Overview of vitamin D – sources, dosing, drug interactions, toxicity

When it was first discovered nearly a century ago, researchers initially classed the compound associated with protection from tuberculosis (TB) and bone disease as vitamin D. However, researchers in the modern era have re-classed it as a hormone, though it is still commonly called a vitamin. As a result of its reclassification, a range of different doctors and researchers have been studying vitamin D, including endocrinologists, nutritionists, cardiologists, immunologists and oncologists. These different fields have enriched our understanding of vitamin D and its potential role in human health.

Where does vitamin D come from?

In general, people get vitamin D from exposure to sunlight, from small amounts in certain foods and from supplements.

A series of steps is involved in the body’s production of vitamin D. First, ultraviolet B radiation in sunlight interacts with a fatty molecule (7-dehydrocholesterol) found in the skin and forms pre-vitamin D. This is then transported to the liver, where vitamin D$_2$ is formed. This is then taken to the kidneys, where vitamin D$_2$ is converted to vitamin D$_3$ (sometimes called ergocalciferol). Vitamin D$_3$ is the form of vitamin D that is used by the body’s cells. The formation of vitamin D$_3$ from its precursor molecules is enabled by enzymes.

If the body produces excessive amounts of vitamin D$_3$ from sunlight, enzymes are activated that convert vitamin D$_3$ into its inactive forms.

Many possible roles for vitamin D

Vitamin D helps the intestine absorb minerals such as calcium and phosphorus. Without sufficient levels of this vitamin, researchers estimate that “only 10% to 15% of dietary calcium and about 60% of phosphorus are absorbed.” These minerals are used to help build bones.

Receptors for vitamin D are found in many tissues, including the following:

- bones
- brain
- hormone-producing glands – pancreas and thyroid
- immune system – T-cells, B-cells and macrophages
- liver
- muscles (including the heart)
- reproductive system – ovary, uterus, prostate and testicles
- skin

The presence of vitamin D receptors in so many different tissues suggests the possibility that vitamin D has a role to play in each one.

Ideal vitamin D levels in the blood

The American Endocrine Society recently released comprehensive guidelines about vitamin D. According to these guidelines, vitamin D deficiency occurs when the level of vitamin D$_2$ in the blood is less than 50 nmol/l (this is equivalent to 20 ng/ml). Much of our overview of vitamin D is based on the Endocrine Society’s comprehensive recommendations and research.
The ideal level of vitamin D for human health is not known. For maintaining a healthy skeleton, the Endocrine Society recommends maintaining an intake of vitamin D such that the levels in the blood are at least 75 nmol/litre. In some cases, to achieve non-skeletal health benefits, perhaps higher concentrations of vitamin D in the blood will be needed. However, there is insufficient data at present to justify higher levels of vitamin D.

**Why is vitamin D$_2$ often assessed?**

Vitamin D$_2$ is the most common form of this vitamin found in the blood. It has a half-life of between two and three weeks. In contrast, vitamin D$_3$ is present in the blood at levels that are about one thousand times less than vitamin D$_2$. Moreover, levels of vitamin D$_3$ in the blood are tightly controlled by the kidneys. The concentration of vitamin D$_3$ in the blood does not reflect the body’s store of vitamin D, and such concentrations are not generally useful for making assessments of human health. Another issue is that the half-life of vitamin D$_3$ is about four hours. Also, researchers have found that people with vitamin D deficiency tend to have normal or even elevated levels of vitamin D$_3$ in their blood. Thus, most researchers prefer to assess vitamin D$_2$ levels.

**Vitamin D and parathyroid hormone**

The amount of vitamin D$_3$ produced by the kidneys is controlled by the body, depending on levels of the minerals calcium and phosphorus in the blood. When the body’s sensors detect less-than-normal levels of these minerals in the blood, the parathyroid glands, located in the chest, release a hormone called parathyroid hormone (PTH). This hormone causes the kidneys to reabsorb calcium from urine and stimulates enzymes to convert vitamin D$_2$ into its active form, vitamin D$_3$.

PTH also stimulates the tearing down of bone so that calcium can be released into the blood. This raises calcium levels in the blood, but at the cost of weakening bone. Prolonged exposure to elevated PTH levels can accelerate vitamin D deficiency and likely plays a role in osteopenia and the more severe loss of bone mineral density called osteoporosis.

Studies have found that PTH levels tend to be higher in cases of vitamin D deficiency but PTH levels tend to reach their lowest levels when the concentration of vitamin D$_2$ in the blood is between 75 nmol/litre and 100 nmol/litre.

Researchers have found that intestinal absorption of calcium increased between 45% and 65% when the concentration of vitamin D$_2$ in the blood rose from 50 nmol/litre to 80 nmol/litre.

Based on these and other studies about PTH, calcium and bone health, leading vitamin D researchers have suggested the following:

- When vitamin D$_2$ levels are 49 nmol/litre or less, vitamin D “deficiency” has occurred.
- When the concentration of vitamin D$_2$ is between 50 nmol/litre and 74 nmol/litre, people have vitamin D “insufficiency.”
- When the concentration of vitamin D$_2$ is greater than 75 nmol/litre, there is sufficient vitamin D present in the body.

However, there is still considerable debate about what the ideal levels of vitamin D$_2$ should be for people with a range of health conditions, including osteoporosis, cardiovascular disease and HIV infection. It is possible that even higher concentrations of vitamin D$_2$ may be necessary for people with these and other health conditions, but research is needed to resolve this controversy.

**Who is at risk for vitamin D deficiency?**

Several studies have documented that less-than-ideal levels of vitamin D are common in both HIV-positive and HIV-negative people living in North America and Western Europe. Furthermore, several studies have found that deficiencies of vitamin D are even common in HIV-positive people who live in relatively sunny countries such as Brazil, India and Tanzania.
In part, these low levels of vitamin D may occur because the average person spends a lot of time indoors and so does not get sufficient exposure to sunlight. But there might be other factors that affect vitamin D levels, including the following:

**Air pollution**

Smog can absorb, scatter or reflect ultraviolet radiation (UV), thereby reducing the amount of UV light that hits the skin and subsequent vitamin D production.

**Sunscreen**

Wearing sunscreen with a sun protection factor (SPF) of 30 reduces the production of vitamin D in the skin by 95%.

**Skin tone**

Dark-skinned people require between three and five times as much sun exposure to make the same amount of vitamin D as light-skinned people.

**Skin temperature**

Conversion of pre-vitamin D to vitamin D\( _3 \) is affected by temperature. More vitamin D is produced at higher temperatures than at lower temperatures. In general, under normal conditions, the temperature of the skin on the body is lower than core body temperature. On cold days, exposed skin temperature may be even lower than usual. This decrease in skin temperature can affect the production of vitamin D.

**Age**

The skin of elderly people contains less of the compounds used to make vitamin D than the skin of younger people. Therefore, given the same sun exposure, elderly people likely produce less vitamin D than younger people.

**Weight**

Very overweight and obese people—those with a body mass index (BMI) of 30 or greater—tend to have vitamin D deficiency.

**Medications and herbs**

As enzymes in the liver and kidneys help convert pre-vitamin D into its active form, drugs or substances that interfere with these enzymes have the potential to reduce vitamin D levels. Also, drugs that speed up or activate the enzymes that help break down vitamin D\( _3 \) and vitamin D\( _2 \) into inactive forms have the potential to reduce levels of this vitamin. Here are some of the medicines and herbs with the potential to reduce vitamin D levels:

- antibiotics - rifampin (rifampicin) and isoniazid, commonly used to treat TB. Vitamin D levels can sometimes fall after as little as two weeks’ exposure to these drugs.
- anti-seizure drugs – phenobarbital, carbamazepine, phenytoin
- anti-cancer drugs – Taxol and related compounds
- antifungal agents – clotrimazole and ketoconazole
- anti-HIV drugs – emerging research suggests that the drugs efavirenz (Sustiva, Stocrin and in Atripla) and AZT (Retrovir, zidovudine and in Combivir and Trizivir) may reduce vitamin D levels in some people. In contrast, exposure to darunavir (Prezista) appears to raise vitamin D levels. Researchers continue to study the possible effects of different medications on vitamin D levels, so expect more news about this in the years ahead.
- herbs – St. John’s wort or its extracts (hypericin, hyperforin)
- anti-inflammatory drugs – corticosteroids

