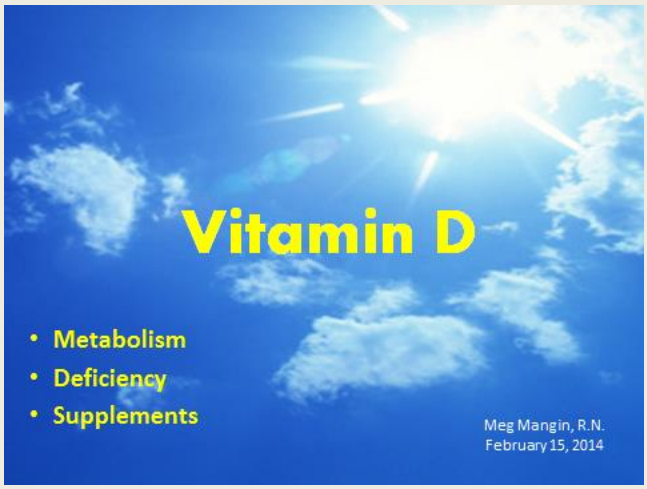
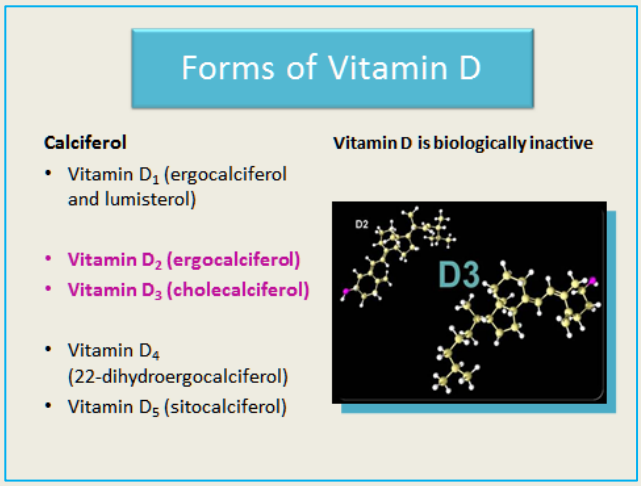
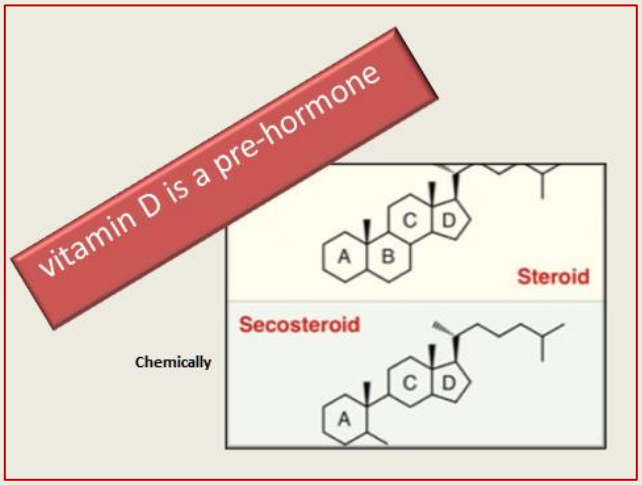


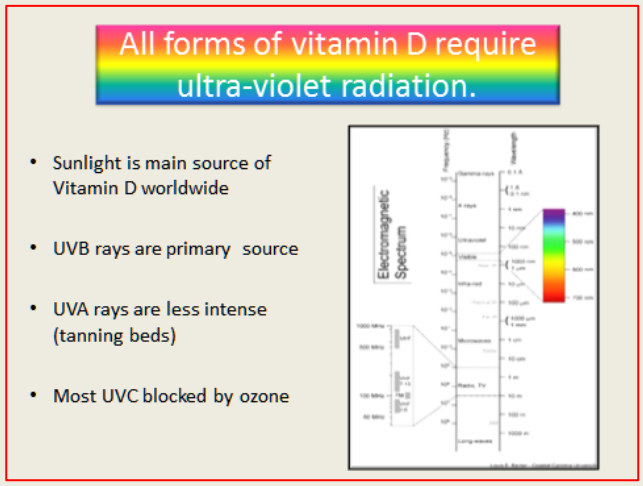
Vitamin D has received much attention in recent years because studies found an association between low serum 25-hydroxyvitamin D (hereafter referred to as 25(OH)D) levels and some disease states. This has caused a heated debate among authorities regarding the definition of vitamin D deficiency and the amount of vitamin D necessary for health.



