DRIs for Vitamin D(1):

- 600 IU/d for males and females 1-70 yo
- 800 IU/d for males and females 71+ yo
- 600 IU/d for females pregnant/lactating 14-50 yo
- Tolerable UL:
  - 0-6 months: 1000 IU/d
  - 6-12 months: 1500 IU/d
  - 1-3 years: 2500 IU/d
  - 4-8 years: 3000 IU/d
  - 9+ years: 4000 IU/d
- Vitamin D can be referenced in IU or mcg
  - To convert IU into mcg, multiply IUs by 0.025.(4)

Forms of Vitamin D

- D<sub>2</sub> (ergocalciferol): is found in the diet in some plants, and used for fortification and supplementation.”(2)
- D<sub>3</sub> (cholecalciferol): is produced in the skin in response to sunlight exposure (ultraviolet B [UVB] radiation), or can be attained in the diet or from supplements.(2)
- Total serum 25-hydroxyvitamin D [25(OH)D] concentration: is the active form of vitamin D from both food and sunlight.
  - Is “the best test to assess body stores of vitamin D.”(3)
  - Is “an indicator of supply rather than function.”(2)
  - Has a half-life of approximately 3 weeks.(2,4)

Serum 25(OH)D Levels

- Current terminology and the cutoff values for serum 25(OH)D: (2,3,5)

<table>
<thead>
<tr>
<th>Term</th>
<th>Serum Level (to convert to nmol/L multiply by 2.496)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficient</td>
<td>≤ 10 ng/mL</td>
</tr>
<tr>
<td>Insufficient</td>
<td>11-29 ng/mL</td>
</tr>
<tr>
<td>Optimal</td>
<td>30-80 ng/mL</td>
</tr>
<tr>
<td>Possible Toxicity</td>
<td>&gt;80 ng/mL</td>
</tr>
</tbody>
</table>

- Set cutoff points of sufficiency vs deficiency used in laboratories have not been determined. Therefore, depending on the laboratory used, a person might be inappropriately considered deficient or sufficient.(1)
- Normal ranges are determined by collecting samples from ‘normal, healthy’ individuals. In the case of vitamin D, many individuals sampled may have had suboptimal levels which shifts the normal range lower than may be appropriate. (4)
Vitamin D Metabolism

- In the presence of sunlight exposure, specifically UVB radiation, the human body is capable of producing vitamin D on its own.(2,4)
- After UVB exposure to the skin, 7-dehydrocholesterol is converted to cholecalciferol (vitamin D₃).(4,5)
- Vitamin D from dietary sources is metabolized in the liver to 25(OH)D.(2,4)
  - Vitamin D₂ and D₃ go through the same mechanism for metabolism.(2)
- 25(OH)D can be stored in the liver, or travel to the kidneys and be metabolized “by the enzyme 25-hydroxyvitamin D-1α-hydroxylase to its active form, 1,25-dihydroxyvitamin D [1,25(OH)₂D].”(2,4,5)
- Though produced in the kidneys, 1,25(OH)₂D acts distally in the intestinal cells (predominantly the duodenum) to increase calcium absorption, or in bone cells to mobilize calcium by stimulating osteoblasts and osteoclasts.(2,4) It also regulates parathyroid hormone (PTH) secretion and may have other roles in maintaining muscle function.(4)
  - PTH, serum calcium and phosphorus levels tightly regulate 1,25(OH)₂D based on the body’s need for calcium.(2,5)
    - Calcium and phosphorous are more efficiently absorbed in the presence of 1,25(OH)₂D.(5)

Sources of Vitamin D

- Dietary sources include:
  - Vegetable sources, egg yolks, oily fish (such as salmon, sardines, tuna, cod liver oil), and fortified foods (margarine, butter, breakfast cereals, milk, juices, yogurt, cheeses).(3,5,6)
  - Infant formulas (5)
  - Oral supplements (3)
- Sun exposure:
  - The amount of time required in direct sunlight depends on time of day, season, latitude, and skin pigmentation. Generally, about 15 minutes between 10 am and 3 pm should suffice.(4,5)
  - Wearing a bathing suit in the summer for about 20 minutes can allow the body to produce as much as 20,000 IU of vitamin D.(2,5)

Recognizing Deficient Populations

- Vitamin D deficiency is a growing problem that affects all age groups of all geographic locations, but may be greater in hospitalized individuals. (3,4)
- Populations at risk:
  - Those who reside at higher latitudes, especially during winter months (3)
  - Those who reside in sunny areas but cover their skin or use sunscreen (3,4,5)
  - Black people (4)
  - Hospitalized patients and homebound elderly persons (4)
Pregnant and lactating women are at risk, despite supplementing with a prenatal vitamin (5)
- Exclusively breastfed infants (5)
- Results of aging, chronic liver and renal diseases, and certain drugs impair vitamin D synthesis (4)

Risks of Deficiency
- Vitamin D deficiency has been associated with several comorbidities including:
  - Rickets in children, osteomalacia in adults, impaired immunity, increased autoimmunity, myopathy and fibromyalgia, diabetes mellitus, increased risk for multiple sclerosis, osteoporosis, secondary hyperthyroidism or secondary hyperparathyroidism, calcium malabsorption, hypertension, and an increased risk of colon, breast, and prostate cancers. (2,3,4)
- If deficiency is present in utero and during childhood, growth retardation and skeletal deformities may develop and may lead to increased risk of hip fracture later in life. (5)

When to Test
- Testing is “expensive and universal screening is not supported.” (3)
- Measure serum 25(OH)D levels to test for vitamin D deficiency when the following are presented (2,3,4,5):
  - Clinical symptoms: Rickets, osteomalacia, bone pain, elevated serum alkaline phosphatase or PTH levels, low serum calcium or phosphorus levels, patients with osteoporosis, those with low bone mineral density, patients with CKD1-3, myalgia, generalized weakness, muscle weakness or pain, and those with fat malabsorption syndromes.
    - Many of these symptoms can be misdiagnosed as other issues. (3,4)
  - Other risk factors: Those at increased risk of falls or fractures, those who are thought to have inadequate sun exposure or dietary intake, and breastfed infants.

