Vitamin D deficiency in adults: Definition, clinical manifestations, and treatment

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INTRODUCTION

Overt vitamin D deficiency, characterized by hypocalcemia and/or hypophosphatemia and rickets and osteomalacia in children and osteomalacia in adults, is now uncommon in most developed countries (see "Epidemiology and etiology of osteomalacia" and "Clinical manifestations, diagnosis, and treatment of osteomalacia"). However, subclinical vitamin D deficiency occurs even in developed countries and is associated with osteoporosis and possibly fractures. Vitamin D stores decline with age, especially in the winter [1-3]. In temperate areas such as Boston and Edmonton, for example, cutaneous production of vitamin D virtually ceases in winter [2]. Thus, identification and treatment of vitamin D deficiency is important for musculoskeletal health and possibly even extraskeletal health, including the immune and cardiovascular systems. (See "Vitamin D and extraskeletal health".)

This topic will review the definition, clinical manifestations, and treatment of vitamin D deficiency in adults. The causes of vitamin D deficiency, vitamin D supplementation in osteoporosis, and the treatment of vitamin D deficiency in children are reviewed separately. (See "Causes of vitamin D deficiency and resistance" and "Calcium and vitamin D supplementation in osteoporosis" and "Vitamin D insufficiency and deficiency in children and adolescents".)

DEFINING VITAMIN D SUFFICIENCY

Serum 25-hydroxyvitamin D — Vitamin D sufficiency is estimated by measuring 25-hydroxyvitamin D (25[OH]D or calcidiol) concentrations. The optimal serum 25(OH)D concentration for skeletal health is controversial. Based upon the trials of vitamin D supplementation [4-7] and National Academy of Medicine (NAM), formerly called the Institute of Medicine (IOM), systematic review [8], we favor maintaining the serum 25(OH)D concentration between 20 and 40 ng/mL (50 to 100 nmol/L). Experts agree that levels lower than 20 ng/mL are suboptimal for skeletal health. The optimal serum 25(OH)D concentrations for extraskeletal health have not been established. (See "Vitamin D and extraskeletal health".)

The NAM supports 25(OH)D concentrations above 20 ng/mL (50 nmol/L) [8]. These recommendations are based upon evidence related to bone health. Other experts (the National Osteoporosis Foundation [NOF], the International Osteoporosis Foundation [IOF], the American Geriatric Society [AGS]) suggest that a minimum level of 30 ng/mL (75 nmol/L) is necessary in older adults to minimize the risk of falls and fracture [9-12]. The systematic review by the NAM concluded there are insufficient data to determine the safe upper limit of serum 25(OH)D [8]. However, there was some concern at serum 25(OH)D concentrations above 50 ng/mL (125 nmol/L). These concerns were based upon the increase in fracture in patients treated with high-dose vitamin D [7] and conflicting studies describing a potential increased risk for some cancers (eg, pancreatic, prostate) and mortality with levels above 30 to 48 ng/mL (75 to 120 nmol/L). (See "Vitamin D and extraskeletal health", section on 'Cancer' and "Vitamin D and extraskeletal health", section on 'Mortality'.)

Given the controversy surrounding optimal serum 25(OH)D concentrations, the definitions of vitamin D sufficiency, insufficiency, and deficiency are only approximate. The majority of groups currently use the following values to categorize the vitamin D status in adults [13].

- Vitamin D sufficiency is defined as a 25(OH)D concentration greater than 20 ng/mL (50 nmol/L)
- Vitamin D insufficiency is defined as a 25(OH)D concentration of 12 to 20 ng/mL (30 to 50 nmol/L)
- Vitamin D deficiency is defined as a 25(OH)D level less than 12 ng/mL (30 nmol/L)
- A "risk" of vitamin D toxicity is defined as a 25(OH)D level >100 ng/mL (>250 nmol/L) in adults ingesting substantial amounts of calcium

Assay issues — Commercial assays measure total 25(OH)D, but some laboratories report 25-hydroxyvitamin D2 and 25-hydroxyvitamin D3 values separately (figure 1). It is the total 25(OH)D concentration that is clinically important.

Serum 25(OH)D levels vary with the assay method used, and assay variability is still a major issue and needs to be addressed by broad adoption of an international standard [14,15]. Since 2010, the Vitamin D Standardization Program has coordinated an international effort to standardize the laboratory measurement of 25(OH)D to the gold standard reference assays or reference measurement procedures developed by the National Institute for Standards and Technology (NIST), Ghent University, and the Centers for Disease Control and Prevention (CDC) [16,17]. Vitamin D (or vitamin D-binding proteins) measured by liquid chromatography/tandem mass spectrometry (LC-MS/MS) or a comparable high-performance liquid chromatography (HPLC) technique when used with the NIST standard is the most accurate [18,19].

Criteria to define optimal 25(OH)D — There are several criteria by which to define the optimal serum 25(OH)D concentration, including maximal suppression of parathyroid hormone (PTH) by vitamin D, adequate renal production of 1,25-dihydroxyvitamin D to ensure adequate intestinal calcium absorption, and optimal level to prevent a defined clinical endpoint (eg, fracture).

- **Maximal suppression of PTH** – As 25(OH)D levels fall, intestinal absorption of calcium falls, leading to a decrease in serum calcium. As a result, serum PTH concentrations rise, resulting in stimulation of the conversion of 25(OH)D to 1,25-dihydroxyvitamin D and thereby maintenance of absorption of calcium (figure 1). Estimates of the 25(OH)D concentration necessary to maximally suppress PTH vary widely, but some reports cluster in the 27.5 to 30 ng/mL (67.5 to 75 nmol/L) range [20]. However, other experts support the thesis that suppression of PTH by 25(OH)D follows a continuum across a wide range of vitamin D concentrations and levels above 20 ng/mL (50 nmol/L) are adequate to suppress PTH, assuming normal renal function [21-24].

- **Adequate intestinal calcium absorption** – When 25(OH)D levels are substantially reduced, there is insufficient substrate for its conversion to 1,25-dihydroxyvitamin D, even with high concentrations of PTH, and intestinal calcium absorption decreases. The 25(OH)D level at which this occurs is estimated to be approximately 4.4 ng/mL (11 nmol/L) [25-27]. Thus, serum 25(OH)D concentrations below 4.4 ng/mL (11 nmol/L) have been associated with decreased calcium absorptive efficiency [25].

- **Fracture prevention** – The optimal 25(OH)D concentration may also be defined by a clinical endpoint, such as fracture reduction. In some trials, vitamin D supplementation to achieve 25(OH)D levels of 28 to 40 ng/mL (70 to 99 nmol/L) lowered fracture risk [4-6]. However, in another trial, there was a higher risk of fracture in patients treated with a single, high-dose vitamin D regimen (500,000 units once yearly) resulting in chronic serum 25(OH)D concentrations of >40 ng/mL (100 nmol/L) [7]. (See "Calcium and vitamin D supplementation in osteoporosis", section on 'Skeletal health outcomes'.)

Population differences — The optimal serum 25(OH)D concentration for skeletal health and extraskeletal health is controversial, and it has not been rigorously established for the population in general or for specific ethnic groups. The increase in circulating levels of vitamin D after oral supplementation are similar in White and Black American women [28]. Black American women have lower fracture risk than White American women, and Black American men higher bone density than White American or Hispanic American men [29,30].

