# Vitamin D deficiency: making a clinical difference

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*Vitamin D deficiency can be caused by a lack of exposure to sunlight, increased skin pigmentation and veiling. Supplementation is the best way to reduce the consequences of this deficiency.*



Vitamin $D_3$ is produced when 7-dehydrocholesterol in the skin is exposed to light of wavelengths from 290 to 310 nm. The conversion of 7-dehydrocholesterol to previtamin D is rapid and reaches maximum levels in two hours. In eight hours, 80% of previtamin D is converted to vitamin D. Ten to 15 minutes of exposure to solar radiation produces about 3000 IU of vitamin $D_3$ (cholecalciferol).

When exposed to higher levels of ultraviolet (UV), a 20-year-old woman produces about four times as much vitamin $D_3$ in the skin as a 70-year-old woman; however, at lower levels of UV exposure, vitamin D production, as assessed by the measurement of serum 25-hydroxy (OH) vitamin D levels, may be similar in younger and older women.[1] A lack of access to sunlight may be an important factor contributing to low serum 25-OH vitamin D levels in older women in aged care who then require supplementation with oral vitamin D. Prolonged exposure to sunlight increases the formation of biologically inactive lumisterol and tachysterol so that toxic amounts of vitamin $D_3$ are not produced on exposure to sunlight.

## Metabolism of vitamin D

Vitamin D is bound to D-binding protein and transported to the liver. 25-OH vitamin D is formed in the liver and most is secreted into the blood and bound to D-binding protein. D-binding protein carrying 25-OH vitamin D is filtered by the glomerulus and reabsorbed by cells of the proximal tubule. 1-α hydroxylase is found on the inner mitochondrial membrane of cells in the proximal tubule and facilitates the formation of 1,25-dihydroxy [$(OH)_2$] vitamin D from 25-OH vitamin D. Serum 1,25-$(OH)_2$ vitamin D stimulates the uptake of calcium and phosphate across the upper gastrointestinal tract and also stimulates absorption of phosphate by renal tubular cells (Figure).[2]

The formation of 1,25-$(OH)_2$ vitamin D is stimulated by circulating parathyroid hormone (PTH) and low serum phosphate levels, and is inhibited by circulating fibroblast growth factor (FGF)-23. The receptor for FGF-23 is FGF receptor-1 and requires the membrane-bound protein klotho as a co-factor for its action. 1,25-$(OH)_2$ vitamin D, acting through its vitamin D receptor, upregulates both

## Key points

- **Despite plentiful sunlight, many people have low levels of vitamin D; older people in aged care and veiled women and their newborn babies are at particular risk of deficiency.**
- **The best marker of vitamin D status is serum 25-hydroxy (OH) vitamin D levels. There is evidence to suggest the levels of serum 25-OH vitamin D should be more than 75 nmol/L for optimal health.**
- **1,25-dihydroxy [$(OH)_2$] vitamin D, formed from 25-OH vitamin D, enhances absorption of calcium and phosphate across the upper gastrointestinal tract.**
- **When the level of serum 25-OH vitamin D is less than 30 nmol/L in neonates, there is an increased risk of developing rickets.**
- **Due to the low level of 25-OH vitamin D in human breast milk, mothers who breastfeed should take a supplement of 4000 IU/day of vitamin D.**
- **In older persons, vitamin D supplementation to raise 25-OH vitamin D levels above 75 nmol/L reduces the risk of falling and fracture and may reduce all-cause mortality.**