The five forms of vitamin D are collectively known as calciferol; the primary forms are vitamin D_2 and vitamin D_3. "Vitamin D" is a generic term that can mean either D_2 or D_3 and may also be used to refer to the metabolites formed from calciferol.

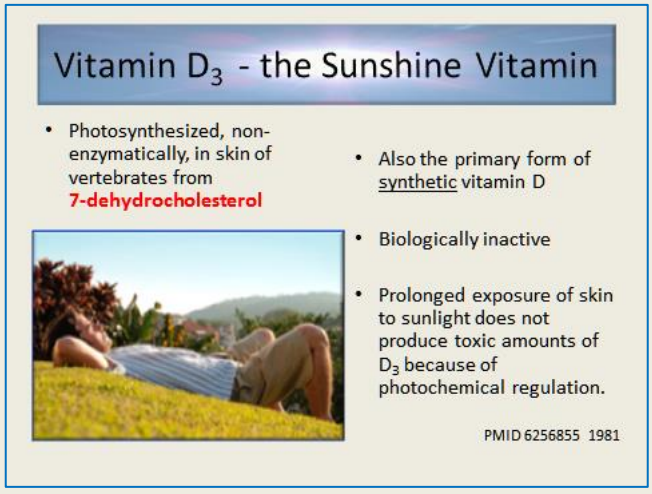


Chemically, vitamin D is a steroid that functions as a hormone. It was identified as a vitamin when it was discovered early in the 20th century because it cured rickets. The vitamin moniker is not a complete misnomer because vitamin D is an essential nutrient for those not exposed to adequate sunlight. However, errors may occur in research studies when authors use vitamin D as a synonym for 1,25(OH)2D because there are very significant structural and biological differences between 1,25(OH)2D and vitamin D_3.



Both vitamin D_2 and D_3 require ultraviolet (UV) radiation. Emissions from the sun include light, heat and UV radiation. Sunlight is the main source of vitamin D worldwide. Artificial sources also emit UV radiation (e.g., tanning beds, halogen lights, lasers, fluorescent lights).

Vitamin D_2 is photosynthesized in some invertebrates (e.g., yeasts, higher fungi, and phytoplankton, etc.) from ergosterol (an organic molecule in the steroid class). Vitamin D_2 isn't naturally present in humans because we lack ergosterol. Because it doesn't come from an animal product, vitamin D_2 is the form of vitamin D supplementation preferred by vegans who aren't exposed to adequate sunlight.

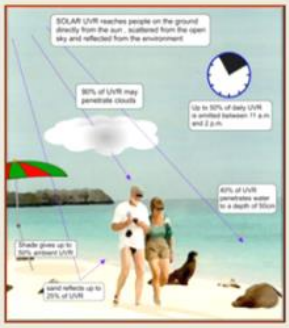


Vitamin D_3 is called the "sunshine vitamin" because it's photosynthesized, non-enzymatically, in the skin of vertebrates from 7-dehydrocholesterol (a steroid molecule). Photochemical regulation mechanisms in the skin prevent the formation of toxic levels of vitamin D_3. During prolonged exposure to the sun, the accumulation of previtamin D_3 is limited to about 10 to 15% of the original 7-dehydrocholesterol content because the previtamin photoisomerizes to two biologically inert photoproducts, lumisterol and tachysterol.

Vitamin D_3 is photosynthesized when the UV index is greater than 3.

- Daily in the tropics
- Daily in spring/summer in temperate regions
- Brief casual exposure of the arms & face is equivalent to ingestion of 200 IU/day

PMID:15570951992



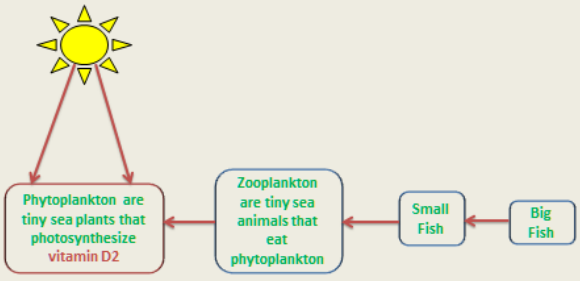
Vitamin D_3 is photosynthesized when the UV index is greater than 3; this occurs daily in the tropics and daily in the spring/summer of temperate regions. Brief casual exposure of the arms and face is equivalent to ingestion of 200 IU/day. 60% of solar UV radiation is received between 10am and 2pm daily.

