Vitamin D is essential for attainment and maintenance of musculoskeletal health and key to calcium homeostasis and phosphorus balance. Chronic insufficiency leads to skeletal abnormalities and fragility fracture and is linked to multiple extra-skeletal disorders including cancer, infection, and cardiovascular disease.

Analysis of nutrient intake, through food and dietary supplements, has shown the majority of American adults fail to meet adequate intake recommendations for vitamin D established by the Institute of Medicine. Many if not most of the patients seen in the typical primary care practice are vitamin D insufficient or deficient. Knowing who is most likely to be severely deficient will help practitioners identify those patients who should have targeted testing and therapy.

Once a patient is found to be deficient, clinical management involves supplementation to raise and maintain serum vitamin D at levels necessary to support optimal bone and general health. This issue of “Osteoporosis: Clinical Updates” will discuss the role of vitamin D in skeletal health, its sources, daily requirements, upper safe limits, and potential for building and maintaining strong bones throughout the lifespan.

Editor-in-Chief, Angelo Licata, MD, PhD.

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**Vitamin D Deficiency in the U.S.**

Over the past decade, researchers and experts in the field have warned of a “silent epidemic” of vitamin D deficiency in the United States, citing prevalence data from the National Health and Nutrition Examination Survey (NHANES), which showed an increased prevalence from 50% to 75% between 1988 and 2004. And yet, in 2010 the Institute of Medicine (IOM) reported that rather than an epidemic, vitamin D deficiency is not a problem for the majority of Americans. Authors writing for the National Center for Health Statistics (NCHS) supported this view, reporting that 67% of the U.S. population has sufficient serum vitamin D, about 25% is at risk of vitamin D inadequacy, and 8% is at risk of vitamin D deficiency. So, is vitamin D deficiency an epidemic or not? Put simply, it depends on how you define your terms: specifically, what blood level constitutes vitamin D insufficiency in an otherwise healthy population. IOM and NCHS conclusions rest on defining insufficiency as 25-hydroxyvitamin D (25[OH]D) blood levels below 20 ng/mL (<50 nmol/L), the level traditionally believed adequate to protect bone health. However, due to increasing evidence that higher levels are needed to achieve skeletal and other health benefits, specialty societies such as the Endocrine Society and the National Osteoporosis Foundation define insufficiency as 25(OH)D at or above 30 ng/mL (<75 nmol/L). This may seem like a small difference, but it has major public health ramifications, raising issues in primary care related to screening, treatment, and monitoring.

All sides of the debate agree that in certain populations, vitamin D insufficiency and deficiency are widespread. Identifying patients at risk requires recognizing the factors that influence vitamin D synthesis, intake, and metabolism.

**The Role of Vitamin D in Bone Health**

Vitamin D is one of several fat-soluble steroids whose metabolism facilitates absorption and regulation of minerals such as calcium and phosphorus. There are two forms of vitamin D: D2 and D3. The vitamin D2 form (ergocalciferol) is found in small amounts in certain plants and made commercially by UV irradiation of yeast. The more potent form, Vitamin D3 (cholecalciferol), is synthesized in the skin of vertebrates in response to exposure to UVB radiation either from the sun or from a synthetic light source. Vitamin D3 is the form commonly used in supplements and fortified foods. Vitamin D3 is available from animal foods such as fatty fish, egg yolks, and liver. It is produced commercially from cholesterol extracted from sheep wool that is exposed to UVB radiation.

**Vitamin D Synthesis and Activation**

Both vitamin D2 and D3 are biologically inactive, whether obtained through cutaneous UVB exposure, diet, or supplements. They go through a two-step process of hydroxylation, first in the liver, where the parent compound D is converted to 25-hydroxyvitamin D (25[OH]D), known as calcidiol, and second in the kidney, where it becomes the biologically active form 1,25 dihydroxyvitamin D (1,25[OH]2D), or calcitriol, which is involved in bone metabolism and absorption of dietary calcium, phosphorus and other minerals.

In the body, activated vitamin D regulates absorption of calcium from the gastrointestinal system and mobilization of calcium from bone. The activation of 25 OH vitamin D to 1,25(OH)2 vitamin D is stimulated by serum parathyroid (PTH) and low phosphorus. PTH is regulated by serum calcium and by the protein hormone FGF23, which is produced by bone.

Adequate calcium absorption depends on adequate levels of 25(OH)D being converted into activated 1,25 dihydroxyvitamin D. In a setting of optimal serum vitamin D, absorption of dietary calcium is approximately 30% to 40 percent. As vitamin D status declines, absorption of dietary calcium declines to about 10% to 15 percent. Maximum absorption of dietary calcium...
Vitamin D Is Produced in the Skin and Converted to Active Metabolites in the Liver and Kidney

UVB = ultraviolet B; proD$_3$ = provitamin D$_3$; preD$_3$ = previtamin D$_3$; PO$_4$$^2-$ = phosphate; 1,25(OH)$_2$D$_3$ = 1,25 dihydroxyvitamin D.