Serum 25(OH)D concentrations are variable, depending upon the assay method used. Using a monoclonal sandwich assay in a multiethnic cohort study, low vitamin D-binding protein levels were more common in Black than White Americans, and consequently, the amounts of bioavailable vitamin D were similar [31]. The variability in vitamin D-binding proteins accounted for a large proportion of the variation in serum total 25(OH)D levels. However, this finding has been disputed because of the assay measurement [19,32]. As an example, when the vitamin D-binding proteins were measured with LS-MS/MS, the values were not low [19], and therefore, it is uncertain whether vitamin D-binding protein levels differ or whether there are racial differences in serum 25(OH)D. These findings underscore the importance of the assay method used to determine vitamin D and its binding proteins. Whether direct measurement of a bioavailable or "free" serum 25(OH)D would be preferable to current assays for determination of vitamin D status is uncertain. (See 'Assay issues' above.)

OPTIMAL INTAKE TO PREVENT DEFICIENCY

- Adults who do not have regular, effective sun exposure year round should consume at least 600 to 800 international units (15 to 20 micrograms) of vitamin D3 (cholecalciferol) daily. (See 'Preparations' below.)
- Older persons confined indoors and other high-risk groups may have low serum 25-hydroxyvitamin D (25[OH]D) concentrations at this intake level and may require higher intakes [33,34].

In 2010, the Institute of Medicine (now the National Academy of Medicine [NAM]) released a report on dietary intake requirements for calcium and vitamin D for normal healthy persons [35]. The Recommended Dietary Allowance (RDA) of vitamin D for children 1 to 18 years, pregnant women, and nonpregnant adults through age 70 years is 600 international units, with the RDA increasing to 800 international units after age 70 years.

The American Geriatrics Society (AGS) and the National Osteoporosis Foundation (NOF) recommend a slightly higher dose of vitamin D supplementation (at least 1000 international

units [25 micrograms], and 800 to 1000 international units daily, respectively) to older adults (≥65 years) to reduce the risk of fractures and falls [11,12]. (See "Falls: Prevention in community-dwelling older persons", section on 'Vitamin D supplementation'.)

Estimates of vitamin D requirements vary and depend in part on sun exposure and the standards used to define a deficient state. The NAM committee assumed minimal sun exposure when establishing the dietary reference intakes for vitamin D and identified a 25(OH)D level of at least 20 ng/mL (50 nmol/L) as necessary to meet the needs of at least 97.5 percent of the population [8,36,37], whereas other experts, including the NOF and the AGS, suggest that a minimum level of 30 ng/mL (75 nmol/L) is necessary in older adults [11,12]. The dietary reference intakes of the NAM were based upon data examining the beneficial effects of calcium and vitamin D on skeletal health in the general population. The evidence supporting a benefit of vitamin D on extraskeletal outcomes was inconsistent, inconclusive as to causality, and insufficient and, therefore, could not serve as a basis for dietary reference intake development. (See "Calcium and vitamin D supplementation in osteoporosis", section on 'Skeletal health outcomes' and "Vitamin D and extraskeletal health".)

VITAMIN D DEFICIENCY

Prevalence — The prevalence of vitamin D deficiency depends upon the definition used. In a systematic review of vitamin D status in different regions of the world, vitamin D levels <20 ng/mL (50 nmol/L) were prevalent in a majority of the regions studied [38]. Data from the National Health and Nutrition Examination Surveys (NHANES) showed no change in the prevalence of vitamin D deficiency (defined as <12 ng/mL [<30 nmol/L]) and a decline in prevalence of vitamin D insufficiency (defined as 12 to 19 ng/mL [30 to 49 nmol/L]) between 2003 to 2014. In the 2011 to 2014 survey, the prevalence in the United States of vitamin D <12 ng/mL was 5 percent, and for vitamin D of 12 to 19 ng/mL, 18 percent [39].

Causes — There are several causes of vitamin D deficiency, including decreased intake or absorption, reduced sun exposure, increased hepatic catabolism, decreased endogenous synthesis (via decreased 25-hydroxylation in the liver or 1-hydroxylation in the kidney), or end-organ resistance to vitamin D (table 1). In patients with 1-alpha hydroxylase deficiency or end-organ resistance to vitamin D, the serum 25(OH)D is typically within the normal range, not reduced. This topic is reviewed in more detail separately. (See "Causes of vitamin D deficiency and resistance" and "Overview of rickets in children", section on 'Laboratory findings'.)

Groups at high risk — Older persons confined indoors may have low serum 25(OH)D concentrations. Cutaneous production of vitamin D declines with age and in the northern

latitudes [3]. In addition, dietary vitamin D intake is often low in older individuals. As an example, in a study of postmenopausal women living in France, mean daily vitamin D intake from food was 144.8 international units /day [40]. More than one-third of women consumed <100 units/day from food.

Vitamin D insufficiency appears to be common among several other populations [41-48], including those who are:

- Taking medications that accelerate the metabolism of vitamin D (eg, phenytoin)
- Hospitalized on a general medical service
- Institutionalized

And those who have:

- Increased skin pigmentation
- Obesity
- Limited effective sun exposure due to protective clothing or consistent use of sun screens
- Osteoporosis
- Malabsorption, including inflammatory bowel disease and celiac disease (see "Metabolic bone disease in inflammatory bowel disease" and "Management of celiac disease in adults")

Candidates for 25(OH)D measurements — There are few data regarding screening for vitamin D deficiency in asymptomatic adults or during pregnancy [49-52]. Most experts agree that it is not necessary to perform broad-based screening of serum 25(OH)D levels in the general population or during pregnancy [37,49,53]. Normal-risk adults do not need assessment. In individuals who are in the high-risk groups described above, however, it is appropriate to measure serum 25(OH)D, to supplement with the amount estimated to be needed to reach the target 25(OH)D level, and then to remeasure three to four months later to verify that the target has been achieved. (See 'Vitamin D replacement' below and 'Monitoring' below.)

We also typically measure vitamin D in pregnant women who are obese, wear protective clothing, have a history of malabsorption (celiac disease, inflammatory bowel disease), or have other risk factors for vitamin D deficiency [46,47].

Clinical manifestations — The clinical manifestations of vitamin D deficiency depend upon the severity and duration of the deficiency. The majority of patients with moderate to mild vitamin D deficiency (serum 25[OH]D between 15 and 20 ng/mL [37.5 to 50 nmol/L]) are asymptomatic. Serum calcium, phosphorus, and alkaline phosphatase are typically normal. Serum parathyroid hormone (PTH) levels have been reported to be elevated in as many as 40 and 51 percent of

patients with serum 25(OH)D levels less than 20 and 10 ng/mL (50 and 25 nmol/L), respectively [54]. Patients with low vitamin D and secondary elevations in PTH are at increased risk for having accelerated bone loss, as evidenced by low bone mass on bone densitometry (dual-energy x-ray absorptiometry [DXA]) and fractures [55-57].

With prolonged, severe vitamin D deficiency, there is reduced intestinal absorption of calcium and phosphorus and hypocalcemia occurs, causing secondary hyperparathyroidism, which leads to phosphaturia, demineralization of bones, and when prolonged, osteomalacia in adults and rickets and osteomalacia in children. Associated symptoms may then include bone pain and tenderness, muscle weakness, fracture, and difficulty walking. Patients with nutritional osteomalacia, from either a gastrointestinal disorder or suboptimal nutrition and inadequate sun exposure, tend to have serum 25(OH)D levels <10 ng/mL (25 nmol/L). The clinical manifestations and biochemical findings of osteomalacia are reviewed in detail separately. (See "Clinical manifestations, diagnosis, and treatment of osteomalacia".)