Animal products are the primary dietary source of vitamin D_3.

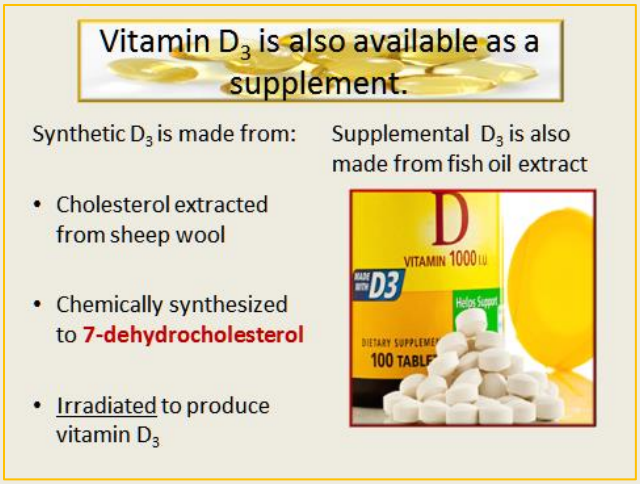
- Fatty fish (salmon, mackerel, tuna, sardines, herring)
- Animal products (eggs, meat, dairy)
- Processed food synthetically fortified with vitamin D
- No dietary requirement for those exposed to sunlight

Animal products are the primary dietary source of vitamin D_3, although there is no dietary requirement for those exposed to adequate sunlight. Fatty fish (e.g., salmon, mackerel, tuna, sardines, herring, etc.) have the highest amounts of D_3 other animal products (e.g., eggs, meat, dairy foods, etc.) contain lesser amounts. Vitamin D_3 can also be found in processed food that has been synthetically fortified (e.g., milk, cereals, breads, margarine, juices, etc.).

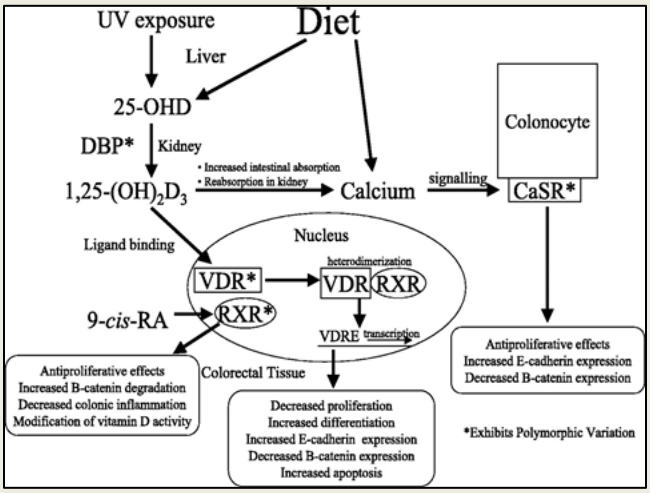
Fatty Fish are high in Vitamin D_2



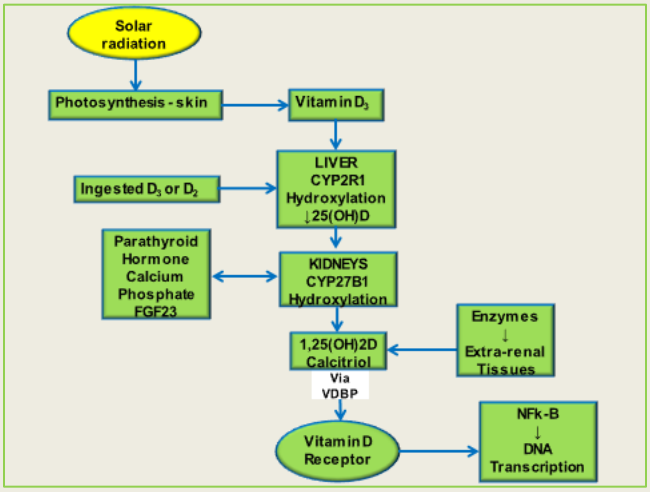
Animals acquire vitamin D indirectly, as this diagram of the fish food chain illustrates. The amount of vitamin D naturally found in other animal products is dependent on the amount in their food source, either naturally acquired or supplemented.



