

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS | AMERICAN COLLEGE OF ENDOCRINOLOGY

Vitamin D Deficiency

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Vitamin D

- Vitamin D is a fat-soluble vitamin involved in the regulation of calcium homeostasis and bone health. It is synthesized in the body when ultraviolet rays from sunlight strike the skin and trigger vitamin D synthesis.
- There are few foods that naturally contain vitamin D or are fortified with it. The major source of vitamin D for both children and adults is exposure to natural sunlight. The major cause of vitamin D deficiency is lack of sun exposure.

Holick MF et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2011; 96:1911-30.

LeFevre M et al. Screening for vitamin D deficiency in adults: U.S. preventive services task force recommendation statement. *Ann Intern Med* 2015; 162:133-141.

National Institutes of Health. Vitamin D: Fact Sheet for Professionals. Available at <https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/>. Accessed August 23, 2018.

Definitions of Vitamin D Deficiency

- There is not yet broad consensus on what constitutes vitamin D deficiency. Different organizations have slightly different definitions, based on serum levels of 25-hydroxyvitamin D, or 25 (OH)D.

The Endocrine Society	The Institute of Medicine (Health and Medicine Division of the National Academies)	The Mayo Clinic	The American Association of Clinical Endocrinologists
Deficiency: ≤ 20 ng/ml	Deficiency: < 12 ng/ml	Severe deficiency: <10 ng/ml	Deficiency: < 30 ng/ml
Insufficiency: 21-29 ng/ml	Insufficiency: 12-20 ng/ml	Mild to moderate Deficiency: 10-24 ng/ml	Optimal: 30-50 ng/ml
Optimal: ≥ 30 ng/ml	Optimal: ≥ 20 ng/ml	Optimal: 25-80 ng/ml	

Kennel KA et al. Vitamin D deficiency in adults: When to test and how to treat. *Mayo Clin Proc* 2010; 85:752-758.

IOM (Institute of Medicine). 2011 Dietary Reference Intakes for Calcium and Vitamin D. Washington DC: The National Academies Press.

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Camacho PM, Petak SM, Binkley N et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. *Endocr Pract.* 2016;22(Suppl 4):1-42.

Consequences of Vitamin D Deficiency

- Vitamin D deficiency results in abnormalities in calcium, phosphorous, and bone metabolism. Severe and prolonged deficiency can cause bone mineralization diseases, such as rickets in children and osteomalacia in adults.
- Vitamin D deficiency has also been associated with fractures, falls, functional limitations, some types of cancer, diabetes, cardiovascular disease, and depression. However the U.S. Preventive Services Task Force notes that, “these associations are inconsistent and may vary by the cut point used to define low vitamin D levels.”

LeFevre M et al. Screening for vitamin D deficiency in adults: U.S. preventive services task force recommendation statement. *Ann Intern Med* 2015; 162:133-141.

Prevalence in the United States

- Using a cutoff of ≤ 20 ng/ml, an analysis of National Health and Nutrition Examination Survey (NHANES) data from 2005-2006 found that the overall prevalence rate of vitamin D deficiency among U.S. adults was 41.6%.
- Rates are significantly higher in blacks and Hispanics compared with whites. In the NHANES study, the highest rate was seen in blacks (82.1%), followed by Hispanics (69.2%).
- Even when using a more conservative definition, many patients routinely encountered in clinical practice will be deficient in vitamin D.

Forrest KY and Stuhldreher WL. Prevalence and correlates of vitamin D deficiency in U.S. adults. *Nutr Res* 2011; 31:48-54.

Kennel KA et al. Vitamin D deficiency in adults: When to test and how to treat. *Mayo Clin Proc* 2010; 85:752-758.

LeFevre M et al. Screening for vitamin D deficiency in adults: U.S. preventive services task force recommendation statement. *Ann Intern Med* 2015; 162:133-141.

Symptoms of Vitamin D Deficiency

- Vitamin D deficiency is often asymptomatic. However, severe or prolonged deficiency may cause the following symptoms:
 - Bone discomfort or pain in the lower back, pelvis, or lower extremities
 - Falls and impaired physical function
 - Muscle aches
 - Proximal muscle weakness
 - Symmetric low back pain (in women)

Bordelon P et al. Recognition and management of vitamin D deficiency. *Am Fam Phys* 2009; 80:841-846.

Who Should be Screened?