In addition to its role in calcium and bone homeostasis, vitamin D could potentially regulate many other cellular functions. However, there are insufficient data to confirm a causal relationship between vitamin D deficiency and the immune, cardiovascular, and metabolic systems. This topic is reviewed in detail elsewhere. (See "Vitamin D and extraskeletal health".)

EVALUATION

The majority of healthy adults with serum 25-hydroxyvitamin D (25[OH]D) of 12 to 20 ng/mL (30 to 50 nmol/L) do not require any additional evaluation. Patients with serum 25(OH)D levels <12 ng/mL are at risk for developing osteomalacia. In such patients, we measure serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), electrolytes, blood urea nitrogen (BUN), creatinine, and tissue transglutaminase antibodies (to assess for celiac disease). Radiographs are necessary in certain settings, such as the presence of bone pain. (See "Clinical manifestations, diagnosis, and treatment of osteomalacia", section on 'Diagnosis' and "Diagnosis of celiac disease in adults", section on 'Serologic evaluation'.)

Some UpToDate editors also measure similar tests in patients with serum 25(OH)D between 12 and 20 ng/mL (30 and 50 nmol/L), particularly if the level is 12 to 15 ng/mL and there is clinical concern for a secondary cause of vitamin D deficiency (eg, malabsorption, celiac disease). (Related Lab Interpretation Monograph(s): "Low vitamin D (25-OH vitamin D) in adults".)

We do not routinely assess bone mineral density in patients whose only risk factor is low serum vitamin D. Patients with low vitamin D require vitamin D supplementation regardless of the

findings on bone mineral density. However, many patients have serum vitamin D levels assessed as part of an evaluation for known osteoporosis (diagnosed on bone mineral density or due to a fragility fracture). In such patients with severely low vitamin D levels (and particularly if the serum PTH is high), the need for osteoporosis therapy should be reevaluated after vitamin D repletion. In severely vitamin D deficient patients, there can be marked increases in bone mineral density after treatment of osteomalacia with calcium and vitamin D supplementation, such that treatment for "osteoporosis" is not necessary. Similarly, treatment of celiac disease with a gluten-free diet can result in significant improvement in bone mineral density. The treatment of osteomalacia is reviewed separately. (See "Clinical manifestations, diagnosis, and treatment of osteomalacia", section on 'Vitamin D deficiency' and "Management of celiac disease in adults", section on 'Prevention of bone loss'.)

VITAMIN D REPLACEMENT

Vitamin D and its metabolites have a significant clinical role because of their interrelationship with calcium homeostasis and bone metabolism. Although rickets (children) and osteomalacia (children and adults) due to severe vitamin D deficiency are now uncommon (except in populations with unusually low sun exposure, lack of vitamin D in fortified foods, and malabsorptive syndromes), subclinical vitamin D deficiency, as measured by low serum 25-hydroxyvitamin D (25[OH]D), is very common. Many patients with subclinical vitamin D deficiency have relative hypocalcemia and high serum parathyroid hormone (PTH) concentrations, which may contribute to the development of osteoporosis and to an increased risk of fractures and falls in older adults. This secondary hyperparathyroidism can be attenuated by the administration of vitamin D supplements [58-60]. (See 'Benefits of vitamin D supplementation' below.)

Preparations — There has been debate regarding which form of vitamin D should be used for supplementation. We suggest supplementation with cholecalciferol rather than ergocalciferol when available.

- Vitamin D3 (cholecalciferol) is available in 400, 800, 1000, 2000, 5000, 10,000, and 50,000 unit capsules. It is available in some countries as an intramuscular injection, which can be extremely painful.
- Vitamin D2 (ergocalciferol) is available for oral use in 400 and 50,000 unit capsules or in a liquid form (8000 unit/mL [200 mcg/mL]). A previously available intramuscular preparation is now difficult to obtain in the United States.

Multiple preparations of vitamin D and its metabolites are available for the treatment of vitamin D deficiency. Vitamin D, rather than its metabolites, is used when possible since the cost is less. The two commonly available forms of vitamin D supplements are cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2). In a meta-analysis of seven randomized trials evaluating serum 25(OH)D concentrations after supplementation with cholecalciferol versus ergocalciferol, cholecalciferol increased serum 25(OH)D more efficiently than ergocalciferol (mean difference in serum 25[OH]D 6 ng/mL [15.23 nmol/L]) [61]. The greatest difference was seen in trials that used weekly or monthly rather than daily dosing. This difference is of uncertain clinical significance, however, particularly in patients with normal baseline serum 25(OH)D levels. In addition, the trials in the meta-analysis used varying doses and treatment time periods, resulting in significant heterogeneity among studies.

Dosing — The amount of vitamin D required to effectively treat vitamin D deficiency depends, in part, upon the baseline level of serum 25(OH)D and also upon an individual's vitamin D absorptive capacity, capacity to convert vitamin D to 25(OH)D in the liver, and, to some extent, unknown genetic determinants.

In patients with normal absorptive capacity, for every 100 units (2.5 mcg) of added vitamin D3, serum 25(OH)D concentrations increase by approximately 0.7 to 1.0 ng/mL (1.75 to 2.5 nmol/L), with the larger increments seen in patients with lower baseline 25(OH)D levels. The increment declines as the 25(OH)D concentration increases above 40 ng/mL (100 nmol/L) [62-64].

- For patients with serum 25(OH)D <12 ng/mL (30 nmol/L), not infrequently associated with hypocalcemia and osteomalacia, we typically treat with 50,000 international units (1250 micrograms) of vitamin D2 or D3 orally once per week for six to eight weeks, and then 800 international units (20 micrograms) of vitamin D2 or D3 daily thereafter. However, the efficacy of this practice compared with daily, weekly, or monthly dosing has not been rigorously established. (See "Clinical manifestations, diagnosis, and treatment of osteomalacia", section on 'Vitamin D deficiency'.)

- For individuals with serum vitamin D levels of 12 to 20 ng/mL, we initially supplement with 800 to 1000 international units (20 to 25 micrograms) daily. A repeat serum 25(OH)D level should be obtained after approximately three months of therapy to assure obtaining the goal serum 25(OH)D level. If goal level is not achieved, higher doses may be necessary. (See 'Monitoring' below.)

- For individuals with serum 25(OH)D levels of 20 to 30 ng/mL (50 to 75 nmol/L), 600 to 800 units (15 to 20 micrograms) of vitamin D2 or D3 daily may be sufficient to maintain levels in the target range. (See 'Defining vitamin D sufficiency' above.)

- For patients with malabsorption, oral dosing and duration of treatment depend upon the vitamin D absorptive capacity of the individual patient. High doses of vitamin D of 10,000 to 50,000 international units (250 to 1250 micrograms) daily may be necessary to treat patients with gastrectomy or malabsorption. Patients who remain deficient or insufficient on such doses will need to be treated with hydroxylated vitamin D metabolites because they are more readily absorbed, or with sun or sunlamp exposure. (See 'Malabsorption' below and 'Vitamin D metabolites' below and 'Ultraviolet B exposure' below.)