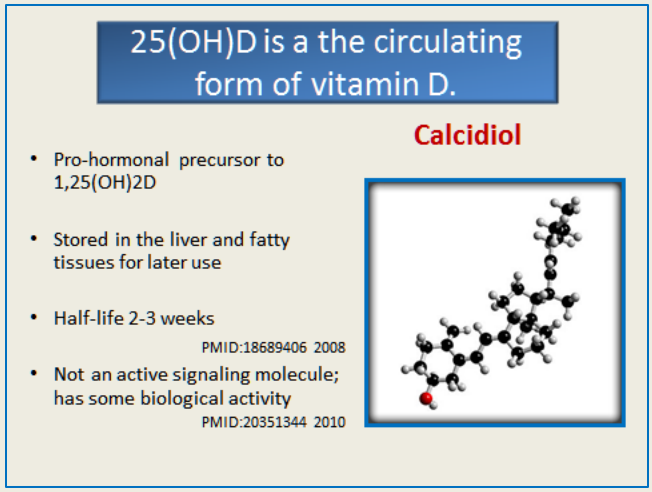
Vitamin D_3 is available as a dietary supplement. Because the chemical processes that lead to the formation of vitamin D_3 are non-enzymatic, they can take place in organic solvents (ex vivo), as well as in vivo. Therefore, vitamin D_3 can be synthesized commercially by extracting cholesterol from sheep wool; chemically synthesizing it to 7-dehydrocholesterol and then irradiating it. Supplemental vitamin D_3 is also made from fish oil extract.



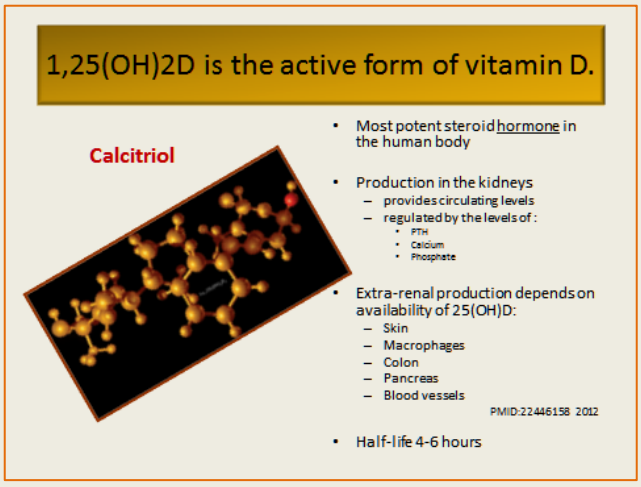
The sequential metabolic processes that convert biologically inactive, parental vitamin D into active metabolites are called the vitamin D endocrine system. The key elements of this system are photo-conversion, the liver, the kidney as an endocrine gland, the vitamin D receptor (VDR) and the vitamin D binding protein (VDBP).



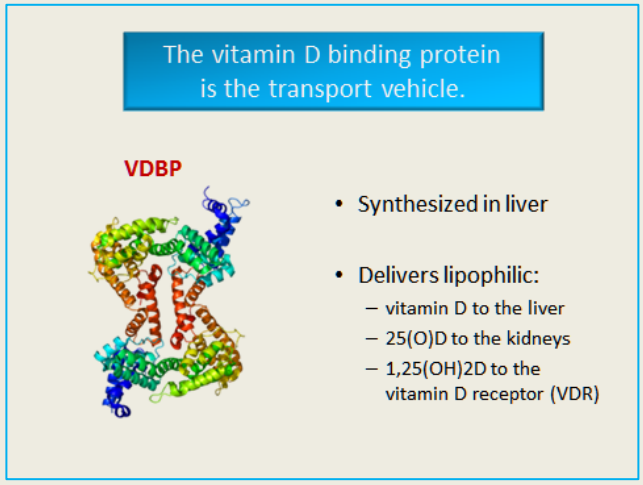
This process begins when vitamin D3 is photosynthesized in the skin or ingested (or when D2 is ingested). Vitamin D is then transported to the liver where it's hydroxylated by an enzyme (CYP2R1) to produce 25(OH)D (25-hydroxyvitamin-D). 25(OH)D is then transported to the kidneys where it's hydroxylated by another enzyme (CYP27B1) to produce 1,25OH2D (1,25-dihydroxyvitamin-D). Many cells outside the kidneys contain VDR and express CYP27B1 (the enzyme that catalyzes 25(OH)D to 1,25(OH)2D).