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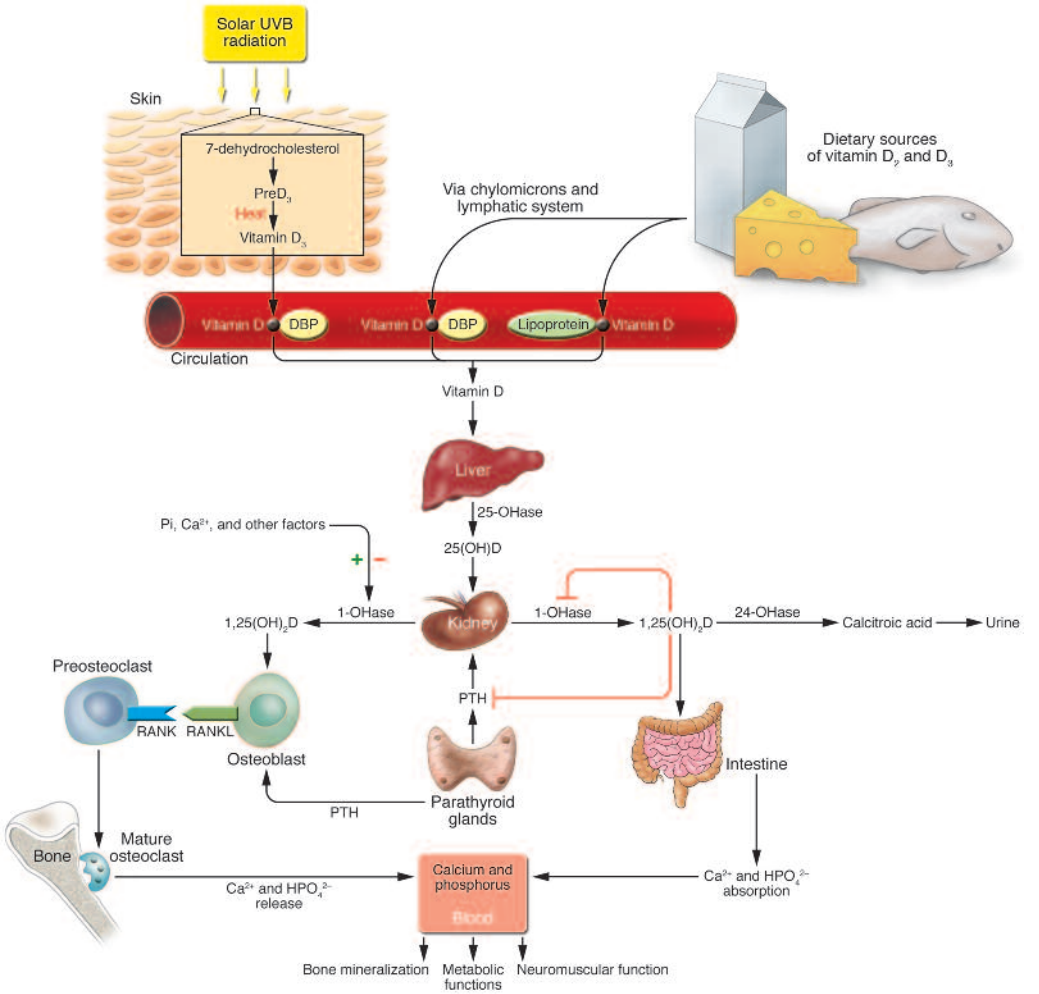


**Figure. The photoproduction and metabolism of vitamin D and the various biological effects of 1,25-$(OH)_2$ vitamin D on calcium, phosphorus and bone metabolism. Vitamin D is either produced in the skin by exposure to UVB radiation or is ingested in the diet. Vitamin D is converted by the vitamin D-25-hydroxylase (25-OHase) in the liver to 25-OH vitamin D. 25-OH vitamin D is converted in the kidneys by 1-OHase to 1,25-$(OH)_2$ vitamin D. Once formed, 1,25-$(OH)_2$ vitamin D enhances intestinal calcium and phosphorus absorption and stimulates the expression of RANKL on the osteoblasts to interact with its receptor RANK on preosteoclasts to induce mature osteoclastic activity, which releases calcium and phosphorus ($HPO_4^{2-}$). In addition, 1,25-$(OH)_2$ vitamin D inhibits the renal 1-OHase and stimulates the expression of the renal 25-OH vitamin D-24-hydroxylase (24-OHase). The induction of the 24-OHase results in the destruction of 1,25-$(OH)_2$ vitamin D into a water-soluble inactive metabolite calcitroic acid.**

Abbreviations: $PreD_3$ = previtamin D; PTH = parathyroid hormone.

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FGF-23 mRNA and klotho mRNA.[3] 1,25-$(OH)_2$ vitamin D also inhibits the secretion of PTH so that serum 1,25-$(OH)_2$ vitamin D is involved in a complex homeostatic mechanism whereby reducing serum PTH levels reduces renal phosphate loss and increasing serum FGF-23 increases renal phosphate loss.

How the set point to produce the optimal level of serum 1,25-$(OH)_2$ vitamin D is achieved has not yet been clearly determined. 1,25-$(OH)_2$ vitamin D formed in the renal tubule is subject to 24-hydroxylation so that the formation of inappropriately high levels of circulating 1,25-$(OH)_2$ vitamin D is prevented. This means that high levels of serum 25-OH vitamin D entering the renal tubule do not necessarily produce high levels of serum 1,25-$(OH)_2$ vitamin D and explains why serum 25-OH vitamin D levels are mostly not correlated with serum 1,25-$(OH)_2$ vitamin D levels except during pregnancy. Serum 25-OH vitamin D levels are inversely correlated with levels of serum PTH in a complex curvilinear

relationship.[4] At serum 25-OH vitamin D levels of more than 75 nmol/L, serum PTH reaches a stable nadir and this has led to the concept that the serum 25-OH vitamin D level should be maintained at or above 75 nmol/L. This is also the serum concentration at which maximal absorption of calcium across the upper gastrointestinal tract is achieved. Below 75 nmol/L a significant decrease in calcium absorption occurs.[5]