Multiple dosing regimens have been shown to treat vitamin D deficiency effectively [65-67]. Although large, intermittent (eg, monthly, yearly) doses of vitamin D3 increase serum 25(OH)D levels, we do not use them in patients with normal absorptive capacity. In one trial, a large, annual oral dose of 500,000 international units of vitamin D3 had the undesirable effect of increasing falls and fractures in older adults [7]. Additionally, monthly dosing with 60,000 international units [68] and 100,000 international units [69] has had the undesirable effect of increasing risk of falling in older adults and nursing home residents, respectively. (See "Falls: Prevention in community-dwelling older persons", section on 'Vitamin D supplementation'.)

Special populations

Pregnancy — The optimal serum 25(OH)D level in pregnancy is unknown but should be at least 20 ng/mL (50 nmol/L). For routine supplementation, we agree with the 2010 Institute of Medicine (IOM, now the National Academy of Medicine [NAM]) report suggesting a recommended daily allowance of 600 international units vitamin D for all reproductive-age women, including during pregnancy and lactation [35]. In a 2011 American College of Obstetricians and Gynecologists (ACOG) Committee Opinion, ACOG recommended routine supplementation with the dose in a standard prenatal vitamin until more evidence is available to support a different dose [49]. Most prenatal vitamins contain 400 international units (10 micrograms) of vitamin D (cholecalciferol, ergocalciferol, or a mixture), but some preparations contain as little as 200 or as much as 1000 to 1200 international units (5 or as much as 25 to 30 micrograms) per serving.

In pregnant women with vitamin D deficiency, the safety of 50,000 international units (1250 micrograms) of vitamin D weekly for six to eight weeks has not been adequately studied, so some UpToDate editors treat vitamin D-deficient and insufficient pregnant women more slowly by giving a total of 600 to 800 international units (15 to 20 micrograms) of vitamin D3 daily. For pregnant women with vitamin D deficiency, other UpToDate editors agree with ACOG that 1000 to 2000 international units (25 to 50 micrograms) of vitamin D daily is safe [49] and may be necessary to maintain a blood level of 25(OH)D >30 ng/mL. Urinary calcium excretion increases

in pregnancy, and it should be monitored when treating vitamin D deficiency, especially in women with a history of renal stones.

There are a growing number of trials examining the efficacy and safety of vitamin D supplementation in pregnant women [47,70-73]. In one trial of vitamin D supplementation (400, 2000, or 4000 international units D3 daily) in 192 pregnant Arab women (12 to 16 weeks gestation) with severe vitamin D deficiency (mean serum 25[OH]D 8.2 ng/mL [20.5 nmol/L]), all doses were safe, and the highest dose was most effective in increasing vitamin D levels to 32 ng/mL [70]. There were no significant differences in the mean birth weight, length, head circumference, and gestational age among the groups.

Trials evaluating the effect of vitamin D supplementation on maternal and infant health outcomes are reviewed in more detail separately. (See "Vitamin D and extraskeletal health", section on 'Pregnancy outcomes'.)

Chronic kidney disease — Patients with an estimated glomerular filtration rate (eGFR) >30 mL/min who have no biochemical evidence for chronic kidney disease-metabolic bone disease (CKD-MBD) (eg, hyperparathyroidism, hyperphosphatemia) should have similar vitamin D supplementation as patients with normal renal function. As renal failure progresses (eGFR <30 mL/min), calcitriol (1,25 dihydroxyvitamin D) production may be low due to diminished glomerular filtration, loss of the 1-alpha-hydroxylase enzyme secondary to structural renal compromise, and suppression of enzyme activity secondary to hyperphosphatemia. The net result is a tendency to hypocalcemia, secondary hyperparathyroidism, and bone disease. Vitamin D repletion in this population is reviewed separately.

Malabsorption — For patients with malabsorption, oral dosing and duration of treatment depend upon the vitamin D-absorptive capacity of the individual patient. High doses of vitamin D of 10,000 to 50,000 international units daily (250 to 1250 micrograms) may be necessary to treat patients with gastrectomy or malabsorption. (See "Bariatric surgery: Postoperative nutritional management", section on 'Fat-soluble vitamins'.)

Patients who remain deficient or insufficient on such doses will need to be treated with hydroxylated vitamin D metabolites (eg, calcidiol or calcitriol) because they are more readily absorbed, or with sun or sunlamp exposure. (See 'Ultraviolet B exposure' below.)

Calcidiol (25[OH]D), which is more hydrophilic than cholecalciferol or ergocalciferol, can be useful in correcting vitamin D deficiency in some patients with fat malabsorption, in particular patients with substantial steatorrhea. The onset of action is more rapid, and the half-life of two to three weeks is shorter than that of vitamin D3 and similar to that of vitamin D2. When available, a typical initial dose is 20 to 40 micrograms daily [74]. Vitamin D deficiency in patients

with severe liver disease can be treated with doses of 50 to 200 micrograms/day [75]. If calcidiol is not readily available, calcitriol may be used in patients who remain deficient after treatment with vitamin D2 or vitamin D3. (See 'Vitamin D metabolites' below.)

For patients taking calcidiol, monitoring is the same as in patients without malabsorption. A repeat 25(OH)D measurement is performed approximately three to four months after initiating therapy. The dose of vitamin D may require further adjustment and additional measurements of 25(OH)D. (See 'Monitoring' below.)

For patients using calcitriol as a supplement, 25(OH)D levels do not indicate clinical vitamin D status. Calcitriol is associated with a fairly high incidence of hypercalcemia, so the serum calcium should be monitored carefully. Monitoring serum 1,25-dihydroxyvitamin D levels is not useful. (See 'Vitamin D metabolites' below.)

Coexisting primary hyperparathyroidism — Some patients with vitamin D deficiency have coexisting primary hyperparathyroidism that is not recognized until vitamin D is supplemented. Hypercalcemia may not be evident initially if the vitamin D deficiency is severe. Calcium concentrations are normal or at the upper-end of the normal range and PTH concentrations are elevated. Vitamin D replacement in these individuals should be provided cautiously as hypercalcemia and hypercalciuria may develop. (See "Primary hyperparathyroidism: Management", section on 'Concomitant vitamin D deficiency'.)

In contrast, in individuals with clinically significant vitamin D deficiency and secondary hyperparathyroidism, calcium concentrations are generally normal or at the lower-end of normal (rarely below normal) and PTH concentrations are mildly elevated. The PTH level should return to normal upon vitamin D repletion.

If there is uncertainty as to whether an individual with vitamin D deficiency has primary or secondary hyperparathyroidism, an assessment of urinary calcium is sometimes helpful. Urinary calcium will be extremely low in patients with vitamin D deficiency and secondary hyperparathyroidism, and it may not normalize for weeks to months as skeletal healing occurs. Urinary calcium may be low or normal in individuals with vitamin D deficiency and primary hyperparathyroidism, but it will increase rapidly with vitamin D repletion. (See "Primary hyperparathyroidism: Management", section on 'Concomitant vitamin D deficiency'.)