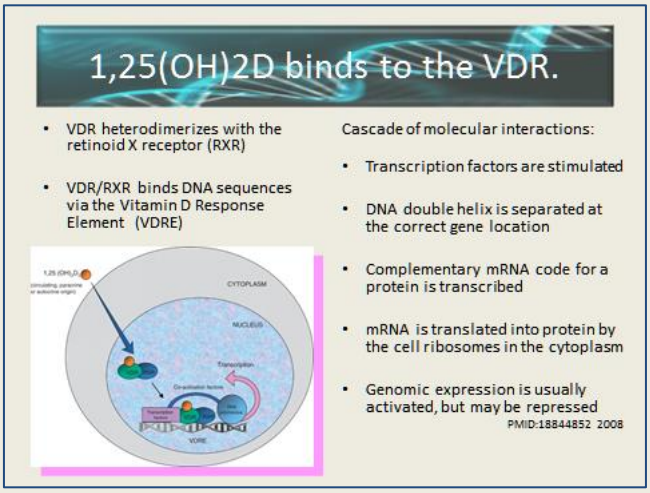
25(OH)D (also known as calcidiol) is the primary circulating metabolite. It has a half-life of two to three weeks but it's stored in the liver and fatty tissues for later use. 25(OH)D is the pro-hormonal precursor to 1,25(OH)2D. Although 25(OH)D is not an active signaling molecule, it does have some biological activity.

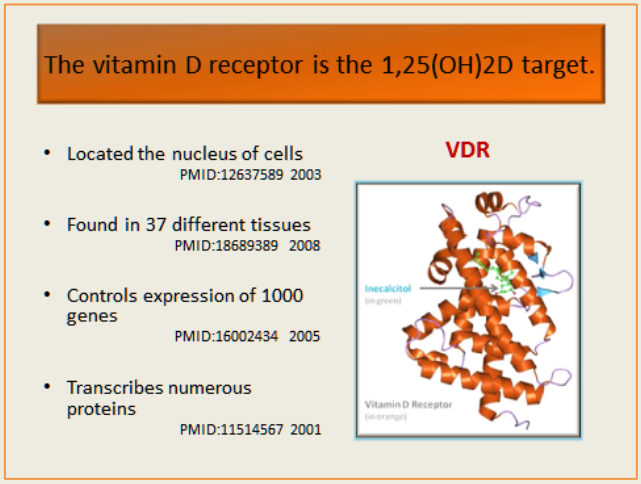


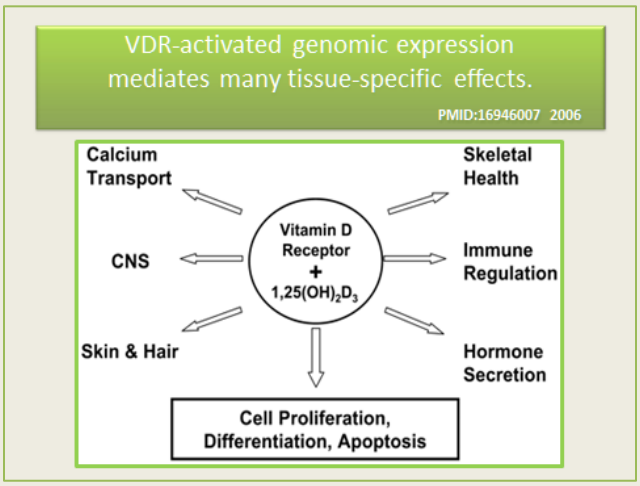
1,25(OH)2D (also known as calcitriol), the active metabolite, is the most potent steroid hormone in the human body. Feedback mechanisms regulate production of 1,25(OH)2D in the kidneys via serum levels of parathyroid hormone (PTH), fibroblast-like growth factor-23 (FGF23) calcium and phosphate. 1,25(OH)2D has a half-life of four to six hours and is also produced in many other tissues (e.g., skin, macrophages, colon, pancreas, blood vessels, etc.) by enzymatic actions.



The VDBP is the transport vehicle. VDBP, which is synthesized in the liver, delivers lipophilic (fat soluble) vitamin D to the liver, 25(OH)D to the kidneys and 1,25(OH)2D to the vitamin D receptor. DBP's primary role is the sequestration of vitamin D sterols in the serum, prolonging their serum half-lives and providing a circulating store of 25(OH)D to meet transient periods of vitamin D deficiency. In so doing, DBP helps to prevent the development of vitamin D deficiency. VDBP maintains stable serum stores of vitamin D metabolites and modulates the rates of its bioavailability, activation, and end-organ responsiveness. As an adjunct to its role in conservation and optimization of vitamin D, DBP appears to minimize direct urinary losses of the sterols and to slow their entry into metabolic breakdown pathways. It would appear that evolution, in establishing high levels of DBP, has favored the need for conservation and optimal utilization of dietary vitamin D in environments with variable vitamin D availability.



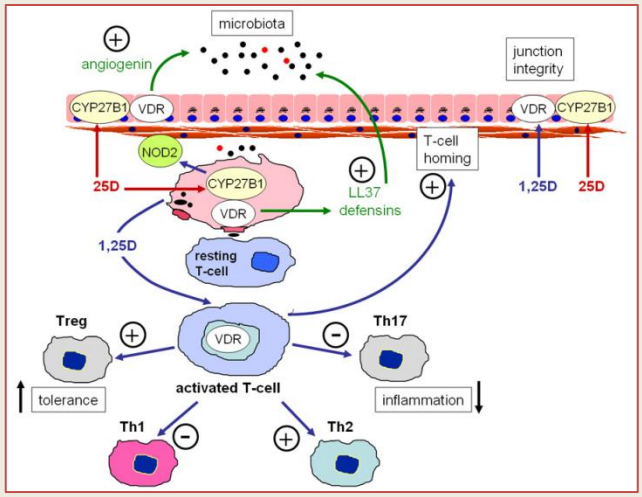




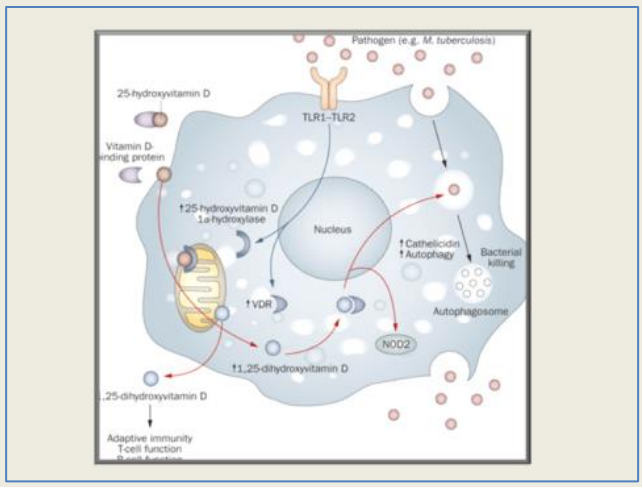
The vitamin D receptor (VDR) belongs to a superfamily of nuclear receptors that transduce hormonal signals from the immediate environment and transactivate genes in response to these signals. The VDR is a member of the nuclear receptor family of ligand-regulated transcription factors. VDR has been identified in 37 different tissues throughout the body (including the nucleus of phagocytic cells of the immune system).

The most important function of 1,25(OH)2D is to bind to the VDR nuclear receptor and mediate the transcription of DNA, triggered by signaling proteins, like Nuclear Factor kappa-ß (NFk-ß). Target genes contain hormone response elements (VDREs) in their promoter to which heterodimers of VDR and retinoid X receptors (RXR) can bind and transactivate expression of the target genes. The effects of 1,25(OH)2D are pleiotropic; it controls expression of over 1000 genes and transcribes numerous proteins. Most dividing cell types, normal and malignant, can express VDR and respond to 1,25(OH)2D. When 1,25(OH)2D binds to the VDR, it heterodimerizes with the retinoid X receptor (RXR). This duo (VDR/RXR) then binds to cellular DNA via the vitamin D response element (VDRE) to initiate a cascade of molecular actions. Transcription factors separate the DNA double helix at the correct gene location and make complementary messenger (mRNA). The mRNA then returns to the cytoplasm to be translated into a specific protein by ribosomes. Consequently, genomic expression is usually activated, but it may also be repressed.