Figure 1. Vitamin D is produced in the skin and converted to active metabolites in the liver and kidney.

occur at a 25(OH)D level of 32 ng/mL or higher.$^{5,6}$

As well as leading to decreased calcium absorption, suboptimal vitamin D leads to increased release of PTH (causing secondary hyperparathyroidism), which increases bone resorption, thus weakening bone and increasing probability of fracture.$^7$ Levels of PTH rise when 25(OH)D levels drop below 30 ng/mL and are often above normal at levels less than 20 ng/mL. In addition, animal studies, cell studies, and meta-analyses that suggest levels near 50 ng/mL may be optimal for bone health. This observation underpins the shift in thinking about what constitutes ideal serum levels.

**Factors that Affect Vitamin D Levels**

A wide range of factors influence the intake, production, and metabolism of vitamin D and contribute to serum levels. Primary among these are exposure to sunlight, dietary intake, absorption in the digestive tract, and conversion in liver and kidneys.

**Sunlight Exposure**

Exposure to UVB radiation from the sun (or a synthetic light source) converts 7-dehydrocholesterol (provitamin D3) in the skin to previtamin D3, which in turn becomes vitamin D3. Factors that affect the skin’s ability to synthesize vitamin D are many. Two intrinsic factors that affect vitamin D production are age (skin loses its reactivity to UVB) and skin color/ethnicity (higher melanin means lower absorption).$^{3,8}$ Observational studies have long shown higher rates of vitamin D deficiency in African Americans (28% higher than in Caucasians).$^9$ Recent research found proportionally lower serum levels of vitamin D binding protein in African Americans, as compared with Caucasians, suggesting an underlying mechanism of action.$^{10,11}$ Paradoxically, these lower vitamin D levels do not increase fracture risk among African Americans. In fact, African Americans have a lower risk of osteoporotic fracture than do Caucasians.

As a result of such observations, it is hypothesized that the Caucasian model of association between vitamin D status, hyperparathyroidism (also higher in African Americans), and fracture risk may not be applicable to other races. However, observational studies such as the 2012 Health ABC Study show that, regardless of ethnicity, low vitamin D combined with PTH in the high end of the reference range is associated with multiple chronic conditions and higher all-cause mortality.

It stands to reason that due to its greater prevalence, vitamin D deficiency has a disproportionally greater negative health impact in the African American and non-black Hispanic American populations. It has been suggested that this phenomenon may contribute to health disparities that exist between racial/ethnic groups.$^{12}$

Extrinsic factors that impede vitamin D synthesis include lifestyle barriers (staying indoors or covering skin with clothing limit exposure) and UVB intensity (cloud cover and pollution). Studies show that latitude does not affect net vitamin D synthesis.$^{13,14}$ The winter shortfall in sunlight exposure at northern latitudes appears to be made up during the rest of the year.
Vitamin D Intake Did Not Reach 400 IU/day for Women 50 Years and Older, Even With Supplementation

Figure 2. In the NHANES III Population study, vitamin D intake did not reach 400 IU/day for women 50 years and older, even with supplementation.

However, measurement of serum vitamin D levels of people living in northern regions such as Canada and Scandinavia show declines in vitamin D sufficiency during the winter and spring, which could result in mineralization issues and other negative health effects during these periods.15

Theoretically, properly applied and replenished sunscreen would significantly reduce the skin’s exposure to UVB rays. However, research indicates that in practice most people don’t use enough sunscreen or reapply it often enough to completely block their exposure to UVB and production of vitamin D.16,17 A more likely culprit is the increasingly indoor lifestyle of Americans, who spend less time outdoors than at any time in the past.

Estimates for adequate UVB exposure range from 5 to 30 minutes of sunlight twice a week on the bare face, arms, legs, or back. Commercial tanning beds with an emission of 2% to 6% UVB used in moderation are roughly equivalent.18,19

Dietary Intake

As discussed earlier, dietary sources of vitamin D are limited. Getting enough vitamin D from diet alone is not possible for most people. The better sources include fatty fish (herring, mackerel, catfish, salmon), fish liver oil, and to a lesser degree cheese, egg yolks, and beef liver.

Mushrooms and lichen are the only known non-animal sources of vitamin D. Vitamin D available from mushrooms varies widely—from 3 IUs per 84-gram serving in raw crimini mushrooms to 943 IUs in raw maitake mushrooms. Exposure to UV light increases mushroom vitamin D content. The increase can be substantial. For example, unexposed portabellas contain approximately 12 IUs per cup, while portabellas exposed to UVB light contain approximately 493 IUs per serving.20 In addition to these sources, dairy products, margarine, cereal, and orange juice are regularly fortified with vitamin D in concentrations displayed on their packaging.

A listing of the vitamin D content of common foods is shown at the bottom of page 5. As is evident in this list, few foods contain high concentrations of vitamin D.

A diet chronically low in vitamin D, coupled with inadequate sunlight exposure, over time can lead to vitamin D deficiency. Unless they get ample sun exposure, people with diets that restrict their intake of vitamin D rich foods, such as those with dairy allergies, lactose intolerance, or ovo-vegetarian and vegan diets, are at increased risk of vitamin D deficiency.

Absorption and Conversion Factors

Even with sufficient dietary intake, patients who have conditions that compromise the absorption or conversion of vitamin D may not benefit from the vitamin D in the foods they eat. Conditions such as cystic fibrosis, Crohn disease, or colitis can cause malabsorption of vitamin D and other nutrients in the digestive tract,
while kidney and liver disorders can disrupt the conversion of vitamin D into its active form.

Evidence regarding the effects of gastric bypass surgery on vitamin D absorption are inconclusive to date, with some data suggesting increase and some indicating attenuation in vitamin D levels following surgery.\textsuperscript{21,22,23} Because vitamin D is fat soluble, it is stored in subcutaneous fat. As a result, body mass index (BMI) 30 or over is associated with lower serum 25(OH)D than BMI in the healthy range. In obese individuals, more vitamin D is sequestered in fat and less released into the bloodstream. Such individuals may need higher intake levels to compensate.\textsuperscript{24}

Many medications and over-the-counter remedies can adversely interact with vitamin D. Some medications can interfere with vitamin D absorption and/or metabolism. Others can have their absorption and/or effects intensified by combination with vitamin D. Potential interactions to be aware of include:

\begin{itemize}
  \item Most anticonvulsants, such as carbamazepine (Tegretol\textsuperscript{®}), phenobarbital (Luminal\textsuperscript{®}), and phenytoin (Dilantin\textsuperscript{®}), and gabapentin (Neurontin\textsuperscript{®}) can cause reduced serum 25(OH)D and calcium absorption.\textsuperscript{25,26,27}
  \item Antiretrovirals agents ritonavir (Norvir\textsuperscript{®}), efavirenz (Sustiva\textsuperscript{®} and Atripla\textsuperscript{®}), and valproic acid (e.g. Depakene\textsuperscript{®}) are associated with reduced 25(OH)D levels.\textsuperscript{28}
  \item Certain calcium channel blockers (brand names: Bosoptin\textsuperscript{®}, Calan\textsuperscript{®}, Covera-HS\textsuperscript{®}, Isoptin\textsuperscript{®}, Verapamil\textsuperscript{®}, and Verelan\textsuperscript{®}) may not be effective when taken with vitamin D.\textsuperscript{29}
  \item Cimetidine: (brand names: Tagamet\textsuperscript{®} and Tagamet HB\textsuperscript{®}) cause disruption of vitamin D metabolism.\textsuperscript{30}
  \item Cholesterol-lowering agent cholestyramine (brand names Questran\textsuperscript{®}, LoCholest\textsuperscript{®}, Prevalite\textsuperscript{®}) can reduce absorption of vitamin D.\textsuperscript{31}
  \item Digoxin (Lanoxin\textsuperscript{®}), Digitalis (Crystodigin\textsuperscript{®}) taken with vitamin D may increase effects of digoxin, causing cardiac irregularities.\textsuperscript{32}
  \item Oral corticosteroids/glucocorticoids (brand names include Aristocort\textsuperscript{®}, Methylprednisolone\textsuperscript{®}, Orasone\textsuperscript{®}) impair vitamin D metabolism.\textsuperscript{33,34,35}
  \item Psoriasis treatments calcipotriol/calcipotriene (brand names: Dovonex\textsuperscript{®}/ Daivonex\textsuperscript{®}), synthetic forms of vitamin D, suppress PTH and 1,25 dihydroxyvitamin D3 and increase absorption of calcium.\textsuperscript{36}
  \item Statin drugs to lower cholesterol can increase serum vitamin D levels.\textsuperscript{37}
  \item Weight loss drug orlistat (brand names Xenical\textsuperscript{®} and Alli\textsuperscript{TM}) and food additive olestra (brand name and Olean\textsuperscript{®}) have been shown to reduce absorption of vitamin D.\textsuperscript{38}
\end{itemize}

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving Size</th>
<th>Vitamin D Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canned salmon (with bone)</td>
<td>1 can (369 grams)</td>
<td>2816 IU</td>
</tr>
<tr>
<td>Salmon, fresh roasted</td>
<td>½ filet</td>
<td>815 IU</td>
</tr>
<tr>
<td>Canned tuna (in oil, drained)</td>
<td>3 ounces</td>
<td>229 IU</td>
</tr>
<tr>
<td>Whole milk (cow)</td>
<td>1 cup</td>
<td>124 IU</td>
</tr>
<tr>
<td>Soy milk (Silk brand plain)</td>
<td>1 cup</td>
<td>119 IU</td>
</tr>
<tr>
<td>Low fat milk (1%)</td>
<td>1 cup</td>
<td>117 IU</td>
</tr>
<tr>
<td>Orange juice (fortified)</td>
<td>1 cup</td>
<td>89 IU</td>
</tr>
<tr>
<td>Kellogg’s All-Bran Cereal (original)</td>
<td>1/2 cup</td>
<td>51 IU</td>
</tr>
<tr>
<td>Egg, whole, hard boiled</td>
<td>1 large</td>
<td>44 IU</td>
</tr>
<tr>
<td>Spinach souffle</td>
<td>1 cup</td>
<td>42 IU</td>
</tr>
<tr>
<td>Mushrooms (fresh, shitake)</td>
<td>1 cup</td>
<td>41 IU</td>
</tr>
<tr>
<td>Cheddar Cheese</td>
<td>1 ounce</td>
<td>7 IU</td>
</tr>
</tbody>
</table>