- Neither the Endocrine Society, the Mayo Clinic, the U.S. Preventive Services Task Force, nor the American Association of Clinical Endocrinologists recommends universal screening for vitamin D deficiency among the general population or asymptomatic individuals. However, they do recommend screening in individuals with risk factors for vitamin D deficiency. These include the following:
 - Malnutrition
 - Sedentary Lifestyle
 - Limited sun exposure
 - Obesity
 - Dark skin
 - Age \geq 65
 - Conditions causing gastrointestinal malabsorption, including short bowel syndrome, pancreatitis, inflammatory bowel disease, amyloidosis, celiac sprue, and bariatric surgery.
 - Liver disease or failure
 - Renal insufficiency or nephrotic syndrome
 - Cystic Fibrosis
 - Medications that alter vitamin D metabolism, including anticonvulsants and glucocorticoids

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Diagnosis

- There is broad consensus that diagnosis of vitamin D deficiency should be made using a reliable assay for 25(OH)D. Testing for serum 1,25-dihydroxyvitamin D is not recommended.
- Available methods include competitive protein binding, immunoassay, high performance liquid chromatography, and combined high-performance liquid chromatography and mass spectrometry.
- The U.S. Preventive Services Task Force cautions that the sensitivity and specificity of these tests are unknown due to the lack of studies using an internationally recognized reference standard. Variability between assay methods and even between laboratories using the same method may range from 10% to 20%. Classification of samples as deficient or normal may vary by 4% to 32%.

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Treatment of Vitamin D Deficiency

- There is broad consensus that increased intake of dietary vitamin D is not enough to correct deficiency. Vitamin D supplementation is required. Vitamin D₂ or D₃ are recommended.

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Treatment: Endocrine Society Recommendations

- **Age 0-1**

2,000 IU per day for Infants and Toddlers or 50,000 IU once weekly for 6 weeks to achieve a blood level 25(OH)D above 30 ng/ml. Followed by maintenance therapy of 400-1,000 IU/day.

- **Children Age 1-18**

2,000 IU per day for at least 6 weeks or 50,000 IU once weekly for at least 6 weeks to achieve a blood level 25(OH)D above 30 ng/ml. Followed by maintenance therapy of 600-1,000 IU/day.

- **Adults**

6,000 IU per day or 50,000 IU per week for 8 weeks to achieve a blood level 25(OH)D above 30 ng/ml. Followed by maintenance therapy of 1,500-2,000 IU/day.

- **Special Cases**

Obese patients, those with malabsorption syndromes, and those on medications affecting vitamin D metabolism should receive a higher dose of 6,000 to 10,000 IU/day to achieve levels above 30 ng/ml. Followed by a maintenance dose of 3,000-6,000 IU/day.

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Prevention: Endocrine Society Recommendations

- The Endocrine Society recommends the following daily intakes of vitamin D to prevent deficiency and maximize bone health.
 - **Children age 0-1:** at least 400 IU/day. May require 1,000 IU/day to achieve > 30ng/ml
 - **Children age 1-18:** at least 600 IU/day. May require 1,000 IU/day to achieve > 30ng/ml
 - **Adults age 19-70:** at least 600 IU/day. May require 1,500-2,000 IU/day to achieve > 30ng/ml
 - **Adults older than 70:** at least 800 IU/day. May require 1,500-2,000 IU/day to achieve > 30ng/ml
- Obese children and adults; those on anticonvulsant medications, glucocorticoids, and antifungals such as ketoconazole; and those taking medications for AIDS should be given at least two to three times more vitamin D for their age group to satisfy their body's requirement.

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Prevention: AACE Recommendations

- Daily supplementation with vitamin D₃ at a dose of 1,000 to 2,000 IU is typically needed to maintain an optimal serum 25(OH)D level.
- Higher doses may be necessary in the presence of certain factors including obesity, malabsorption, and certain ethnicities. Transplant patients and older individuals may also need higher doses.

Camacho PM, Petak SM, Binkley N et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016. *Endocr Pract.* 2016;22(Suppl 4):1-42.

Prevention: Institute of Medicine Recommendations

- Children and adults age 1-70: 600 IU per day
- Adults older than 70: 800 IU per day

IOM (Institute of Medicine). 2011 Dietary Reference Intakes for Calcium and Vitamin D. Washington DC: The National Academies Press.

Vitamin D Toxicity

- Excess vitamin D supplementation can lead to hypercalcemia, but vitamin D toxicity is extremely rare. It generally occurs only after ingestion of large doses of vitamin D (>10,000 IU/day) for prolonged periods in patients with normal gut absorption or those ingesting excessive amounts of calcium.
- Patients with vitamin D toxicity can present with clinical symptoms of hypercalcemia, including nausea, dehydration, and constipation, or symptoms of hypercalciuria such as polyuria and kidney stones.
- The lowest reported 25(OH)D level associated with toxicity in patients without primary hyperparathyroidism and with normal renal function is 80 ng/ml. Most patients with vitamin D toxicity have levels greater than 150 ng/ml.
- One dosing study reported that vitamin D supplementation with 1,600 IU/day or 50,000 IU monthly was not associated with any laboratory parameters of toxicity and even failed to increase total 25(OH)D levels above 30 ng/mL in 19% of participants.

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