A very important issue is that many cells possess vitamin D receptors and 1-α hydroxylase, and can therefore respond to prevailing levels of serum 25-OH vitamin D. This includes cells in the brain, muscles and myocardium, and osteoblasts, osteoclasts and macrophages. Macrophages exposed to 25-OH vitamin D rapidly form cathelicidin, a potent antibacterial agent.[6] In humans, the innate immune response to a microbial challenge is dependent on the prevailing levels of serum 25-OH vitamin D.

## Vitamin D and pregnancy

The optimal level of serum 25-OH vitamin D during pregnancy is not clear. There is a relation between levels of maternal serum 25-OH vitamin D and fetal skeletal calcium. The levels of serum 25-OH vitamin D in the neonate are highly correlated with levels of maternal serum 25-OH vitamin D at term. However, in a study of pregnant mothers who were supplemented with vitamin D, the levels of 25-OH vitamin D in neonatal cord blood were about two-thirds of the maternal serum 25-OH vitamin D concentration.[7] In another study, the serum 25-OH vitamin D level in neonatal blood was found to be higher than the maternal serum 25-OH vitamin D levels.[8]

Many women with dark skin or who are veiled will have a serum 25-OH vitamin D level below 25 nmol/L. Serum 1,25-$(OH)_2$ vitamin D levels increase during pregnancy and are correlated with levels of serum 25-OH vitamin D. The increase in serum 1,25-$(OH)_2$ vitamin D levels is probably due to increased 1-α hydroxylase acting in the placenta. By the end of the first trimester, the serum 1,25-$(OH)_2$ vitamin D is about three times higher than the average value in nonpregnant women and may be responsible for the increased calcium absorption in pregnant women. Human breast milk contains very little 25-OH vitamin D, about 16 IU/L, but rises as the maternal serum 25-OH vitamin D level rises. It has been recommended that women who are breastfeeding take a supplement of 4000 IU/day of vitamin $D_3$.[9]

## Vitamin D in children

Serum 25-OH vitamin D levels of less than 30 nmol/L are associated with rickets and osteomalacia. A supplement of 400 IU/day of vitamin $D_3$ prevents rickets in children. Children given 340 to 600 IU/day of vitamin $D_3$ show maximum linear growth. In a study in Finland, children were given 2000 IU/day of vitamin $D_3$ for the first year of their life and an 88% reduction in the incidence of type 1 diabetes was seen during the subsequent 31 years of life.[10]

In the UK in the 1950s, the fortification of milk with vitamin D was associated with many cases of nephrocalcinosis and renal impairment. A recent study has defined a genetic disorder in which a mutation in the gene encoding for the 24-hydroxylation of 1,25-$(OH)_2$ vitamin D causes impaired function of the enzyme leading to inappropriately high levels of 1,25-$(OH)_2$ vitamin D at prevailing levels of serum 25-OH vitamin D.[11] In normal controls, 10,000 IU/day of vitamin D for five months was not associated with an increase in serum or urine calcium.[12] In the USA, the NHANES-III study showed that 50% of adolescent girls had a serum 25-OH vitamin D level below 62 nmol/L.[13]

## Vitamin D and falling

In older persons with vitamin D deficiency, supplemental vitamin D and calcium given daily has been found to significantly reduce the number of falls but the achieved serum 25-OH vitamin D level must be more than 60 nmol/L.[14] However, if vitamin D supplementation was given as 500,000 IU once yearly, the risk of falling was increased.[15]

## Vitamin D and fractures

A meta-analysis of studies in older aged persons in which 800 IU/day of vitamin D was given together with calcium showed a 26% reduction in hip fracture rates compared with people given calcium alone.[16] The optimal level of serum 25-OH vitamin D to prevent fractures appears to be 75 nmol/L.

In adults, no excess of osteoid was seen in bone biopsies when the serum 25-OH vitamin D level was greater than 75 nmol/L.[17] Below this value, there is increasing amounts of osteoid suggesting impaired mineralisation of bone.

## Vitamin D and cardiovascular risk

Vitamin D receptor knockout mice have an increased occurrence of premature cardiovascular disease and heart failure.[18] In humans, a low serum 25-OH vitamin D level is a risk factor for hypertension. There are currently no placebo-controlled, randomised studies examining the effect of supplemental vitamin D on the risk of developing coronary heart disease.

