Fortified food sources: Milk, bread products, orange juices, cereals, yogurts & cheeses

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B PHARMACOLOGICAL THERAPY (CONT'D)**Vitamin D (Cont'd)**

- Suggested dietary intakes of vitamin D
 - Infants & children aged 0-1 year old: At least 400 IU/day; at least 1000 IU/day to maintain blood levels >30 ng/mL (75 nmol/L)
 - Children >1-18 year old & adults ≤70: At least 600 IU/day; at least 1500-2000 IU/day to maintain blood levels >30 ng/mL (75 nmol/L)
 - Adults aged >70 years old: At least 800 IU/day; at least 1500-2000 IU/day to maintain blood levels >30 ng/mL (75nmol/L)
 - Pregnancy & lactating women: At least 600 IU/day; at least 1500-2000 IU/day to maintain blood levels >30 ng/mL (75nmol/L)
 - Obese children & adults, children & adults on anticonvulsant medications, antifungals (eg Ketoconazole), antiretrovirals, & glucocorticoids: At least 2-3 times more than doses for their age group to achieve body's vitamin D requirements
- Major functions:
 - Increases intestinal absorption of calcium & phosphorus
 - Prompts osteoclast maturation to resorb calcium from bones

C PREVENTION

- Adequate sun exposure between 10:00 AM & 3:00 PM but should be done w/ caution in children ≤6 months
- Fortification of food w/ vitamin D₂ or D₃
- Vitamin D supplementation would help to prevent osteomalacia/rickets due to vitamin D deficiency
 - 1-12 months & exclusively breastfed infants - at least 400 IU/day
 - 1 -70 years old - 600 IU/day
 - ≥70 years old - 800 IU/day
 - In pregnant or lactating women, obese person, & on patients on anticonvulsants, steroid, antifungals & antiretroviral medication, should receive 2-3 times higher dose
- Children w/ increased risk of vitamin D deficiency (eg chronic fat malabsorption, chronic intake of anticonvulsants) may be given higher doses of vitamin D supplementation w/ 25-OH-D level monitoring every 3 months & PTH & bone-mineral status monitoring every 6 months until normal levels have been achieved
- Idiopathic infantile hypercalcemia may be triggered in infants receiving 600 IU bolus every 3 months
 - Attributed to mutation in CYP24A1
 - Manifests as dehydration, failure to thrive, hypercalcemia, nephrocalcinosis & vomiting
- Most bone & mineral problems are prevented by 50,000 units of ergocalciferol given once monthly
- Larger doses should be given in patients who underwent bypass surgery for obesity, celiac disease, gastric surgery
- If osteomalacia is due to hypophosphatemia, lifelong phosphorus supplementation is needed
- Increase in calcium-rich diet has been shown to increase serum 25(OH)D & decrease serum 1,25 (OH)₂D concentration

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Dosage Guidelines

AGENTS AFFECTING BONE METABOLISM		
Drug	Dosage	Remarks
Calcitriol (1, 25[OH] ₂ D ₃)	0.25 mcg PO 24 hrly, may be increased at 2-4 wk intervals Usual range: Adult: 0.5-2 mcg PO 24 hrly Childn 1-5 yr: 0.25-0.75 mcg PO 24 hrly	Adverse Reactions <ul style="list-style-type: none"> Abdominal pain, headache, nausea, skin rash, polydipsia, urinary tract infection Excessive intake can lead to hypercalcemia Special Instructions <ul style="list-style-type: none"> May be taken w/ or without food Dose must be adjusted based on individual needs Careful monitoring of serum Ca & P levels is needed
Ergocalciferol	50,000 IU PO wkly	Adverse Reactions <ul style="list-style-type: none"> GI effects (N/V, dry mouth, constipation, metallic taste, anorexia); CNS effects (headache, somnolence, irritability); Other effects (polyuria, polydipsia, nocturia, weight loss, mild acidosis, hypercalciuria, anemia, reversible azotemia) Special Instructions <ul style="list-style-type: none"> Should be taken w/ food Contraindicated in patients w/ hypercalcemia, evidence of vit D toxicity, malabsorption syndrome, hypervitaminosis D, abnormal sensitivity to vit D, decreased renal function Use w/ caution in elderly w/ coronary disease Adequate fluid intake is recommended to prevent dehydration Monitor serum Ca, phosphate, Mg, alkaline phosphatase periodically

VITAMINS A, D & E		
Drug	Dosage	Remarks
Vitamin D ₃ (Colecalciferol)	400-1000 IU PO 24 hrly or 1 amp IM, renewed once 1-6 mth later	Adverse Reactions: <ul style="list-style-type: none"> Confusion, constipation, dehydration, fatigue, irritability, N/V, loss of appetite, weakness, weight loss Special Instructions <ul style="list-style-type: none"> Should be taken w/ food Effects of vitamin D₃ overdose may last ≥2 mth after discontinuation Greater risk of toxicity in patients w/ hepatic or renal impairment & obesity

All dosage recommendations are for non-pregnant & non-breastfeeding women, & non-elderly adults w/ normal renal & hepatic function unless otherwise stated.

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Products listed above may not be mentioned in the disease management chart but have been placed here based on indications listed in regional manufacturers' product information.*

Specific prescribing information may be found in the latest MIMS.

Please see the end of this section for the reference list.