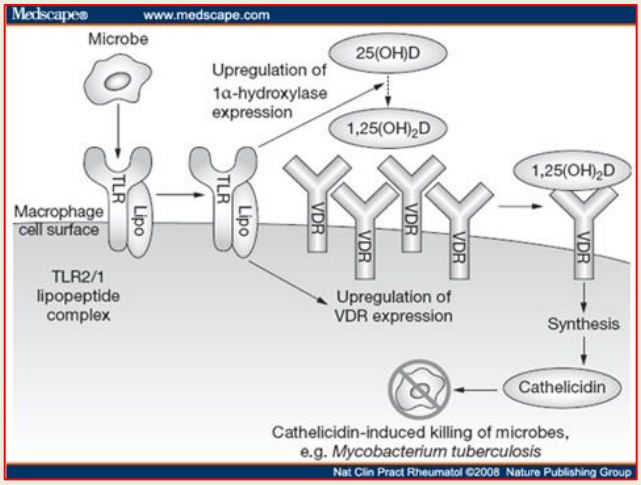
Recent insights suggest that 1,25(OH)2D-activated VDR gene regulation is even more complex than previously appreciated. VDR-activated genomic expression mediates many tissue-specific biological effects. Classical effects (e.g., calcium transport and bone health, etc.) are well known. The non-classical, extra-skeletal effects (e.g., cell differentiation, central nervous system, skin/hair, immune regulation, hormone secretion, etc.) have only been recognized for about 25 years.



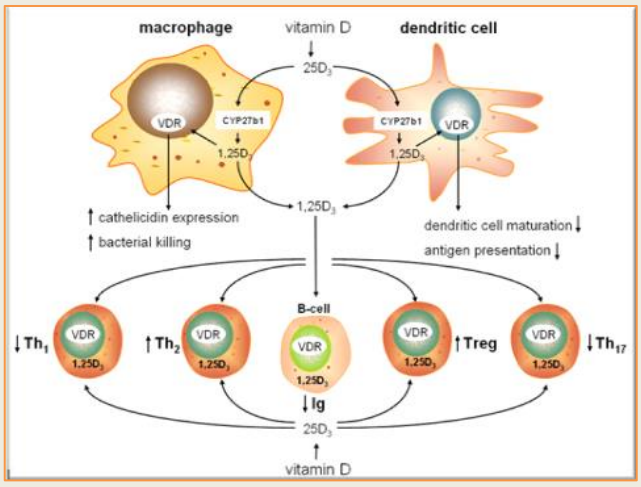
In addition to the classical VDR-mediated genomic pathway, 1,25(OH)2D also has been shown to elicit rapid responses. The term rapid response is used to describe the biological effects of 1,25(OH)2D that occur within a few minutes after hormone treatment and are considered too rapid to be explained by a VDR-mediated genomic pathway. Rather, the rapid responses are thought to be mediated by a direct action of 1,25(OH)2D on the plasma membrane of target cells stimulating a signal transduction pathway involving the rapid opening of voltage-sensitive Ca2+ channels and activation of protein kinases.



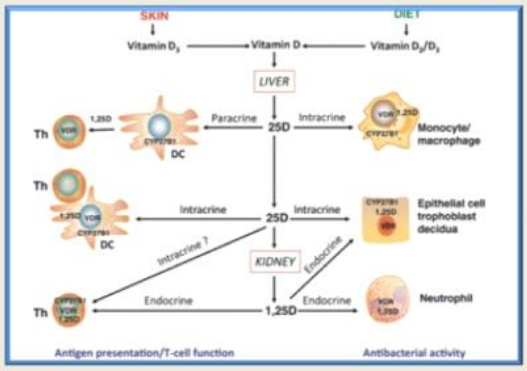
VDR are present in most cell types of the immune system, particularly in antigen-presenting cells (APCs) such as monocyte, macrophages and dendritic cells. The influence of 1,25(OH)2D on the immune system is one of its most important roles. In general, the innate system is enhanced and the adaptive system is inhibited by 1,25(OH)2D.



1,25(OH)2D activates the VDR to express antimicrobial peptides (AMPs) such as cathelicidin and beta defensins which attack pathogens. Recently, 1,25(OH)2D-induced autophagy has been reported (autophagy contributes to anti-aging, antimicrobial defense, and tumor suppression). VDR immune system regulation also involves cell proliferation, differentiation and apoptosis. The VDR is also expressed in both B and T white blood cells (lymphocytes).