Monitoring — Although healthy adults initiating vitamin D supplementation (600 to 800 international units daily) do not require an initial or follow-up serum 25(OH)D measurement after starting supplementation, patients being treated specifically for serum 25(OH)D <20 ng/mL (50 nmol/L) require a repeat 25(OH)D measurement approximately three to four months

after initiating therapy. The dose of vitamin D may require further adjustment and additional measurements of 25(OH)D.

As an example, patients who have substantially increased their serum 25(OH)D level but who have not reached an optimal 25(OH)D concentration after an initial course of treatment (eg, vitamin D 800 to 1000 international units), may require a higher dose (eg, 2000 international units daily). Alternatively, patients who are treated but remain substantially below the optimal serum 25(OH)D level may require treatment with high-dose vitamin D (50,000 international units once weekly for six to eight weeks). The dose of vitamin D may require further adjustment after additional measurements of 25(OH)D.

For such patients who are compliant with vitamin D supplementation but have no or minimal increase in the serum 25(OH)D levels, we measure tissue transglutaminase antibodies to assess for celiac disease. (See "Diagnosis of celiac disease in adults".)

Adverse effects — The first measurable consequences of vitamin D toxicity are hypercalciuria and hypercalcemia, which have been observed only at 25(OH)D levels above 88 ng/mL (220 nmol/L) [76-78]. In 2010, the IOM defined the Safe Upper Limit for vitamin D as 4000 international units/day [35]. (See "Overview of vitamin D", section on 'Excess'.)

Many patients, especially older adults, take vitamin and mineral supplements that contain vitamin D. The patient may not be aware that these supplements contain vitamin D. It is important to inquire about additional dietary supplements that patients may be taking before prescribing extra vitamin D.

Vitamin D metabolites — Vitamin D metabolites can be used to treat vitamin D deficiency, particularly when there is abnormal vitamin D metabolism (renal or liver disease). The recommended preparation and dose vary with the clinical condition. (See "Overview of vitamin D", section on 'Metabolism'.)

- **Calcidiol** – Calcidiol (25[OH]D) is available in a variety of strengths. It does not require hepatic 25-hydroxylation, and is therefore most useful in patients with liver disease. Calcidiol, which is more hydrophilic than cholecalciferol or ergocalciferol, can also be useful in correcting vitamin D deficiency in some patients with fat malabsorption. The onset of action is more rapid and the half-life of two to three weeks is shorter than that of vitamin D3 and similar to that of vitamin D2. Vitamin D deficiency in patients with severe liver disease can be treated with calcidiol (30 to 200 micrograms/day) [75,79].

- **Calcitriol** – If calcidiol is not readily available, calcitriol may be used in patients who remain deficient after treatment with vitamin D2 or vitamin D3. Calcitriol (1,25-

dihydroxyvitamin D) is available in capsules of 0.25 and 0.5 micrograms. It is most useful in those with decreased synthesis of calcitriol, as occurs in chronic renal failure or in type 1 vitamin D-dependent rickets (due to an inactivating mutation in the 1-hydroxylase gene). (See "Management of secondary hyperparathyroidism in adult dialysis patients" and "Management of secondary hyperparathyroidism in adult nondialysis patients with chronic kidney disease" and "Etiology and treatment of calcipenic rickets in children", section on '1-alpha-hydroxylase deficiency'.)

Calcitriol has a rapid onset of action and a half-life is only six hours. It is associated with a fairly high incidence of hypercalcemia, so the serum calcium should be monitored carefully. If using calcitriol as a supplement, 25(OH)D levels do not indicate clinical vitamin D status.

- **Dihydrotachysterol** – Dihydrotachysterol is available as tablets of 0.125, 0.2, and 0.5 mg. It is functionally equivalent to 1-alpha-hydroxyvitamin D. It requires hepatic 25-hydroxylation prior to becoming therapeutically active. Dihydrotachysterol can be used in the disorders for which calcitriol is used. It has a rapid onset of action and a relatively short duration of action.

Ultraviolet B exposure — Artificial ultraviolet B (UVB) radiation exposure from tanning beds (sunbeds, sunlamps) is effective in increasing and maintaining serum 25(OH)D levels [80-82]. However, because there are no defined safe exposure limits for UVB exposure [83], we do not typically use UVB radiation to treat vitamin D deficiency. One possible exception is patients with malabsorption who remain vitamin D deficient even with high-dose, oral supplementation (50,000 international units daily). In such patients, serum 25(OH)D levels should be monitored to determine the optimal UVB dose and frequency.

Calcium — All patients should maintain a daily total calcium intake (diet plus supplement) of 1000 mg (for ages 19 to 70 years) to 1200 mg (for women ages 51 through 70 years and all adults 71 years and older) [35]. The Upper Level (UL) of intake for calcium in most adults is 2000 to 2500 mg daily. However, a higher calcium dose (up to 4 g/day) may be necessary in patients with malabsorption. (See "Metabolic bone disease in inflammatory bowel disease", section on 'Calcium and vitamin D'.)

BENEFITS OF VITAMIN D SUPPLEMENTATION

Skeletal — Evidence supporting the skeletal benefits of calcium and vitamin D supplementation comes largely from prospective, randomized, placebo-controlled studies of calcium and vitamin

D in community-dwelling older individuals. The details of the protocols and overall results of the studies are reviewed separately. (See "Calcium and vitamin D supplementation in osteoporosis", section on 'Skeletal health outcomes'.)

Prevention of falls — Vitamin D supplementation may also contribute to a reduction in fracture risk due to improved muscle function and a reduction in the risk of falls. This topic is reviewed separately. (See "Falls: Prevention in community-dwelling older persons", section on 'Vitamin D supplementation'.)

Extraskeletal benefits — In addition to improvements in bone density and prevention of fracture, vitamin D may have several other putative benefits, including beneficial effects on the immune and cardiovascular systems. (See "Vitamin D and extraskeletal health".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Vitamin D deficiency".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Vitamin D deficiency (The Basics)" and "Patient education: Calcium and vitamin D for bone health (The Basics)")
- Beyond the Basics topics (see "Patient education: Vitamin D deficiency (Beyond the Basics)" and "Patient education: Calcium and vitamin D for bone health (Beyond the

Basics)")

SUMMARY AND RECOMMENDATIONS

- **Defining vitamin D sufficiency** – The optimal serum 25-hydroxyvitamin D (25[OH]D) concentration for skeletal health and extraskeletal health is controversial, and it has not been rigorously established for the population in general or for specific ethnic groups. We favor maintaining the serum 25(OH)D concentration between 20 and 40 ng/mL (50 to 100 nmol/L). (See 'Defining vitamin D sufficiency' above.)

- **Causes of vitamin D deficiency** – There are several causes of vitamin D deficiency, including decreased intake or absorption, reduced sun exposure, increased hepatic catabolism, decreased endogenous synthesis (via decreased 25-hydroxylation in the liver or 1-hydroxylation in the kidney), or end-organ resistance to vitamin D (table 1). (See 'Causes' above and "Causes of vitamin D deficiency and resistance".)

- **Clinical manifestations** – The clinical manifestations of vitamin D deficiency depend upon the severity and duration of the deficiency. The majority of patients with serum 25(OH)D between 12 and 20 ng/mL (37.5 and 50 nmol/L) are asymptomatic. With prolonged severe vitamin D deficiency, there is reduced intestinal absorption of calcium and phosphorus and hypocalcemia occurs, causing secondary hyperparathyroidism, which leads to phosphaturia, demineralization of bones, and, when prolonged, osteomalacia in adults. (See 'Clinical manifestations' above and "Clinical manifestations, diagnosis, and treatment of osteomalacia".)