\textbf{Table 1.} Typical foods that contain vitamin D with serving size and vitamin D content. Source: USDA National Nutrient Database for Standard Reference, Release 25. Available at: https://www.ars.usda.gov/SP2UserFiles/Place/12354500/Data/SR25/nutrist/sr25a324.pdf.
Table 2. Individuals at Risk for Vitamin D Deficiency

- Infants fed only breast milk
- Homebound and institutionalized individuals and others with restricted sun exposure
- People with dark skin (e.g., people of African, Middle Eastern, Native American, Hispanic, or South Asian descent)
- People with conditions that cause fat malabsorption, such as Crohn’s disease, colitis, inflammatory bowel disease, and cystic fibrosis
- People with liver or kidney disease, including kidney transplant
- People who have undergone gastric bypass (conflicting research)
- Older adults (over age 60)
- Obese individuals (BMI ≥ 30)
- People with dietary restrictions, such as vegan, milk-allergic, ovo-vegetarian, and lactose-intolerant individuals

Before prescribing vitamin D supplementation, a careful medication review is necessary to avoid potentially harmful interactions.

**Role of Vitamin D in Prevention of Falls and Fractures**

Vitamin D protects the bones of older individuals through two mechanisms: maintaining bone mineral density (BMD) and preventing falls. It is well established that vitamin D sufficiency is required to absorb calcium and maintain bone density. Less well understood is the process by which vitamin D benefits muscle strength and function.

Possible mechanisms for this effect have been illuminated in recent animal research isolating vitamin D receptors in specialized fast-twitch muscle fibers that are activated when a person starts to fall. In healthy young people, these muscles make it possible to catch oneself before losing one’s balance. Age weakens these muscle fibers, as does insufficient vitamin D. Animal studies have demonstrated vitamin D repletion to thicken and strengthen these specific fibers.

It is speculated that in humans this translates into fewer falls, fewer fractures, and lower rates of all-cause mortality. Recent data from a large population-based prospective observational study of elderly community-dwelling men showed a U-shaped association between
vitamin D serum level and fracture risk. The highest risk of fracture was seen in men with serum levels of \( \leq 36 \text{nmol/L} \) or \( > 72 \text{nmol/L} \). The lowest risk was in men with serum 25OHD \( \geq 60 \) to \( \leq 72 \text{nmol/L} \).\(^{43}\)

Heterogeneous studies of vitamin D supplementation and fall risk have reported effects that range from 20\% reduction in falls at a dose of 700-1000 IU/s/day, to no effect, to an increase in falls and fractures with very-high-dose supplementation of 500,000 IU/s/year.\(^{44-49}\)

In order to draw reliable inferences from such divergent data, the Agency for Healthcare Research conducted a meta-analysis, which concluded that evidence supports an association between vitamin D supplementation and small to moderate reductions in fall risk, particularly in high-risk individuals, such as institution-dwelling elderly.\(^{50}\)

Vitamin D at \( \geq 800 \text{IU} \) per day resulting in a 25OHD level of 65-75 nmol/L is needed to lower risk of falls.

**How Much Vitamin D Is Needed and How to Get It**

The goal of vitamin D supplementation is to achieve and maintain serum 25(OH)D levels in the healthy range. As mentioned above, what constitutes an adequate serum 25(OH)D level? The IOM report concluded that, based on current data from randomized controlled clinical trials, people with less than 12 ng/mL are at risk for deficiency, 12-20 ng/mL are at risk for inadequacy, \( \geq 20 \text{ng/mL} \) have adequate circulating levels, while those with levels \( > 100 \text{ng/mL} \) are at risk for adverse effects.\(^1\)

Specialty societies such as the National Osteoporosis Foundation and the Endocrine Society recommend using the cut point of 30 ng/mL to denote sufficient serum 25(OH)D. In support of this designation are data indicating that intestinal absorption of calcium is maximized above 32 ng/mL, and parathyroid hormone (PTH) concentrations in adults are at their lowest at between 30 and 40 ng/mL.\(^{2,6,51,52,53}\)

The IOM’s guidelines for vitamin D intake are based on what healthy individuals need to ingest daily to maintain serum 25(OH)D in the healthy range. These guidelines, or dietary reference intakes (DRIs), are a set of reference values for vitamins, minerals, and other nutrients used for dietary planning and assessment. DRIs are specific to age group, gender, and, for women, reproductive status.