How to Treat
- When treating vitamin D insufficiency or deficiency, the objective is to raise serum 25(OH)D to the sufficient level, and maintain it at or above that level. (4)
  - Symptoms such as muscle weakness may take as long as 4-8 weeks before relief ensues. (4)
- Treatment type and dosage is dependent on the baseline level of serum 25(OH)D. (4)
  - “Large bolus doses of vitamin D are necessary to elevate low serum 25(OH)D, which can then be maintained with daily oral supplements.” (4)
- Current recommendations to treat adults with vitamin D deficiency are to provide 50,000 IU once weekly for about 2-3 months to achieve sufficiency (3,4), and 50,000 IU once every 2-4 weeks to maintain sufficiency. (5)
  - Mild and moderate deficiency may only need a shorter length of treatment, or smaller dose. (3)
- Calcium intake will vary the requirements needed for vitamin D supplementation. (2)
Supplementation

- Is safe and inexpensive.(3)
- A common mistake that occurs when serum 25(OH)D reaches a sufficient level is to stop treatment altogether. Supplementation should continue to occur to maintain sufficiency and prevent future deficiency at a daily dose of 800-2000 IU.(3)
  - 2000 IU/d maintains “current safe upper limit guidelines.”(3)
- Standard multivitamins:

  Vitamin D supplement availability and cost (4)

<table>
<thead>
<tr>
<th>Type of Vitamin D</th>
<th>D2</th>
<th>D2</th>
<th>D2</th>
<th>D2</th>
<th>D2 (centrum multivitamin)</th>
<th>D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vendor</td>
<td>Walgreens</td>
<td>CVS</td>
<td>GNC</td>
<td>GNC</td>
<td>Walgreens</td>
<td>GNC</td>
</tr>
<tr>
<td>Dose, IU</td>
<td>50,000</td>
<td>50,000</td>
<td>400</td>
<td>700</td>
<td>400</td>
<td>1000</td>
</tr>
<tr>
<td>Suggested frequency</td>
<td>Weekly</td>
<td>Weekly</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
<td>Daily</td>
</tr>
<tr>
<td>Cost/month, $</td>
<td>11.99</td>
<td>10.99</td>
<td>1.21</td>
<td>1.17</td>
<td>4.19</td>
<td>1.67</td>
</tr>
<tr>
<td>Availability</td>
<td>Prescription Only</td>
<td>Prescription Only</td>
<td>OTC</td>
<td>OTC</td>
<td>OTC</td>
<td>OTC</td>
</tr>
</tbody>
</table>

- TPN:
  - Standard multivitamins for TPN only provide 200 IU, which helps to maintain serum 25(OH)D levels, but may not correct deficiency.(3)
- Tube feeding (3):
  - Vitamin D dosing requirements are similar to those patients eating orally.
  - Vitamin D2 capsules should not be used in enteral feeding because they are contained in oil, which can clog the tube.
  - Vitamin D3 capsules are contained in a powder form and do not clog feeding tubes.
- Malabsorption:
  - Patients with malabsorption syndromes often require larger maintenance doses of vitamin D.(3,5)
    - “Patients with malabsorptive gastric bypass procedures may require 50,000 IU of D2 or D3 maintenance dosing from once weekly to as frequently as daily to maintain sufficiency.”(3)
  - In extreme cases, patients who do not respond to large oral doses may benefit from sunlight exposure or phototherapy to raise vitamin D levels.(3)
- Vegetarian and Vegan Diets:
  - To ensure maximum absorption, vitamin D should be taken with a meal containing fat.(3)
- Breast-fed Infants and Children:
  - Human breast milk contains very little vitamin D. Mothers who are deficient and breast feeding provide even less to their infants.(5)
  - By supplementing with 4000 IU/d of vitamin D3, lactating moms were able to increase their own serum 25(OH)D and pass enough through their breast milk to meet the infants’ requirements.(5)
**Signs/Symptoms of Toxicity**

- Toxicity is rare and is usually seen after megadoses of vitamin D supplementation (i.e., more than 10,000-50,000 IU/d for prolonged periods) with a normal functioning gut, and are known to cause kidney and tissue damage.(1,3,5)
  - If limited to 5 months, doses of 10,000 IU/d of vitamin D₃ do not cause toxicity.(5)
- Signs and symptoms of toxicity include:
  - "Patients having secondary hypercalcemia and presenting with weakness, lethargy, headaches, nausea, polyuria, ectopic calcification in the tissue, and possibly altered mental status in late stages" as well as dehydration, constipation, polyuria, and kidney stones.(3,4)
- Toxicity should not be diagnosed on elevated 25(OH)D levels alone; hypercalcemia, “in which hyperphosphatemia and hypercalciuria also commonly (although not always) occur” should be present as well.(3)
- “The rarity of reports of vitamin D toxicity can be explained in part by the kidney’s ability to limit production of active calcitriol. Increased calcitriol levels inhibit PTH both directly…and indirectly…causing calcitriol production in the kidney to decrease.”(3)

References:


