

## **Vitamin D. Time to get some more sun**

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Vitamin D is one of the essential nutrients required by the human body. It is unique in that, unlike most other vitamins, it is one that we can manufacture on our own, given the right conditions. Despite this, across many populations vitamin D is one of the most widespread and critical nutrient deficiencies. This deficiency is linked to many diseases and disorders, causing untold pain and suffering and costing billions of dollars each year. Our changing lifestyles, including increased indoor living and a campaign of telling people to stay out of the sun, have meant that most people don't get enough vitamin D. The resulting deficiency is compounded by the consumption of processed foods devoid of any vitamin D.

Vitamin D refers to two biologically inactive precursors: D3, also known as cholecalciferol, and D2, also known as ergocalciferol. Both D3 and D2 precursors are hydroxylated in the liver and kidneys to form 25-hydroxyvitamin D (25(OH)D), the non-active "storage" form and 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D), the biologically active form that is tightly controlled by the body.

Vitamin D is the only nutrient that can be synthesized by the human body, meaning that, technically, it is not a vitamin (by definition, vitamins cannot be synthesized by the body). Rather it is a steroid or, to be more specific, a secosteroid (Dixon and Mason 2008). The synthesizing of vitamin D in the body can be achieved through contact with solar ultraviolet B radiation emitted by the sun (Stolzenberg-Solomon 2008). Without the presence of this solar radiation the only way to get vitamin D is through diet—hence, it is still referred to as a "vitamin."

It is becoming increasingly common to find low levels of vitamin D in Western populations (Wolff et al. 2008). Vitamin D uptake from the sun is not affected by seasonal changes but by how much time people spend in the sun (Vieth 2006). Vitamin D deficiency is even more common in people in northern countries (Porojnicua et al. 2007). People require between 70nmol/L (nanomoles per liter) to 100nmol/L of vitamin D and, in winter, when people spend less time outdoors, it is

difficult to achieve these levels (Laaksi et al. 2006; Vieth 2006). Furthermore, current sun avoidance advice combined with the dietary habits of the general populous make the situation much worse—the average level in adults is around 25nmol/L (Vieth 2006)—not even half the recommended level.

In addition to vitamin D obtained through UVB exposure to the sun, this vitamin can be found in foods such as eggs, butter and fortified milk, with the highest levels found in fish. Vitamin D can also be provided by supplements (Cannell et al. 2006; Wolff, Jones and Hansen 2008). Numerous studies have concluded that sensible sun exposure and supplementation are the most effective ways of increasing vitamin D levels (Grant 2002; Holick 2006). However, it is important to remember that the amount of vitamin D required varies among individuals (Binkley et al. 2007).

Once in the body, vitamin D is either stored in the body's fat adipocytes or enters the liver. The vitamin D gets broken down in the kidneys for the regulation of calcium and dozens of metabolic functions. The broken-down vitamin D then interacts with vitamin D receptors in the small intestine and on osteoblasts to regulate calcium and phosphorous metabolism. It not only assists calcium uptake in the bones but also works as an immunity modulator (Wolff, Jones and Hansen 2008). It continues to be metabolised in various tissues and cells for regulating cellular proliferation and differentiation as well as in the functioning of the immune system and macrophages. It suppresses inflammatory cytokines and increases the "oxidative burst" in macrophages. Even more important, it stimulates neutrophils, monocytes (natural killer cells) and the epithelial cells lining the lungs and protecting them from infection (Cannell et al. 2006). In addition, circulating concentrations of the broken-down vitamin D may help increase insulin production, decrease renin production and alter adipocyte lipogenesis (Holick 2007).

Deficiencies in vitamin D have been linked with a range of problems with the musculoskeletal system (including low bone density and muscle problems), cardiovascular disease, diabetes and metabolic syndrome, cancer and impacts on the immune system, Parkinson's disease (Evatt et al. 2008), asthma (Brehm et al. 2008), the perception of pain (Hooten et al. 2008) and preeclampsia (Haugen et al. 2009).

People who are deficient in vitamin D can suffer from a range of problems with the musculoskeletal system. Low levels of vitamin D can reduce the amount of calcium uptake in the bones, which, over time, can lead to a loss in bone density (Wolff,

Jones and Hansen 2008). Pregnant mothers with vitamin D deficiency have been found to give birth to children who are at greater risk of being unable to store calcium in their bones, reducing their bone density and increasing the risk of bone fractures (Javaid et al. 2006) as well as at higher risk of dental caries (Schroth et al. 2008). Vitamin D deficiency over time leads to osteopenia, which precipitates and exacerbates osteoporosis, causing the painful bone disease osteomalacia and increased muscle weakness (Holick 2006; Wolff, Jones and Hansen 2008). The occurrence of every one of these musculoskeletal conditions can be reduced by supplementation of a combination of calcium and vitamin D (Avenell et al. 2006; Holick 2006). Vitamin D deficiency is also associated with and increased risk of falling (Broe et al. 2007; Prince et al. 2008) and fractures (Avenell et al. 2005; Hitz et al. 2007; Lappe et al. 2008; Cauley et al. 2008).

Numerous studies have shown that vitamin D deficiency is strongly associated with an increased risk in developing cardiovascular disease. Epidemiological studies report that the rates of coronary heart disease (Wang et al 2008; Dobnig et al. 2008), higher diabetes, and hypertension and elevated LDL cholesterol (Maki et al. 2009; Kumar et al. 2009) are strongly correlated with decreased vitamin D status. Vitamin D appears to be necessary to maintain adequate apolipoprotein A-I concentrations, the main component of HDL (good) cholesterol (Botella-Carretero et al. 2007). Vitamin D deficiency increases the risk of “all-cause mortality” with a 122% increase in the risk of “cardiovascular mortality” compared to the highest average 25(OH)D levels (28.4 ng/mL) (Melamed et al. 2008; Dobnig et al. 2008). Researchers also found that low 25(OH)D levels were linked to higher levels of inflammation markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6) (Dobnig et al. 2008), which are important markers for chronic illnesses, including cardiovascular disease.

Deficient or insufficient vitamin D levels have been documented in patients who experience myocardial infarction (Scragg et al. 1990; Wang et al. 2008), stroke (Poole et al. 2006; Wang et al. 2008), heart failure (Zittermann 2006; Wang et al. 2008) and peripheral arterial disease (Melamed et al. 2008). Peripheral arterial disease (PAD) is associated with decreased blood flow in the legs and occurs when arteries in the legs become narrowed or clogged with fatty deposits (Melamed et al. 2008).

Low vitamin D levels are linked with the formation of atherosclerosis. When researchers exposed macrophage cells with and without vitamin D, they found that

vitamin D inhibits the uptake of cholesterol by the macrophage cells. When people are deficient in vitamin D, the macrophage cells take in more cholesterol and cannot get rid of it. The macrophages get clogged with cholesterol and become foam cells, which are one of the earliest markers of atherosclerosis (Oh et al. 2009). When human macrophages were placed in a vitamin D-rich environment, the uptake of cholesterol was suppressed, and hence these cells did not become foam cells. Macrophage activation is higher in people with diseases such as diabetes; when found in combination with low vitamin D levels, the macrophages become loaded with cholesterol and eventually stiffen blood vessels and block blood flow (Oh et al. 2009).

A number of studies have also shown a link between low vitamin D and diabetes (Cigolini et al. 2006), and metabolic syndrome (Lu et al. 2009; Botella-Carretero et al. 2007; Maki et al. 2009). In a study of 15,088 subjects from the NHANES (National Health and Nutrition Examination Survey) III national cohort registry, vitamin D levels were inversely associated with hypertension, diabetes mellitus, hypertriglyceridemia and obesity (Martins et al. 2007). Other cross-sectional studies have confirmed the links between vitamin D deficiency and both hypertension and diabetes (Scragg et al. 2007). Vitamin D deficiency also predisposes people to insulin resistance, pancreatic beta cell dysfunction, and the metabolic syndrome (Riachy et al. 2006). One study reported that a daily intake of 800 IU of vitamin D compared to a daily intake of less than 400 IU of vitamin D reduced the risk of type 2 diabetes by one-third (Pittas et al. 2006). In a study of 10,366 Finnish children, those given 2,000 IU of vitamin D3 per day throughout the first year of life experienced a 78% reduced risk of type 1 diabetes (Hyppönen et al. 2001).

Numerous studies have found a strong correlation with low levels of vitamin D and increased cancer rates. People living at higher latitudes in the Northern hemisphere are at a higher risk of developing cancer (Peller 1937; Apperly 1941; Garland et al. 1980; Grant 2002). Interestingly, people who are diagnosed with cancer in autumn and spring have a greater survival rate than those diagnosed in winter (Porojnicua et al. 2007). There is now overwhelming evidence that supports lowering the risk of developing and dying of prostate, breast, colon, ovarian, esophageal, non-Hodgkin's lymphoma and a variety of other lethal cancers through intake of vitamin D (Bertone-Johnson et al. 2005; Freedman et al. 2002; Garland and Garland 2006; Holick 2006; Janowsky et al. 1999; Skinner et al. 2006; Blackmore et al. 2008).

In a ten-year study of 1,179 healthy, postmenopausal women, those taking large amounts of vitamin D3 in conjunction with calcium had a 60% or higher chance of not getting cancer than their peers; interestingly, no such association was found with calcium alone (Lappe et al. 2007). In a review of data from 177 countries, extrapolation of results showed that increasing intake of vitamin D could prevent as many as half of the breast cancer cases and colon cancer cases. According to the study, the median adult intake of vitamin D in the U.S. is only 230 IU per day, versus the researchers' recommended 2,000 IU per day (Garland et al. 2007). For every increase of 25 nmol/L in 25(OH)D levels in people's blood, there was a 34% cancer risk reduction, with the most common cancers being those of the lung, colon and pancreas (Pilz et al. 2008).

One explanation for cancers being reduced by vitamin D is related to vitamin D receptors (VDR). These are found in the tissues of the body and help maintain cellular growth, preventing the cells from becoming malignant. Studies on both colon cancer cells (Tangpricha et al. 2005) and healthy prostate cells (Bao et al. 2008) have demonstrated protective effects of vitamin D at a cellular level.

Vitamin D deficiency is inversely related to a range of diseases, including respiratory infections such as influenza (Cannell et al. 2006; Garland and Garland 2006). In support of this, clinical trials have shown that vitamin D supplementation can reduce the risk of reactivation of latent tuberculosis infection (Garland and Garland 2006; Martineau et al. 2007). Vitamin D (in particular, D3) activates cells responsible for destroying cells that cause infection (Cannell et al. 2006).

Supplementing the diet of pregnant women with vitamin D has been found to improve placental innate immunity. In support of this, cells infected with *Escherichia coli* (*E. coli*) showed reduced numbers of *E. coli* when treated with vitamin D. A reduction in cell death as a result of *E. coli* exposure was also observed after exposing the cells to both forms of the vitamin (Liu et al. 2009).

Studies have indicated that vitamin D supplementation may reduce the risk and difficulties associated with autoimmune disorders (Deluca and Cantorna 2001). In particular, there is strong case-control and ecologic evidence that vitamin D reduces the risk of multiple sclerosis and type 1 diabetes mellitus, and weaker evidence regarding rheumatoid arthritis, osteoarthritis, systemic lupus and erythematosus (Kamena et al. 2006; Scragg, Sowers and Bell 2004; Yanoff et al. 2006; Deluca and Cantorna 2001).

There is no doubt about the link between vitamin D shortage and multiple sclerosis (VanAmerongen et al. 2004; Embry 2004; Barnes et al. 2007; Kampman et al. 2007). There is a 41% decrease in MS risk for every 50 nanomoles per liter increase in 1,25-hydroxyvitamin in the blood (VanAmerongen et al. 2004). The role of vitamin D is supported by animal studies in which mouse models have shown that vitamin D-deficient mice succumb faster to MS but, once administered with vitamin D, the symptoms diminish (Mandavilli 2007).

### **Vitamin D Shortage**

Vitamin D deficiency is widespread in developed countries such as the U.S., U.K., Australia, New Zealand and Europe. U.S. studies have found that vitamin D deficiency is present in approximately 30% to 60% of the general population, with 12% of otherwise healthy infants and toddlers vitamin D deficient (Gordon et al. 2008); other U.S. findings indicate that 9% of the pediatric population is vitamin D deficient and 61% of children and adolescents have insufficient intake of vitamin D (Kumar et al. 2009). Only 4% studied had taken 400 IU of vitamin D per day during the prior 30 days.

Based on the abundance of evidence, there is an overwhelming agreement among researchers that current recommendations of 200 IU of vitamin D per day for children and adults up to age 50 years need to be increased to 800-1000 IU of vitamin D3 daily (Holick 2007; Vieth et al. 2007).

Sensible sun exposure (or UVB irradiation) along with supplements are required to satisfy the body's vitamin D requirements. To achieve adequate levels of vitamin D, we need to get one to two hours of *sensible* sun exposure every day. This should be during the morning and late afternoon. While it is prudent to avoid too much sun, it is important to remember that the costs of vitamin D deficiency far outweigh the costs of the skin cancer about which we are constantly warned. In fact, some sun may be necessary to reduce skin cancers. Remember: we did evolve in the sun; but be sure to avoid the hot midday sun, especially if you have fair skin.

Numerous studies have shown supplementation to be effective in raising blood levels of 25(OH)D (Talwar et al. 2007; Nelson et al. 2009; Maalouf et al. 2008) with no evidence of vitamin D intoxication reported in either the short- or long-term trials (Maalouf et al. 2008).

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