- **Approach to testing for vitamin D deficiency** – The approach to testing is based upon an initial assessment of a patient's risk for having a low serum 25(OH)D level. For low-risk adults, we suggest not routinely screening individuals for vitamin D deficiency (**Grade 2C**). Rather than screen, we suggest intake of 600 to 800 international units (15 to 20 micrograms) of vitamin D daily (**Grade 2B**). (See 'Optimal intake to prevent deficiency' above.)

  For high-risk adults in whom there is a clinical suspicion that the usual doses are inadequate (eg, older homebound or institutionalized individuals, those with limited sun exposure, obesity, dark skin, osteoporosis, malabsorption), measurement of serum 25(OH)D concentration is useful to ensure that supplementation is adequate. (See 'Groups at high risk' above and 'Candidates for 25(OH)D measurements' above.)

- **Evaluation** – The majority of healthy adults with serum 25(OH)D in the range of 12 to 20 ng/mL (30 to 50 nmol/L) do not require any additional evaluation. Patients with serum 25(OH)D levels <12 ng/mL are at risk for developing osteomalacia. In such patients, we measure serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone (PTH), electrolytes, blood urea nitrogen (BUN), creatinine, and tissue transglutaminase antibodies (to assess for celiac disease). Some UpToDate editors also measure similar tests in patients with serum 25(OH)D between 12 and 20 ng/mL, particularly if the level is 12 to 15 ng/mL (30 to 37.5 nmol/L) and there is clinical concern for a secondary cause of vitamin D deficiency (eg, malabsorption, celiac disease). Radiographs are necessary only in certain settings, such as the presence of bone pain. (See 'Evaluation' above.)

- **Vitamin D replacement** – For high-risk adults with serum 25(OH)D levels <20 ng/mL (50 nmol/L), we recommend vitamin D replacement (**Grade 1A**). (See 'Defining vitamin D sufficiency' above.)

  - **<12 ng/mL (30 nmol/L) –** For patients with serum 25(OH)D <12 ng/mL, we typically treat with 50,000 international units (1250 micrograms) of vitamin D2 or D3 orally once per week for six to eight weeks, and then 800 international units (20 micrograms) of vitamin D2 or D3 daily thereafter. (See 'Dosing' above.)

  - **12 to 20 ng/mL (30 to 50 nmol/L)** – For individuals with serum 25(OH)D levels in the range of 12 to 20 ng/mL (30 to 50 nmol/L), we often supplement initially with 800 to 1000 international units (20 to 25 micrograms) daily. If goal level is not achieved, higher doses may be necessary. (See 'Dosing' above.)

  - **>20 to 30 ng/mL (50 to 75 nmol/L)** – For individuals with serum 25(OH)D levels of >20 to 30 ng/mL (50 to 75 nmol/L), 600 to 800 international units (15 to 20 micrograms) of vitamin D2 or D3 daily may be sufficient to maintain levels in the target range. (See 'Dosing' above.)

  These dosing recommendations assume that the patient is not vitamin D resistant (see "Hypophosphatemia: Causes of hypophosphatemia", section on 'Vitamin D deficiency or resistance' and "Epidemiology and etiology of osteomalacia"). Such patients need a higher dose of vitamin D.

- **Vitamin D preparations** – We suggest cholecalciferol (vitamin D3), when available, rather than ergocalciferol (vitamin D2) for vitamin D supplementation (**Grade 2C**). (See 'Preparations' above.)

- **Monitoring** – Patients being treated specifically for serum 25(OH)D <20 ng/mL (50 nmol/L) should have a repeat 25(OH)D measurement approximately three to four months after initiating therapy to confirm that the target level has been achieved. The dose of vitamin D may require further adjustment and additional measurements of 25(OH)D. (See 'Monitoring' above.)

- **Calcium intake** – All patients should maintain a daily total calcium intake (diet plus supplement) of 1000 mg (for ages 19 to 70 years) to 1200 mg (for women ages 51 through 70 years and all adults 71 years and older). (See 'Calcium' above.)

- **Special populations** – Vitamin D supplementation for patients with inflammatory bowel disease or celiac disease (many of whom have osteoporosis) is discussed elsewhere. (See "Metabolic bone disease in inflammatory bowel disease" and "Management of celiac disease in adults".)

REFERENCES

1. Tsai KS, Wahner HW, Offord KP, et al. Effect of aging on vitamin D stores and bone density in women. Calcif Tissue Int 1987; 40:241.
2. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988; 67:373.
3. MacLaughlin J, Holick MF. Aging decreases the capacity of human skin to produce vitamin D3. J Clin Invest 1985; 76:1536.
4. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. N Engl J Med 1997; 337:670.
5. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int 2002; 13:257.
6. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003; 326:469.
7. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010; 303:1815.

8. http://books.nap.edu/openbook.php?record_id=13050 (Accessed on December 08, 2010).
9. Vieth R. What is the optimal vitamin D status for health? Prog Biophys Mol Biol 2006; 92:26.
10. Dawson-Hughes B, Mithal A, Bonjour JP, et al. IOF position statement: vitamin D recommendations for older adults. Osteoporos Int 2010; 21:1151.
11. American Geriatrics Society Workgroup on Vitamin D Supplementation for Older Adults. Recommendations abstracted from the American Geriatrics Society Consensus Statement on vitamin D for Prevention of Falls and Their Consequences. J Am Geriatr Soc 2014; 62:147.
12. 2013 Clinician's guide to prevention and treatment of osteoporosis http://nof.org/files/nof/public/content/resource/913/files/580.pdf (Accessed on January 23, 2014).
13. Giustina A, Adler RA, Binkley N, et al. Controversies in Vitamin D: Summary Statement From an International Conference. J Clin Endocrinol Metab 2019; 104:234.
14. Holmes EW, Garbincius J, McKenna KM. Analytical variability among methods for the measurement of 25-hydroxyvitamin D: still adding to the noise. Am J Clin Pathol 2013; 140:550.
15. Sempos CT, Vesper HW, Phinney KW, et al. Vitamin D status as an international issue: national surveys and the problem of standardization. Scand J Clin Lab Invest Suppl 2012; 243:32.
16. Binkley N, Dawson-Hughes B, Durazo-Arvizu R, et al. Vitamin D measurement standardization: The way out of the chaos. J Steroid Biochem Mol Biol 2017; 173:117.
17. Sempos CT, Betz JM, Camara JE, et al. General Steps to Standardize the Laboratory Measurement of Serum Total 25-Hydroxyvitamin D. J AOAC Int 2017; 100:1230.
18. Tai SS, Bedner M, Phinney KW. Development of a candidate reference measurement procedure for the determination of 25-hydroxyvitamin D3 and 25-hydroxyvitamin D2 in human serum using isotope-dilution liquid chromatography-tandem mass spectrometry. Anal Chem 2010; 82:1942.
19. Hoofnagle AN, Eckfeldt JH, Lutsey PL. Vitamin D-Binding Protein Concentrations Quantified by Mass Spectrometry. N Engl J Med 2015; 373:1480.
20. Durazo-Arvizu RA, Dawson-Hughes B, Sempos CT, et al. Three-phase model harmonizes estimates of the maximal suppression of parathyroid hormone by 25-hydroxyvitamin D in persons 65 years of age and older. J Nutr 2010; 140:595.
21. http://books.nap.edu/openbook.php?record_id=13050&page=260 (Accessed on June 08, 2011).

