Vitamin D is a steroid hormone produced in the skin during exposure to sunlight, or consumed in the diet, primarily in the form of fatty fish and fortified milk. Because individuals with adequate sun exposure do not require supplementation, the term “vitamin” is actually a misnomer. Vitamin D influences not only bone and mineral homeostasis, but many other tissues and functions in the body. Vitamin D insufficiency has been associated with disorders such as osteoporosis, multiple sclerosis, cancer, cardiovascular disease, diabetes, and auto-immune disease. Recent studies suggest that subclinical vitamin D deficiency is much more common than previously thought.

The likelihood of vitamin D insufficiency is increased in malabsorption syndromes, aging (elderly individuals have a reduced capacity for vitamin D3 formation), darker skin (higher concentrations of melanin reduce efficiency in vitamin D3 production), obesity (fat-soluble vitamin D is stored in adipose, which reduces bioavailability), and minimal sun exposure, such as in winter or at more northern latitudes.

Serum concentration of 25-hydroxyvitamin D, or 25(OH)D, is the best indicator of vitamin D status. Besides reflecting cutaneous synthesis and absorption of vitamin D from the diet, the production of 25(OH)D, unlike its active metabolite 1,25(OH)2D, is not regulated. The metabolite 1,25(OH)2D is also known as calcitriol and vitamin D3.

Traditional analysis of vitamin D is based on average serum concentrations considered consistent with prevention of hyperparathyroidism, osteomalacia and rickets. However, many individuals with vitamin D levels in the “normal” range are still found to have elevated parathyroid hormone (the body’s response to low vitamin D) and/or additional signs of insufficiency. In light of this new research, customarily recommended intakes of vitamin D are increasingly recognized as inadequate for maintaining optimal health. Therapeutic correction of low 25(OH)D levels is possible with appropriate amounts of vitamin D3 and UVB exposure.

The following ranges for 25(OH)D reflect a compilation of revised recommendations suggested by scientists in the field:

- **Deficiency** = <20 ng/mL (50 nmol/L)
- **Insufficiency** = 20-40 ng/mL (50-100 nmol/L)
- **Optimal** = 40-80 ng/mL (100-200 nmol/L)
- **Excessive** = >80 ng/mL (200 nmol/L)

According to a 2004 survey in the U.S., only 31% of whites aged 20-49 yrs, <9% of older whites, and an even smaller fraction of Mexican-American and African-American adults were found to have serum 25(OH)D concentrations of >36 ng/mL.

**Physiology & Clinical Significance of Vitamin D**

Vitamin D3 production in the skin is accomplished via conversion of 7-dehydro-cholesterol to pre-vitamin D by UVB radiation, specifically. UVB predominates over UVA when the sun is high in the sky, around solar midday. At higher altitudes, such as in Boston, MA or Edmonton, Alberta, the sun is only high enough in the sky for UVB radiation during the summer months.

Pre-vitamin D from both diet and sun exposure is converted to 25(OH)D in the liver and then activated in the kidneys to 1,25(OH)2D (vitamin D3). Renal activation is homeostatically controlled by parathyroid hormone (PTH).

While adequate calcium is critical for tissues such as bone, calcium’s dependency upon vitamin D is often overlooked. Vitamin D3 serves to increase intestinal absorption of orally ingested calcium and stimulate tubular reabsorption of calcium. Thus, vitamin D deficiency leads to reduced calcium absorption. Increasing 25(OH)D concentrations from ~20 ng/mL to ~32 ng/mL (still below the optimal range) improve calcium’s absorption by up to 65%.
Most cells and tissues in the body contain vitamin D receptors as well as the enzyme required to make vitamin D3, including breast, prostate, lung, ovary, skin, lymph nodes, colon, pancreas, adrenal medulla, brain, neurons, and B and T cells. Vitamin D3 is known to regulate immune function, suppress cellular growth, inhibit renin production, modulate neurotransmitter and neurologic function, and stimulate insulin secretion.

**Interpretation of Test Results**

**Deficient or Insufficient levels (<40 ng/mL):**
Owing to its diverse actions in numerous tissues, vitamin D insufficiency is thought to increase the risk of infection, cancer, autoimmune disease, hypertension, arteriosclerosis (vitamin D3 suppresses secretion of pro-inflammatory cytokines), diabetes and/or insulin resistance, musculoskeletal pain, epilepsy, and migraine. Vitamin D deficiency can also lead to the development of rickets or osteomalacia due to under-mineralization of the growing skeleton or demineralization of the adult skeleton, respectively. Calcium absorption is reduced and PTH is increased, resulting in increased bone turnover, reduced bone mineral density, and increased risk of fracture.

**Excessive levels (>80 ng/mL):**
Excessive levels of 25(OH)D generally result from over-supplementation of the vitamin (e.g., regular intake of >100,000 iu/d in adults, or >40,000 in children) or industrial accident, and can be reversed over time by avoiding supplementation, vitamin D-rich foods, and UVB exposure. Toxic effects are thought to be due to hypercalcemia, resulting from intestinal hyperabsorption and, to a lesser degree, from calcium release from bone. Levels of PTH are typically elevated. Hypercalcemia may lead to kidney stones, coronary sclerosis, bone loss, and soft-tissue calcifications. Acute signs and symptoms of hypervitaminosis D include anorexia, nausea, and vomiting, weakness, nervousness, pruritis, excessive thirst and/or urination, and renal impairment. High serum calcium is the most important indicator of vitamin D toxicity, thus should be monitored in patients receiving high-dose vitamin D.