Vitamin D supplements are available in over-the-counter tablets, liquids, and capsules in doses ranging from 200-5000 (D2/D3) and 10 000 IU/s (D3). Prescription dosages of 50 000 D2 and 8000 U/mL are available for physician use. In addition, for renal disease patients the synthetic vitamin D analog calcitriol and several analogues are available in tablet or injectable form. Raising the serum to ideal 25(OH)D levels may take much higher intakes of supplemental D than expected. This is why clinicians must recheck patients to ensure therapeutic response.

**Current Daily Recommended Intakes for Vitamin D**

Daily recommended intakes (DRIs) are based on data for the following:

**Estimated Average Requirements (EAR):** The average daily nutrient intake level estimated to meet the requirements of half of the healthy individuals in a given population.

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**Figure 3.** This illustration shows the continuum of 25(OH)D intake with area of controversy indicated in shading.
Recommended Dietary Allowances (RDA): The daily dietary intake level of a nutrient considered sufficient by the IOM Food and Nutrition Board to meet the requirements of nearly all (97–98%) healthy individuals in each life-stage and gender group. Based on EAR and ≈20% higher than EAR.

Adequate Intake (AI). Where not enough evidence exists to establish an RDA, an estimate of the amount sufficient to ensure health in a given healthy population.

Tolerable upper intake levels (UL): The highest level of consumption that current data have shown to be safe.

In its 2010 report, the IOM revised its recommendations for vitamin D based on new research. The new recommendation for daily intake of vitamin D tripled the value previously considered adequate for children and adults from 200 IU to 600 IU/day, still considered too low by many experts.  

Current RDAs & AIs for Vitamin D

The following RDAs were established for children, teenagers, and adults by the recent IOM report:

- Children 1-13 years: 15 micrograms (600 IU)/day
- Teenagers 14-18 years: 15 micrograms (600 IU)/day
- Adults 19-70 years: 15 micrograms (600 IU)/day
- Adults above 70 years: 20 micrograms (800 IU)/day
- Pregnant and lactating women: 15 micrograms (600 IU)/day
- The following AIs were established for infants (RDAs have not been developed for children under 1 year):
  - Infants 0-6 months: 10 micrograms (400 IU)/day
  - Infants 6-12 months: 10 micrograms (400 IU)/day

These recommendations may be adjusted upwards if research supports benefit and safety of higher doses.

Assessing Vitamin D Status

It is reasonable to assume that most if not all patients in an average primary care setting have less than optimal serum vitamin D and would benefit from supplementation at recommended doses. Many patients, however, will be severely deficient and in need of more intensive intervention. These patients can be initially identified on the basis of predictable patterns of routine biochemical indices associated with severe deficiency. For example, in a person with normal liver function, vitamin D deficiency would be suspected if laboratory findings showed normal serum calcium and normal to low phosphorus with high-normal to elevated levels of PTH and alkaline phosphatase.

Severe vitamin D deficiency obstructs calcium mineralization in bone, causing osteomalacia (called rickets in children). Resulting bone is soft and prone to deformity and fracture. A red flag for osteomalacia is chronic musculoskeletal pain of unknown etiology. Studies have found very high prevalence of severe vitamin D deficiency in patients suffering from persistent nonspecific bone and muscle pain, headache, and fatigue. The effect was seen in all ages and ethnicities, affecting men and women alike. Prevalence was most pronounced in African American, East African, Middle Eastern, South Asian, Hispanic, and American Indian patients with diffuse nonspecific pain, of whom 80% to 100% had levels at or below 20 ng/mL.  

D-deficient osteomalacia resolves with vitamin D repletion.

Be Sure to Treat the Right Disease

Osteomalacia and osteoporosis have overlapping clinical indices. Without accurate measurement of serum vitamin D, practitioners can easily mistake osteomalacia for osteoporosis. Both present with low BMD on DXA and fragility fractures. However, they are different disorders with different treatments. Osteomalacia is caused by poor deposition of calcium in bone matrices, leading to soft, fragile bones. Treatment with antiresorptives intended for osteoporosis amplify this pathological process by slowing the remodeling process. Antiresorptives should never be used in a patient with osteomalacia.

Many patients have both osteomalacia and osteoporosis. Osteomalacia must be corrected before initiation of osteoporosis therapy. Osteomalacia is correctable with vitamin D supplementation (and calcium if needed), often in a matter of months. Once serum vitamin D reaches optimal levels, assessment of BMD can be repeated. Osteoporosis may need treatment with the usual drugs in those with diagnostic T-scores, FRAX scores, and/or other risk factors.
and other factors. As a result, serum vitamin D measurement provides a more accurate picture of a given patient’s vitamin D status.