22. Saliba W, Barnett O, Rennert HS, et al. The relationship between serum 25(OH)D and parathyroid hormone levels. Am J Med 2011; 124:1165.
23. Sai AJ, Walters RW, Fang X, Gallagher JC. Relationship between vitamin D, parathyroid hormone, and bone health. J Clin Endocrinol Metab 2011; 96:E436.
24. Bouillon R, Van Schoor NM, Gielen E, et al. Optimal vitamin D status: a critical analysis on the basis of evidence-based medicine. J Clin Endocrinol Metab 2013; 98:E1283.
25. Need AG, O'Loughlin PD, Morris HA, et al. Vitamin D metabolites and calcium absorption in severe vitamin D deficiency. J Bone Miner Res 2008; 23:1859.
26. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 2001; 22:477.
27. Gallagher JC, Jindal PS, Smith LM. Vitamin D does not increase calcium absorption in young women: a randomized clinical trial. J Bone Miner Res 2014; 29:1081.
28. Gallagher JC, Jindal PS, Smith LM. Vitamin D supplementation in young White and African American women. J Bone Miner Res 2014; 29:173.
29. Cauley JA, Lui LY, Ensrud KE, et al. Bone mineral density and the risk of incident nonspinal fractures in black and white women. JAMA 2005; 293:2102.
30. Hannan MT, Litman HJ, Araujo AB, et al. Serum 25-hydroxyvitamin D and bone mineral density in a racially and ethnically diverse group of men. J Clin Endocrinol Metab 2008; 93:40.
31. Powe CE, Evans MK, Wenger J, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med 2013; 369:1991.
32. Nielson CM, Jones KS, Bouillon R, et al. Role of Assay Type in Determining Free 25-Hydroxyvitamin D Levels in Diverse Populations. N Engl J Med 2016; 374:1695.
33. Gloth FM 3rd, Gundberg CM, Hollis BW, et al. Vitamin D deficiency in homebound elderly persons. JAMA 1995; 274:1683.
34. Hamid Z, Riggs A, Spencer T, et al. Vitamin D deficiency in residents of academic long-term care facilities despite having been prescribed vitamin D. J Am Med Dir Assoc 2007; 8:71.
35. Institute of Medicine. Report at a Glance, Report Brief: Dietary reference intakes for calciu m and vitamin D, released 11/30/2010. http://www.iom.edu/Reports/2010/Dietary-Referenc e-Intakes-for-Calcium-and-Vitamin-D/Report-Brief.aspx (Accessed on December 01, 2010).
36. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011; 96:53.

37. Manson JE, Brannon PM, Rosen CJ, Taylor CL. Vitamin D Deficiency - Is There Really a Pandemic? N Engl J Med 2016; 375:1817.
38. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol 2014; 144 Pt A:138.
39. Herrick KA, Storandt RJ, Afful J, et al. Vitamin D status in the United States, 2011-2014. Am J Clin Nutr 2019; 110:150.
40. Czernichow S, Fan T, Nocea G, Sen SS. Calcium and vitamin D intake by postmenopausal women with osteoporosis in France. Curr Med Res Opin 2010; 26:1667.
41. Yetley EA. Assessing the vitamin D status of the US population. Am J Clin Nutr 2008; 88:558S.
42. Looker AC, Pfeiffer CM, Lacher DA, et al. Serum 25-hydroxyvitamin D status of the US population: 1988-1994 compared with 2000-2004. Am J Clin Nutr 2008; 88:1519.
43. Gallagher JC, Peacock M, Yalamanchili V, Smith LM. Effects of vitamin D supplementation in older African American women. J Clin Endocrinol Metab 2013; 98:1137.
44. Wortsman J, Matsuoka LY, Chen TC, et al. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000; 72:690.
45. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. N Engl J Med 1998; 338:777.
46. van der Meer IM, Karamali NS, Boeke AJ, et al. High prevalence of vitamin D deficiency in pregnant non-Western women in The Hague, Netherlands. Am J Clin Nutr 2006; 84:350.
47. Yu CK, Sykes L, Sethi M, et al. Vitamin D deficiency and supplementation during pregnancy. Clin Endocrinol (Oxf) 2009; 70:685.
48. Compher CW, Badellino KO, Boullata JI. Vitamin D and the bariatric surgical patient: a review. Obes Surg 2008; 18:220.
49. ACOG Committee on Obstetric Practice. ACOG Committee Opinion No. 495: Vitamin D: Screening and supplementation during pregnancy. Obstet Gynecol 2011; 118:197. Reaffirmed 2019.
50. http://www.aafp.org/patient-care/clinical-recommendations/all/vitamin-D-deficiency.html (Accessed on January 29, 2015).
51. US Preventive Services Task Force, Krist AH, Davidson KW, et al. Screening for Vitamin D Deficiency in Adults: US Preventive Services Task Force Recommendation Statement. JAMA 2021; 325:1436.
52. Kahwati LC, LeBlanc E, Weber RP, et al. Screening for Vitamin D Deficiency in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force.

JAMA 2021; 325:1443.

53. McChesney C, Singer A, Duquette D, et al. Do not routinely test for vitamin D. BMJ 2022; 378:e070270.
54. Valcour A, Blocki F, Hawkins DM, Rao SD. Effects of age and serum 25-OH-vitamin D on serum parathyroid hormone levels. J Clin Endocrinol Metab 2012; 97:3989.
55. Garg MK, Tandon N, Marwaha RK, et al. The relationship between serum 25-hydroxy vitamin D, parathormone and bone mineral density in Indian population. Clin Endocrinol (Oxf) 2014; 80:41.
56. Cauley JA, Parimi N, Ensrud KE, et al. Serum 25-hydroxyvitamin D and the risk of hip and nonspine fractures in older men. J Bone Miner Res 2010; 25:545.
57. LeBoff MS, Kohlmeier L, Hurwitz S, et al. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. JAMA 1999; 281:1505.
58. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet 1998; 351:805.
59. Need AG, O'Loughlin PD, Morris HA, et al. The effects of age and other variables on serum parathyroid hormone in postmenopausal women attending an osteoporosis center. J Clin Endocrinol Metab 2004; 89:1646.
60. Hollis BW. Circulating 25-hydroxyvitamin D levels indicative of vitamin D sufficiency: implications for establishing a new effective dietary intake recommendation for vitamin D. J Nutr 2005; 135:317.
61. Tripkovic L, Lambert H, Hart K, et al. Comparison of vitamin D2 and vitamin D3 supplementation in raising serum 25-hydroxyvitamin D status: a systematic review and meta-analysis. Am J Clin Nutr 2012; 95:1357.
62. Vieth R. Critique of the considerations for establishing the tolerable upper intake level for vitamin D: critical need for revision upwards. J Nutr 2006; 136:1117.
63. Heaney RP, Davies KM, Chen TC, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003; 77:204.
64. Gallagher JC, Sai A, Templin T 2nd, Smith L. Dose response to vitamin D supplementation in postmenopausal women: a randomized trial. Ann Intern Med 2012; 156:425.
65. Ish-Shalom S, Segal E, Salganik T, et al. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. J Clin Endocrinol Metab 2008; 93:3430.
66. Dawson-Hughes B, Heaney RP, Holick MF, et al. Estimates of optimal vitamin D status. Osteoporos Int 2005; 16:713.