**Health conditions**

There are many health conditions that are associated with vitamin D deficiency, including the following:
• intestinal inflammation (occurring in Crohn’s disease, cystic fibrosis and so on)
• receipt of transplanted organs – perhaps the medicines used to suppress the immune system interfere with vitamin D production
• liver damage – a healthy liver helps to produce vitamin D₂
• kidney damage – the kidneys help to produce vitamin D₃

Increasingly, HIV infection has become associated with vitamin D deficiency. It is not clear why this is the case. Some researchers think that because HIV triggers ongoing inflammation, this somehow alters or reduces the body’s ability to produce vitamin D. Another possible explanation is that vitamin D deficiency and insufficiency are common in most HIV-negative people, so it should not be surprising to see the same issues in people at high risk for or who have HIV infection. More research will be needed to understand why vitamin D deficiency and insufficiency are so common in HIV-positive people and if vitamin D deficiency is clearly linked to co-morbidities such as cardiovascular disease, insulin resistance, kidney disease and other issues.

**Sources of vitamin D**

Vitamin D is not found in many foods. But here are some foods that are relatively rich in vitamin D₃, with their approximate amounts per serving shown:

- salmon (fresh and wild caught) – between 600 international units (IU) and 1,000 IU of vitamin D₃ per 100 grams
- salmon (fresh, farmed) – between 100 and 250 IU per 100 grams
- salmon (wild, canned) – between 300 and 600 IU per 100 grams
- sardines (canned) – 300 IU per 100 grams
- tuna (canned) – 236 IU per 100 grams
- egg yolk – 20 IU

Some foods are rich in vitamin D₂, such as these:

- shiitake mushrooms, fresh – 100,000 IU per 100 grams
- shiitake mushrooms, sun-dried – 1,600 IU per 100 grams

Some foods in North America and parts of Europe are fortified, or have added vitamin D₂ or D₃:

- fortified milk – 100 IU per 236 ml
- fortified yoghurt – 100 IU per 236 ml
- fortified breakfast cereals – 100 IU per serving
- fortified margarine – 429 IU per 100 grams

The amount of vitamin D that can be made from exposure to sunlight is affected by many factors, including:

- season
- time of day
- distance from the equator (latitude)
- skin tone
- age

When taking the complexities of these factors into account it is difficult to make general recommendations for the ideal amount of time to be in the sun in order to achieve sufficient vitamin D.

The panel noted that the skin of older people contains fewer of the precursor molecules needed to make vitamin D from sunlight. However, intestinal absorption of high doses of vitamin D from supplements is not affected by this change in the skin.

**Vitamin D and bone density**

The Endocrine Society’s vitamin D panel examined data from a large observational study involving 13,432 adults of...
diverse ethno-racial backgrounds. In general, it found that greater concentrations of vitamin D2 in the blood were associated with modestly increased bone density.

**A healthy skeleton**

German researchers extracted samples of bone from 401 men (average age: 58 years) and 270 women (average age: 68 years) for analysis. They did not find bone abnormalities (less-than-normal levels of bone density) in samples from patients whose vitamin D levels in the blood were greater than 75 nmol/litre. They concluded that in order to maintain a healthy skeleton, sufficient calcium should be taken and vitamin D intake should be enough to achieve a minimum of 75 nmol/litre in the blood.

Analysis of several randomized placebo-controlled studies in which elderly participants received 400 IU/day of vitamin D found that this dose was too low to significantly raise the concentration of vitamin D in the blood.

In a clinical trial that used doses between 400 and 1,000 IU/day, researchers found that the process of slowly wearing down the skeleton was significantly reduced. Moreover, a randomized placebo-controlled study in elderly women with a combination of calcium and 800 IU/day of vitamin D significantly reduced rates of fractures.

Analysis of many vitamin D studies has found that vitamin D’s anti-fracture effects become apparent when the concentration of vitamin D in the blood is at least 75 nmol/litre.

While vitamin D is essential for a healthy skeleton, by itself it is not enough to help rebuild bone density that has been lost as a result of age or other factors. Medically supervised assessments and therapy with drugs that help maintain or increase bone density, increased calcium intake and prescribed or supervised exercise are all necessary to help strengthen bones.