Serum vitamin D levels are assessed by measuring circulating calcidiol, 25(OH)D. Calcidiol is preferred over calcitriol because of its relatively long and stable concentration in the blood. Calcitriol has a much shorter half-life than calcidiol (15 hours vs. 15 days) and is closely regulated by calcium, phosphorus, and parathyroid hormone. Assays for measurement of serum calcidiol have been criticized by the IOM and others for lack of consistency and standardization. This has led many specialists to err on the side of caution and assume a slightly higher acceptable serum vitamin D levels.

How Much Is too Much?

The upper limit set by the Institute of Medicine’s Food and Nutrition Board is 4,000 IU/day. However, evidence supports the view of many experts that this level is too conservative and that higher doses can be safe and beneficial. It is instructive that the IOM set the “No Observed Adverse Effects Level,” or NOAE, at 10,000 IU/day, this being the dose at which there are no published studies showing any adverse effects.

Because increased vitamin D leads to higher serum calcium levels, it was once thought that prolonged exposure to doses over safe limits could lead to vascular and tissue calcification with damage to heart, vessels, and kidneys. Clinical trial data from multiple investigations into this question contradict this hypothesis, demonstrating calcium levels do not significantly increase in response to increases in vitamin D intake up to about the level of 10,000 IU/day.\(^5\)

While intakes of 700 to 800 IU per day lower fall risk by an average of 15% to 20%, higher vitamin D intake are associated with higher fall risk. Data from a large randomized trial of elderly women (aged > 70) on high-dose vitamin D (500,000 units given in a single annual dose) showed increased risk of both falls and fractures.\(^5\)

Chronic megadose supplementation (such as >50,000 IU/day) over an extended period has been demonstrated to cause can lead to hypercalciuremia and hypercalcemia, which can have life-threatening consequences. Symptoms of acute vitamin D toxicity range from mild (headaches, weight loss, increased urination) to severe

CME Program Eligibility

Method of Participation in the Learning Process: Clinician learners will read and analyze the subject matter, conduct additional informal research through related internet searches on the subject matter, and complete a post-test assessment of knowledge and skills gained as a result of the activity.

After participating in this activity, the reader has the option of taking a post-test with a passing grade of 70% or better to qualify for continuing education credit for this activity. It is estimated it will take 1.0 hour(s) to complete the reading and take the post-test. Continuing education credit will be available for two years from the date of publication.

Accreditation

The National Osteoporosis Foundation is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. The National Osteoporosis Foundation designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

The National Osteoporosis Foundation is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

The National Osteoporosis Foundation designates this educational activity for a maximum of 1.0 continuing nursing education credit(s).

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Statement Regarding Off-Label Use

Any publication of the Osteoporosis Clinical Updates that discusses off-label use of any medications or devices will be disclosed to the participant.
(kidney stones, cardiac arrhythmia).

Consistent blood levels of >200 ng/mL are considered toxic and potentially dangerous. Fortunately the body regulates conversion of 25(OH)D to 1,25(OH)2D, its potent biologically active form. This is why reports of vitamin D toxicity are so rare. Clinicians can be reassured that doses well over the current IOM recommendations are safe for most patients.

IOM 2010 Daily Vitamin D Tolerable Upper Intake Level
- 0-6 months: 1000 IU (25 mcg)
- 7-12 months: 1500 IU (38 mcg)
- 1-3 years: 2500 IU (63 mcg)
- 4-8 years: 3000 IU (75 mcg)
- ≥9 years, 4000 IU (100 mcg)

These tolerable upper limits are meant as conservative guidelines. The level of 25(OH)D absorbed and circulated in the blood is what determines toxicity in a given individual.

**Ensuring Vitamin D Sufficiency**

How can a clinician determine the appropriate dose for a patient who is vitamin D deficient? IOM recommendations are based on what it takes to maintain adequate 25(OH)D levels in a population of healthy people.

In the elderly, infirm, or chronically ill, these recommendations may not apply. In these patients, vitamin D supplementation must be overseen on a case-by-case basis to ensure that healthy serum levels are reached and held steady over the long term. This means experimenting with dosage and following up with serum measurement at regular intervals.

It may be difficult to estimate the dose that will be most effective for a specific patient. Serum response to supplementation is nonlinear, with greater proportional impact at low serum levels than at high. In other words, it takes a higher dose to raise circulating levels in a D-replete patient than in a D-deficient patient.

Data from NHANES III has been used to calculate the daily intake required to ensure that 97.5% of women over age 60 have 25(OH)D values at or above desirable levels (30 ng/mL). The estimate is ≈2600 IU of vitamin D per day. This is way above recommended intake levels, but well below the tolerable UL and could easily be accomplished through oral supplementation.

Correction of vitamin D deficiency is commonly accomplished by administering high initial doses for several weeks or months, followed by a maintenance dose once target levels have been reached. For example, a typical regimen could start with 50,000 IU once weekly for 2 to 3 weeks. When follow-up testing shows adequacy, the dose could be reduced to 50,000 IU monthly or 2,000 daily for maintenance.

