

Indications and Limitations of Coverage and/or Medical Necessity

Vitamin D is a commonly used collective term for a family of closely related seco-steroids. Vitamin D, originally described as a vitamin, is more appropriately categorized as a prohormone, synthesized by the skin and converted in the liver to 25-hydroxycholecalciferol, and then further converted mainly by the kidney to 1,25-dihydroxycholecalciferol, the active hormone, also known as calcitriol, which then acts throughout the body on target organs. The synthesis of the prohormone in the skin depends on UV B radiation, a process that is inhibited by sunscreen with a skin protection factor (SPF) of 8 or greater. Vitamin D₃ (cholecalciferol, derived from animal sources) and vitamin D₂ (ergocalciferol, derived from fungal and plant sources) may also be obtained by dietary supplementation or from a limited number of foods, predominately oily fish. Vitamin D₂ is metabolized in a similar way to vitamin D₃.

Being hydrophobic, vitamin D is stored in adipose tissue and enters the circulation bound to carrier proteins, mainly vitamin D binding protein (VDBP) and albumin. The conversion in the liver is only loosely regulated, whereas the second conversion in the kidney by 1 α -hydroxylase, an enzyme that is also present in many target cells other than proximal renal tubular cells - indicating autocrine and paracrine functions for 1,25-dihydroxycholecalciferol in the control of cell proliferation and differentiation - is tightly regulated and serves as a major control point. 1 α -hydroxylase (also known as CYP27B1) in the kidney is regulated by nearly every hormone involved in calcium homeostasis, and its activity is stimulated by PTH, estrogen, low calcium levels, and low phosphorus levels. Its activity is inhibited by calcitriol, thus providing the feedback loop that regulates calcitriol synthesis. Further hydroxylation and metabolism of calcitriol, the activated form of vitamin D, produces compounds that are water soluble and readily excreted.

Since hepatic vitamin D-25-hydroxylase activity is not tightly regulated, changes in cutaneous production of vitamin D₃, or ingestion of vitamin D (D₃ or D₂), will result in changes in circulating levels of 25-hydroxycholecalciferol, also known as calcidiol.

Modern literature refers to 25-hydroxycholecalciferol (calcidiol), the storage form of vitamin D, as 25-hydroxyvitamin D [25(OH)D], and to 1,25-dihydroxycholecalciferol (calcitriol), the biologically active form of vitamin D, as 1,25-dihydroxyvitamin D [1,25(OH)₂D].

Serum concentration of 25-hydroxyvitamin D is considered to be the most reliable measure of overall vitamin D status and should be used to determine whether a patient is vitamin D sufficient or not. Although more than 50 metabolites of vitamin D have been identified, it is 1,25-dihydroxyvitamin D that is the most significant in terms of biological activity, but the concentration of 1,25 dihydroxyvitamin D is about 1,000 fold lower than 25 hydroxyvitamin D.

An excess of vitamin D is unusual, but may lead to hypercalcemia.

Vitamin D deficiency may lead to a variety of disorders, the most infamous of which is rickets in the growing child or osteomalacia in the adult.

1,25(OH)₂D stimulates intestinal absorption of calcium and phosphate and makes calcium and phosphate available for bone mineralization. In mild or moderate vitamin D deficiency, a lower serum calcium concentration causes stimulation of the parathyroid glands. The increased serum PTH increases the conversion of 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D as

compensatory mechanism. However, the increased level of PTH causes bone resorption of calcium and thus contributes to the pathogenesis of osteoporosis.

In chronic kidney disease, secondary hyperparathyroidism occurs, resulting in several manifestations, two of which are hypocalcemia and hyperphosphatemia. Progressive kidney disease also interferes with the endocrine functions of the kidney, one of which is the production of 1,25-dihydroxyvitamin D; the lowered production of 1,25(OH) vitamin D causes reduced absorption of calcium from the intestine. As chronic kidney disease progresses, “renal osteodystrophy” develops in patients as the mechanism for calcium and phosphorus regulation by the PTH and 1,25(OH) vitamin D feedback loops fails. Renal osteodystrophy is a term referring to skeletal lesions in CKD; these may include, to varying degrees, rickets, osteomalacia, osteitis fibrosa, osteosclerosis, or osteoporosis.

The vitamin D system is thus very complex, influencing expression of more than 200 genes.

A growing body of evidence, greatly expanded by key publications in major journals in 2008, has established clear association between low levels of Vitamin D in adults and cardiovascular disease⁵⁻¹⁵.