67. Wamberg L, Pedersen SB, Richelsen B, Rejnmark L. The effect of high-dose vitamin D supplementation on calciotropic hormones and bone mineral density in obese subjects with low levels of circulating 25-hydroxyvitamin d: results from a randomized controlled study. Calcif Tissue Int 2013; 93:69.

68. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. JAMA Intern Med 2016; 176:175.

69. Ginde AA, Blatchford P, Breese K, et al. High-Dose Monthly Vitamin D for Prevention of Acute Respiratory Infection in Older Long-Term Care Residents: A Randomized Clinical Trial. J Am Geriatr Soc 2017; 65:496.

70. Dawodu A, Saadi HF, Bekdache G, et al. Randomized controlled trial (RCT) of vitamin D supplementation in pregnancy in a population with endemic vitamin D deficiency. J Clin Endocrinol Metab 2013; 98:2337.

71. Roth DE, Al Mahmud A, Raqib R, et al. Randomized placebo-controlled trial of high-dose prenatal third-trimester vitamin D3 supplementation in Bangladesh: the AViDD trial. Nutr J 2013; 12:47.

72. Grant CC, Stewart AW, Scragg R, et al. Vitamin D during pregnancy and infancy and infant serum 25-hydroxyvitamin D concentration. Pediatrics 2014; 133:e143.

73. Chakhtoura M, El Ghandour S, Shawwa K, et al. Vitamin D replacement in children, adolescents and pregnant women in the Middle East and North Africa: A systematic review and meta-analysis of randomized controlled trials. Metabolism 2017; 70:160.

74. Minisola S, Cianferotti L, Biondi P, et al. Correction of vitamin D status by calcidiol: pharmacokinetic profile, safety, and biochemical effects on bone and mineral metabolism of daily and weekly dosage regimens. Osteoporos Int 2017; 28:3239.

75. Basha B, Rao DS, Han ZH, Parfitt AM. Osteomalacia due to vitamin D depletion: a neglected consequence of intestinal malabsorption. Am J Med 2000; 108:296.

76. Gertner JM, Domenech M. 25-Hydroxyvitamin D levels in patients treated with high-dosage ergo- and cholecalciferol. J Clin Pathol 1977; 30:144.

77. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr 1999; 69:842.

78. Dudenkov DV, Yawn BP, Oberhelman SS, et al. Changing Incidence of Serum 25-Hydroxyvitamin D Values Above 50 ng/mL: A 10-Year Population-Based Study. Mayo Clin Proc 2015; 90:577.

79. Brandi ML, Minisola S. Calcidiol [25(OH)D3]: from diagnostic marker to therapeutical agent. Curr Med Res Opin 2013; 29:1565.

80. Datta P, Bogh MK, Olsen P, et al. Increase in serum 25-hydroxyvitamin-D3 in humans after solar exposure under natural conditions compared to artificial UVB exposure of hands and face. Photochem Photobiol Sci 2012; 11:1817.

81. Bogh MK, Schmedes AV, Philipsen PA, et al. A small suberythemal ultraviolet B dose every second week is sufficient to maintain summer vitamin D levels: a randomized controlled trial. Br J Dermatol 2012; 166:430.

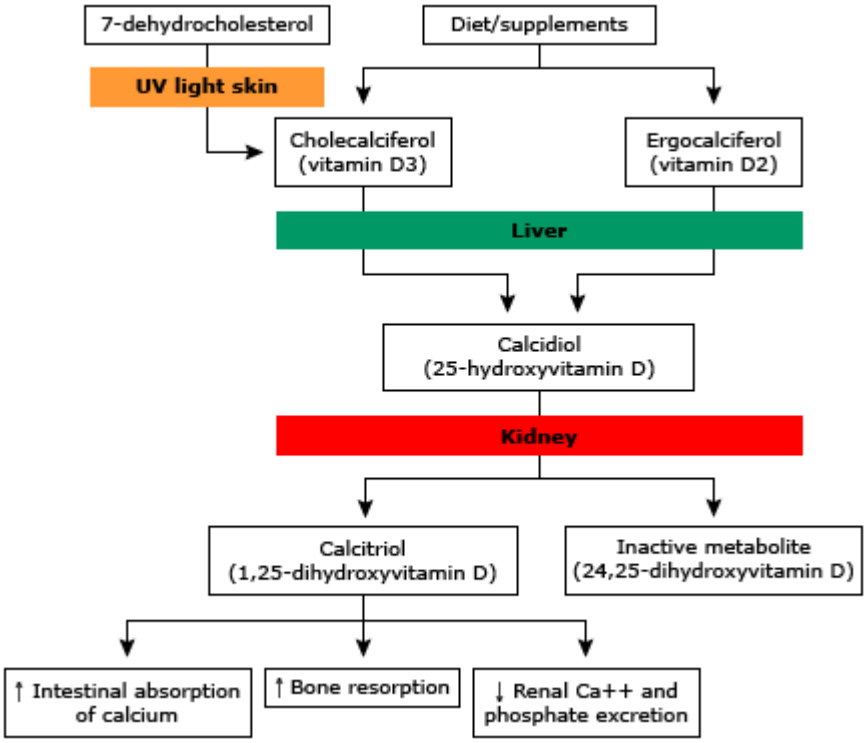
82. Lagunova Z, Porojnicu AC, Aksnes L, et al. Effect of vitamin D supplementation and ultraviolet B exposure on serum 25-hydroxyvitamin D concentrations in healthy volunteers: a randomized, crossover clinical trial. Br J Dermatol 2013; 169:434.

83. Dawe RS. There are no 'safe exposure limits' for phototherapy. Br J Dermatol 2010; 163:209.

Topic 2022 Version 61.0

GRAPHICS

Pathways of vitamin D synthesis



Metabolic activation of vitamin D to calcitriol and its effects on calcium and phosphate homeostasis. The result is an increase in the serum calcium and phosphate concentrations.

UV: ultraviolet; Ca: calcium.

Graphic 65360 Version 7.0

Causes of vitamin D deficiency or resistance

Deficient intake or absorption
Dietary
Malabsorption
Gastric bypass (bariatric surgery, gastrectomy)
Small bowel disease
Pancreatic insufficiency
Decreased skin synthesis
Inadequate sunlight exposure
Full sunscreen use
Darkly pigmented skin
Defective 25-hydroxylation
Cirrhosis
Increased catabolism of vitamin D to inactive metabolites
Antiseizure medications
Loss of vitamin D binding protein
Nephrotic syndrome
Defective 1-alpha 25-hydroxylation
Hypoparathyroidism
Renal failure
1-alpha hydroxylase deficiency (vitamin D-dependent rickets, type 1)
Defective target organ response to calcitriol
Hereditary vitamin D-resistant rickets (vitamin D-dependent rickets, type 2)

Graphic 58837 Version 7.0

Contributor Disclosures

Bess Dawson-Hughes, MD Consultant/Advisory Boards: AgNovos Healthcare - Data safety and monitoring board[Bone health]. All of the relevant financial relationships listed have been mitigated. **Clifford J Rosen, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Katya Rubinow, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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