Note: According to most studies, toxicity is unlikely when 25(OH)D levels remain below 80 ng/mL. If, however, high normal levels of 25(OH)D are accompanied by hypercalcemia, hypercalciuria, or hyperparathyroidism, then vitamin D supplementation may be excessive and reducing the dosage is recommended. Hypercalcemia has also been known to occur with a vitamin D hypersensitivity syndrome. Regardless of the cause of the hypercalcemia, vitamin D administration should be discontinued until the cause is identified.

**Treatment Guidelines**

Serum vitamin D levels can be increased via UVB radiation, dietary intake, or vitamin D3 supplementation.

**Sunlight**
More than 90% of the vitamin D requirement for most people comes from casual exposure to sunlight. A minimal erythematosous dose (MED) is the minimum amount of energy necessary to produce slight pinkness in the skin within 24 hours of sunlight exposure. One MED of UVB radiation has been observed to increase blood concentrations of 25(OH)D that are equivalent to 10,000-20,000 iu of oral vitamin D. Even intensive sunlight exposure has not been observed to produce toxicity in healthy adults, most likely explained by the production of vitamin D-inactive substances following 15-30 minutes of UVB exposure. Holick has suggested that exposure to sunlight for 5-15 minutes between 10 a.m. and 3 p.m. during spring, summer, and autumn is usually sufficient exposure for individuals with skin type II or III*. This constitutes 25% of an MED for most individuals. In determining optimal sun exposure, bear in mind the influence of season, skin color, and latitude. It is also worth noting that sunscreens absorb the UVB radiation responsible for vitamin D production. Depending on the SPF, sunscreens can reduce vitamin D3 formation by up to 99%.

*Skin types:
- Type I: always burns, never tans
- Type II: burns easily, tans minimally
- Type III: burns moderately, tans gradually
- Type IV: burns minimally, always tans
- Type V: rarely burns, tans dark
- Type VI: never burns, deeply pigmented

As mentioned, sun exposure beyond the MED does not further increase vitamin D production. However, concerns regarding the development of skin cancers and acceleration of skin aging make oral vitamin D supplementation a better option for many individuals.

**Supplementation**
Both cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2) are available as supplemental sources of vitamin D. As vitamin D2 is a fungal metabolite and may be associated with adverse effects, vitamin D3 is the preferred form of supplementation. Oral vitamin D3 also results in a 70% higher 25(OH)D level compared to the same amount of vitamin D2. Concomitant calcium supplementation is recommended.

Dietary Reference Intakes (DRI) were established in 1997 as follows:
- 5 ug (200 iu)/day for infancy through age 50 yrs
- 20 ug (400 iu)/day for ages 51-70 yrs
- 15 ug (600 iu)/day for >70 yrs of age

© 2008 Genova Diagnostics
More recent research, however, indicates that significantly higher oral intakes than 5-15 ug/day are necessary to maintain adequate serum 25(OH)D levels in the absence of UVB irradiation.

**Without exposure to sunlight, a minimum of 1000 iu/d (40 ug) vitamin D is required.**

- Individuals with baseline concentrations between 8 and 16 ng/mL may require, in addition to sun exposure, a daily oral intake of >2200 iu (55 ug) to achieve 25(OH)D concentrations of at least 32 ng/mL.
- Doses as high as 4,000 iu/day for adults and 1,000 iu/day for children have been established as safe in most cases.
- Dose-response studies have demonstrated that a dose of ~1700 iu (43 ug) per day would roughly increase a 25(OH)D level from 20 ng/ml to 32 ng/ml.
- Some researchers have also advocated short-term, very high-dose supplementation to rapidly increase levels in vitamin D-deficient individuals.

**Diet**

Very few foods naturally contain vitamin D. Dietary sources include cod liver oil and oily fishes such as salmon, mackerel, and sardines. The amount of cod liver oil required to obtain a dose of 4,000 iu/day would be 3 tbsp, or >18 capsules of most commercial preparations. Foods fortified with vitamin D (at least in the U.S.) include milk (100 iu per 8 oz serving), orange juice (same), and some breads and cereals.

**Follow-up Testing**

The half-life of 25(OH)D in the circulation is ~1 month. Levels generally plateau after ~3 months of vitamin D supplementation or UVB exposure. When dosing higher than 1000 iu/day, regular monitoring of 25(OH)D (along with serum calcium) is recommended until optimal levels are achieved, above 40 ng/mL. Persistently low levels may indicate malabsorption or non-compliance. Levels higher than 80 ng/mL suggest excessive supplementation.

**How do I order this test?**

For more information about Vitamin D testing options, please call a Client Services representative at 800-522-4762 or order online at www.GDX.net.
References


27 Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 2003 May; 89(5):552-7.


31 Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 2003 May; 89(5):552-7.


38 Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 2003 May; 89(5):552-7.


44 Zittermann A. Vitamin D in preventive medicine: are we ignoring the evidence? Br J Nutr 2003 May; 89(5):552-7.


This information is for the sole use of a licensed health care practitioner and is for educational purposes only. It is not meant for use as diagnostic information. All claims submitted to Medicare/Medicaid for Genova Diagnostics laboratory services must be for tests that are medically necessary. “Medically necessary” is defined as a test or procedure that is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. Consequently, tests performed for screening purposes will not be reimbursed by the Medicare program.