Retrospective analysis of multiple repletion regimens published by Pepper, et al., observed that a minimum total dose of 600,000 IU administered over 40 to 60 days was needed to correct vitamin D insufficiency (reach 30 ng/mL) in the population of older men studied.

Because vitamin D is fat soluble, it is best absorbed if eaten with a meal containing fat, ideally the largest meal of the day. Data suggest that this results in about a 50% increase in serum levels.

![Estimated Additional Vitamin D Intake (Up to 1886 IU/day) Needed to Correct Vitamin D Insufficiency](image)

**Figure 4.** Estimated additional vitamin D intake (up to 1886 IU/day) needed to correct vitamin D inadequacy.
of 25(OH)D levels achieved. Compliance with daily supplementation is consistently low (about 50%) in reported studies. Simple reminder strategies can help patients stay on track, such as putting a note on the refrigerator door or keeping the vitamin bottle on the dining table.

Nonskeletal Effects of Vitamin D

Multiple large prospective studies have observed extraskeletal benefits of vitamin D. Correlations have been reported between high intake of vitamin D and lower rates of chronic diseases such as colon, prostate, breast, and several other cancers, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes. Because these data came from observational studies, they were not included in the IOM’s analysis of vitamin D benefit, which restricted its analysis to data from placebo-controlled randomized clinical trials. Further research is needed to clarify the full spectrum of benefits and risks associated with vitamin D supplementation.

Patient Cases: Clinical Management of Vitamin D Deficiency

Case 1: Eighty-Year-Old African American Man with Vertebral Fracture

The first patient we will discuss is an 80-year-old retired teacher who has suffered a spinal fracture while golfing. He reports having severe pain in his back despite analgesics. A review of his medical history shows a decline of 4” in height since it was last measured (3 years). The patient has lost about 20 pounds in that same time period. He had gall bladder cancer 25 years ago, underwent chemotherapy, and is currently in remission.

The patient is asked about his diet and activities. He reports having very little outdoor activity since his fracture due to pain. Since that time, he walks very little at home and cannot walk the golf course. He routinely uses a wheelchair to ambulate.

The patient doesn’t have much of an appetite and avoids dairy, fish, and fatty foods because they make him feel queasy.

Is this patient at risk of vitamin D deficiency? Yes. His risk factors include his age, diet low in vitamin D, history of gall bladder disease (potential fat malabsorption), and lack of exposure to sunlight. It is likely that the patient is deficient in vitamin D, which may have contributed to low bone density and to his vertebral fracture.

The patient is referred for bone density measurement by DXA. His spinal T-score is -5.0, and his hip T-score is -3.0.

Does this patient have osteoporosis? At first glance, one might say “Yes.” However, it is not as simple as that. The patient’s T-scores, history of fracture, lack of activity, and diet low in calcium and vitamin D all point to high future fracture risk. But does he have progressive remodeling-related bone loss (osteoporosis) or is his severe vitamin D deficiency responsible for poor mineralization (osteomalacia)?

What can be done to refine his diagnosis? Running a series of lab tests can determine his levels of serum calcium, phosphorus, alkaline phosphatase, vitamin D, PTH, and urinary calcium excretion.

Lab results:

- Calcium: 7.9 mg/dL (normal 8.5 – 10.9 mg/dL)
- Phosphorus: 2.2 mg/dL (normal 2.4 – 4.1 mg/dL)
- Bone-specific alkaline phosphatase: 590 U/L (normal 20 – 140 IU/L)
- Serum 25(OH)D: 10 ng/mL normal (30 – 80 ng/mL)
- Intact PTH: 565 pg/mL (normal 10 – 65 pg/mL)
- Urine calcium: 23 mg/d (normal 100 – 300 mg/day)

What is the diagnosis? Clearly, this patient is at risk for further fractures. His serum calcium is low, and his 25(OH)D and urine calcium are very low. His PTH is quite high. His low phosphorus is consistent with osteomalacia. When coupled with the patient’s low DXA T-score and history of fracture, these lab values are sufficient to make a diagnosis of osteomalacia due to vitamin D deficiency and high fracture risk.

When can a diagnosis of osteoporosis be made? Until the vitamin D deficiency is corrected, we cannot know whether or not he actually has osteoporosis. Whereas osteomalacia is characterized by low bone mineralization as a result of vitamin D deficiency, osteoporosis is characterized by progressive decline in
bone density due to bone lost to unbalanced bone remodeling. The treatment for osteomalacia is vitamin D; the treatment for osteoporosis is an antiresorptive or anabolic agent.

What are the options for treatment?
First, the patient’s calcium and vitamin D deficiencies need to be corrected. He is prescribed 1200 mg calcium and 10,000 IU vitamin D to be taken daily for 2 months. Next, because primary osteoporosis is relatively rare in men, the clinician looks for correctable secondary causes of bone loss.

Are there “red flags” in the patient’s history?
Taken together, the patient’s history of weight loss and digestive discomfort strongly suggest the possibility of celiac disease. The patient is tested for celiac disease. Results are positive. The clinician refers him to a nutritionist for guidance on gluten-free eating.