## Vitamin D and cancer

In a randomised, placebo-controlled study involving postmenopausal women older than 55 years given 1400 to 1500 mg/day of supplemental calcium and 1100 IU/day of vitamin $D_3$ during a four-year period, the incidence of cancer was found to be significantly less ($p<0.03$) compared with the placebo group.[19]

## Vitamin D and mortality

A meta-analysis of 14 prospective cohort studies has been carried out looking at the relation of serum 25-OH vitamin D to all-cause mortality. A nonlinear fall in mortality was found with rising levels of serum 25-OH vitamin D above a reference value of 27.5 nmol/L. The risk ratio was 0.69 for those whose serum 25-OH vitamin D level was 50 nmol/L above the reference value.[20] There was no further benefit above this level. A study had previously shown that low serum 25-OH vitamin D levels were independently associated with an increase in all-cause mortality in the general population.[21]

## Vitamin D and glucose metabolism

The relation of vitamin D to glucose metabolism is controversial. In the Women's Health Initiative study, the intake of 150 IU/day of vitamin $D_3$ was associated with an incidence of type 2 diabetes of 5.6%, whereas with an intake of 511 IU/day the incidence was 2.7%.[22] In patients with fasting glucose intolerance, the subsequent rise in fasting plasma glucose was less rapid in those given 1000 IU/day of vitamin $D_3$.

## Vitamin D and multiple sclerosis

Low levels of serum 25-OH vitamin D correlate with a higher prevalence of multiple sclerosis. However, in a double-blind placebo-controlled study in which persons with relapsing remitting multiple sclerosis were given 6000 IU/day of vitamin $D_2$ (ergocalciferol) for six months, there was no significant difference when compared with the control group with respect to the number of MRI-defined lesions or the physical disability score.[23]

There is ongoing discussion as to what the optimal level of serum 25-OH vitamin D should be for health maintenance. From fracture and mortality studies, 75 nmol/L seems like a reasonable value. An important unanswered question is whether serum 25-OH vitamin D levels above 150 nmol/L are harmful in the long term.

## Vitamin D therapy

The optimal level of serum 25-OH vitamin D in pregnancy is unknown but values of 75 nmol/L are commonly recommended. If the pregnant woman's serum 25-OH vitamin D level is less than 30 nmol/L, the neonate, especially if breastfed, is likely to develop rickets. The serum 25-OH vitamin D level should be measured early in pregnancy and before the end of the second trimester and vitamin D given, usually 1000 IU/day, if the serum 25-OH vitamin D level is less than 75 nmol/L. This regimen seems to be safe for both the mother and fetus. During breastfeeding, up to 4000 IU/day of vitamin $D_3$ has been recommended.

In infancy and childhood, 600 IU/day of vitamin D will prevent rickets and facilitate maximal linear growth.

In adults, impairment of mineralisation of bone begins when serum 25-OH vitamin D levels fall below 75 nmol/L. Vitamin D for therapeutic use is available in four forms: capsules, tablets, drops and injections. If injections are used, permission from the Therapeutic Goods Administration is required. The tablets and capsules contain 1000 IU of vitamin D.

If the patient's serum 25-OH vitamin D level is below 20 nmol/L, 2000 IU/day of vitamin D is recommended and if the patient's serum 25-OH vitamin D level is between 20 and 50 nmol/L, 1000 IU/day is recommended. It takes several weeks for the increase in serum 25-OH vitamin D to plateau after the beginning of therapy, and the first measurement of serum 25-OH vitamin D to assess response should be made at three months. Usually if compliance with therapy is maintained, the serum 25-OH vitamin D level will remain stable at this dose.

## Conclusion

Vitamin D affects the function of about 200 genes and has a wide influence on bodily function. Most vitamin D is made in the skin on exposure to the sun. Only a small fraction of the daily requirement of vitamin D comes from the diet. Lack of exposure to sunlight, increased skin pigmentation and veiling can cause vitamin D deficiency. Vitamin D deficiency is common in our community.

Vitamin D, through its metabolites, facilitates the absorption of calcium and phosphorus across the upper gastrointestinal tract. It also influences the function of osteoblasts and osteoclasts.

Vitamin D deficiency in children causes rickets and impaired linear growth. Vitamin D deficiency in older persons increases the risk of falls, fractures and all-cause mortality.

A serum 25-OH vitamin D level of 75 nmol/L seems a reasonable therapeutic target according to current available evidence. **ET**

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