Muscles are anchored to bones and exercising them can help strengthen bones. Clinical trials have found that vitamin D can help improve muscle strength and reduce the risk of falls in elderly people, particularly those who are deficient in vitamin D.

**Used for analysis**

The Endocrine Society’s vitamin D panel also incorporated into its analysis other findings from clinical trials with women before and after menopause, and data from trials of men who received 10,000 IU per day of vitamin D3 for months, as well as additional data from a study in adults who were given 50,000 IU of vitamin D2 (equivalent to 3,000 IU of vitamin D3 daily) for up to six consecutive years. In these studies there were no alterations in calcium concentrations in the blood or urine. This suggests that in the absence of other health conditions, high doses of vitamin D by itself do not cause unsafe increases in the amount of calcium in the blood. Also, there were no reports of toxicity in these particular high-dose studies.

**Vitamin D panel’s dosing recommendations**

Based on the wealth of accumulated data, including those from many studies as well as their own clinical and research experience, the vitamin D panel made the following recommendations for people at risk of vitamin D deficiency:

- Keep the level of vitamin D2 in the blood consistently above 75 nmol/litre (30 ng/ml).
- Adults aged 19-70 years “require at least 600 IU/day of vitamin D to maximize bone health and muscle function.” It is unknown if 600 IU/day is enough to provide “all the potential non-skeletal health benefits associated with vitamin D. However, to raise the blood level of vitamin D2 consistently above 75 nmol/litre may require at least 1,500 to 2,000 IU/day of vitamin D.”
- Adults should not take more than 4,000 IU/day without medical supervision.
- Adults aged 70 years or older require “at least...800 IU/day.” Again, the panel remarked that to achieve levels of 75 nmol/litre in the blood might require daily doses of between 1,500 and 2,000 IU/day.
- The panel suggested using either vitamin D2 or vitamin D3 for the prevention and treatment of deficiency.
- Physicians treating adults who have vitamin D deficiency may prescribe “50,000 IU of vitamin D2 or D3 once weekly for eight weeks or its equivalent of 6,000 IU/day of vitamin D2 or D3” also for eight weeks. The purpose...
of such a high dose is to raise vitamin D levels in the blood to at least 75 nmol/litre within eight weeks. After this point, a maintenance dose of 1,500 to 2,000 IU/day of vitamin D can be used.

- Special populations – in people who are “obese or who have malabsorption syndromes, and patients on medications affecting vitamin D metabolism, we suggest a higher dose (two to three times higher; at least 6,000 to 10,000 IU/day) of vitamin D to treat vitamin D deficiency to maintain a vitamin D level [in the blood] above 75 nmol/litre, followed by maintenance therapy of 3,000 to 6,000 IU/day.”

- Special populations – people who are HIV positive and/or those who are taking anti-seizure drugs, corticosteroids or antifungal agents such as ketoconazole “should be given at least two to three times more vitamin D for their age group to satisfy their body’s vitamin D requirement.” Obviously the appropriate dose of vitamin D for adults with HIV infection is going to vary from one person to the next, depending on the concentration of vitamin D in their blood. However, the panel’s recommendations provide plenty of guidance for physicians seeking to raise and then maintain vitamin D levels.

Although vitamin D is dissolved in fat, it can be taken with or without a meal, as it does not appear to require fat for absorption.

**Concerns about toxicity**

Vitamin D is fat soluble, and is therefore stored in the body’s fat. As a result, levels of this vitamin can build up, so some researchers are concerned about its potential for toxicity.

In adults, a dose of 50,000 IU/day of vitamin D can eventually increase levels in the blood to more than 374 nmol/litre. At such a concentration, abnormal levels of calcium and phosphorus can also build up in the blood.

Several studies that have lasted for up to five months have found that doses of 10,000 IU/day of vitamin D₃ are not toxic to adults.

A study in people with multiple sclerosis who received an average of 14,000 IU/day of vitamin D for one year also did not detect toxicity.

Based on these and other studies, the panel recommends an upper limit of 10,000 IU/day of vitamin D for adults.

—Sean R. Hosein

**REFERENCES:**


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Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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