What follow up should be done?
To ensure that he is reaches optimal serum 25(OH)D and other chemical indices, follow-up blood chemistry should be done after 3 to 4 months.

The patient has bone specific chemistries run. His 25(OH)D is 56 ng/mL, PTH is normal, and serum calcium is 9.3 mg/d.

What further interventions should be made at this point?
Correction of vitamin D deficiency has been demonstrated to increase bone mass in severely deficient cases such as this. However, it may not be enough to protect against fracture.

How can the clinician determine if the patient is still losing bone?
The patient can have biochemical markers of bone turnover measured, such as bone-specific alkaline phos- phatase. Biomarkers above reference values in a setting of replete vitamin D point to elevated bone resorption and continued bone loss.

The patient’s bone specific alkaline phosphatase (BALP) is measured. His BALP level is lower than before vitamin D supplementation but is still high at 355 U/L, indicative of osteoporosis.

What are the patient’s therapeutic options to preserve bone and prevent fracture?
There are many FDA-approved medications available for male patients with osteoporosis. Options range from daily oral alendronate to yearly injectable zoledronic acid and the daily injectable anabolic, teriparatide.

The clinician discusses the options for treatment. The patient decides on yearly infusions of zoledronic acid and schedules his first infusion.

Are there additional measures that can be taken to help this patient avoid fracture?
Yes, Falling is a significant risk for this patient due to his low activity level and fragile bones. The vast majority of fractures in patients with low bone density occur as the result of falls. Preventing falls means preventing fractures.

The clinician refers the patient to a physical therapist for muscle strengthening and weight-bearing program of exercise. Physical therapy that includes principles of safe movement and exercise to build muscle strength and improve balance will help him avoid falls and additional vertebral fractures in the course of daily activities. The order for physical therapy includes a request for instruction on fall proofing the home environment. In addition to physical therapy, the patient is referred to an ophthalmologist to address any vision impairment, a known risk factor for falling.

Case 2: 77-Year-Old Caucasian Woman in Nursing Home

The second case we will discuss is a 77-year-old woman who has resided in an assisted living complex for five years since breaking a hip, which was surgically repaired with no complications. The patient is 5’2” and weighs 190 pounds. Since her hip fracture, the patient has used a walker. At the time of her fracture, she was prescribed daily oral alendronate for osteoporosis. She reports having discontinued it after a few months due to gastric upset. She has now been referred for bone loss evaluation and potential treatment.

What risk factors does this patient have for vitamin D deficiency?
The patient has several risk factors for compromised vitamin D: her age, her lack of sun exposure, and her obesity. She is tested for serum 25(OH)D, serum calcium, and PTH and found to have a low serum calcium (6.5 mg/dL) and very low circulating 25(OH)
D (8 ng/mL). Her PTH is high at 300 pg/mL and her phosphorus is low normal (2.8 mg/mL). Her spine and hip DXA measurements show T-scores of -3 and -3.5 respectively.

**What impact could her 25(OH)D status have on osteoporosis therapy?**
Optimal vitamin D repletion is necessary to maximize response to antiresorptives in terms of BMD and anti-fracture efficacy. In studies, vitamin D deficient and vitamin D repleted subjects differed significantly for annualized spine and hip BMD changes adjusted for all available confounding factors (type of treatment, age, calcium intake, baseline BMD values, etc.).

**What treatment is recommended?**
Because the patient is obese, a higher dose of vitamin D will probably be required to raise her deficient circulating 25(OH)D level to the optimal range. The patient is prescribed 50,000 IU/day vitamin D and 1000 mg calcium (in split dose) for three months.

**What follow-up would be recommended?**
The patient’s labs are rechecked in one month to assess her vitamin D and calcium status. If it is normal, she will be started on monthly oral risedronate and her vitamin D supplementation reduced to 2000 IU daily (with 1000 mg calcium).

If she tolerates the risedronate and her labs show improvement in 25(OH)D (30ng/mL), her regimen will be maintained, with a planned follow-up twice yearly.

**Are there any other interventions recommended?**
The patient is referred to the in-house exercise classes in her assisted living complex. She is encouraged to spend time outdoors and to improve her overall activity level in a supervised setting. She is also referred to the in-house nutritionist for guidance on a healthy diet.

**Summary**
Vitamin D plays a complex role in calcium homeostasis, PTH regulation, and promotion of overall health. Maintenance of serum 25(OH)D levels is critical to skeletal health and is influenced by multiple factors, endogenous and exogenous to the individual.

Vitamin D deficiency is widespread in the U.S. The elderly and institutionalized are at particularly high risk for severe deficiency. Resulting low bone density
and fractures may indicate osteomalacia, osteoporosis, or both. Ensuring appropriate patient care requires accurate vitamin D measurement and correction of any D deficiency before diagnosis and treatment of osteoporosis.

Additional research is needed to clarify the many unanswered questions about the full effects and function of vitamin D in human health.

References

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