These publications support a relationship between insufficient or deficient levels of Vitamin D and cardiovascular disease, which includes:

- Activation of the rennin-angiotensin-aldosterone system which can predispose to:
 - Hypertension
 - Left ventricular hypertrophy
- increased PTH levels and predisposition for:
 - Increased insulin resistance associated with:
 - Diabetes, hypertension, inflammation, and increased cardiovascular risk
- Increased cardiovascular event risk
- Increased myocardial infarction (MI) risk
- Death due to heart failure, sudden cardiac death, and stroke

The linkage between low Vitamin D levels and cardiovascular disease was first described in a review of the 3rd NHANES survey data by Martins et al., published in 2007 in the *Archive of Internal Medicine*⁵. In this study of ~15,000 men and women, low Vitamin D levels were associated with cardiovascular disease, hypertension, and diabetes mellitus.

The utility of measuring vitamin D for both characterizing and monitoring patients with cardiovascular disease was described in the *Journal of the American College of Cardiology* by John Lee et al. in December, 2008⁶. They estimated that 57% of US adults are Vitamin D deficient and that this deficiency is linked to an adverse impact on cardiovascular health. They describe a physiological relationship between low Vitamin D levels and:

- activation of the rennin-angiotensin-aldosterone system which predisposes to hypertension and left ventricular hypertrophy
- increased PTH levels which predisposes to diabetes, hypertension, inflammation, and increased cardiovascular risk

Wang et al published a study on a ~1700 participant subset of the Framingham Offspring Study population in which they provided a margin of circulating 25(OH)D levels that may decrease cardiovascular risk⁷ based on cardiovascular risk events in this prospective study.

Giovannucci et al published a prospective study from the Physician's Health Study in the Archives of Internal Medicine⁸ in 2008 indicating that men with low levels were more than two-fold more likely to experience myocardial infarction independent of major covariates. Based on their observations, the authors suggested that the levels of Vitamin D required for optimal health greatly exceed the current AMA recommendations of 200 to 600 IU vitamin D₃/day, and that the current guidelines should be increased to an upper limit of 10,000 IU D₃/day.

In a review article titled "*The Predictive Value of Vitamin D Status for Deaths Due to Heart Failure, Sudden Cardiac Death and Stroke*" in Clinical Diagnostic News in 2008⁹, Blocki reviewed recent publications from the LURIC study of 3300 patients referred for coronary angiography¹⁰⁻¹². Vitamin D deficiency was associated with death due to heart failure, sudden cardiac death, cardiac mortality, and stroke. The LURIC study authors postulated that maintenance of optimal vitamin D status could reduce risk of death due to myocardial disease.

The efficacy of Vitamin D supplementation on lowering risk and events has also been documented recently. An 18-study meta-analysis published in the Archives of Internal Medicine by Autier et al in 2007 described the impact of Vitamin D supplementation on lowering all cause mortality¹³. Additional publications in 2008 by Cannell and Hollis presented further clinical evidence for using vitamin D testing level to identify patients at increased CVD risk and to monitor for efficacy of supplementation¹⁴⁻¹⁵. These authors also indicated that therapeutic targets for managing normal circulating levels of Vitamin D should be higher than current goal of > 30 ng/mL for healthy adults, and suggested even higher goals for patients who are under management for chronic diseases. Lastly, they suggest that Vitamin D deficient patients require individualized supplementation and monitoring in order to reach goal, and that patients with serious illness require even more aggressive supplementation and monitoring.

Evaluating the vitamin D of levels patients is accomplished by measuring the level of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D. Although the treatment of vitamin D deficiency is relatively straightforward, the insidious occurrence of vitamin D deficiency and its association with serious chronic medical conditions, based upon scientific evidence, indicates medical necessity for testing for 25-hydroxyvitamin D for vitamin D deficiency and 1,25-dihydroxyvitamin D serum concentration to diagnose hypercalcemia..

Indications:

Measurement of vitamin D levels is indicated with patients for:

- Hypovitaminosis D
- rickets
- osteomalacia
- falls/neuromuscular function loss
- osteopenia
- osteoporosis
- secondary hyperparathyroidism
- hyperthyroidism
- hypercalcemia
- chronic kidney disease
- diabetes

- tuberculosis
- cardiovascular disease
- malabsorption syndromes

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CPT/HCPCS Codes:

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| 82306 | Assay for Vitamin D (25-Hydroxyvitamin D) |
| 82652 | Assay of dihydroxyvitamin D (1,25-Dihydroxyvitamin D) |