In monocytes and macrophages (innate immune system), synthesis of 1,25(OH)2D from 25(OH)D promotes an antibacterial response to infection. Monocytes sense pathogen-associated molecular patterns (PAMPs) by utilizing pattern-recognition receptors (PRR), such as toll-like receptors (TLRs). Induction of CYP27B1 occurs following PAMP-sensing by TLR2/1. The inflammatory cytokine interferon γ (IFNγ) also stimulates expression of CYP27B1 by macrophages. As a result, 1,25(OH)2D production is increased in response to a pathogen immune challenge.

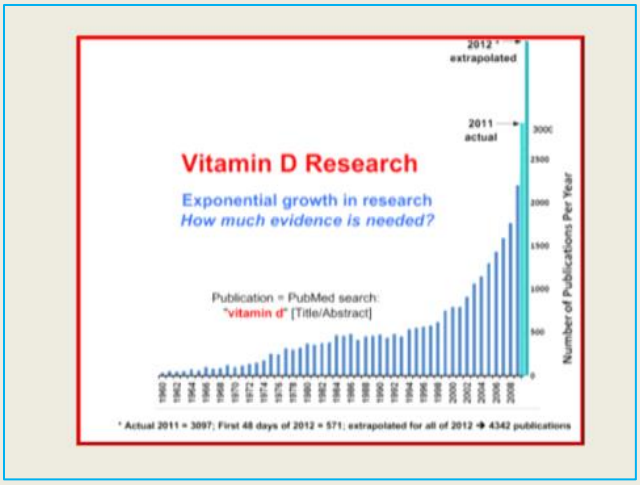


1,25(OH)2D modulates the adaptive immune system by inhibiting dendritic cell maturation, reducing T helper (Th) cells, and shifting Th1/Th17 cells to the Th2 and T regulatory pathways. In addition, 1,25(OH)2D inhibits Th1 cytokines that support cell-mediated immunity and promotes Th2 cytokines that support humoral immunity (antibodies circulating in bodily fluids). The immune response is heavily dependent on the vitamin D endocrine system, performing a balancing act of inflammation/anti-inflammation.

The amazing vitamin D molecule has inspired a number of current trends.

- Explosion research
- Concerns about deficiency
- More patient screening
- Increased Vitamin D supplementation

The realization that vitamin D is vital for so many essential biological functions has prompted a number of current trends. Research has led to concerns about vitamin D deficiency and increased use of serum 25(OH)D testing. Karen Lusky reported, in the June 2009 Cleveland Clinic newsletter, an increase from 1,500 tests/month in 2006 to 12,000/month in 2009. Another trend is the increased use of vitamin D supplements, as reported by Alex Williams April 4, 2009 in the New York Times.



There's been an explosion in vitamin D research; more scientific articles have been published about vitamin D in the 21st century than about any other vitamin (there were 28,047 listed in Medline between January 1, 2000 and December, 2012). An Internet search reveals over 600 clinical trials currently underway concerning vitamin D.

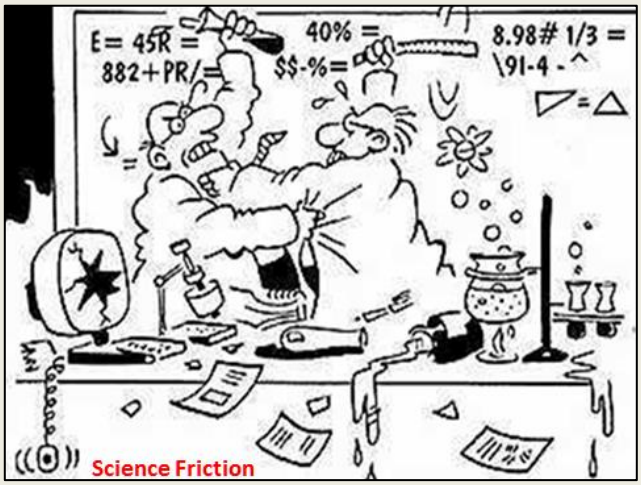
Concerns About Vitamin D Deficiency.

- Serum levels of 25(OH)D were lower in patients with autoimmune diseases.
- Subjects given vitamin D seemed to have lower rates of autoimmune diseases and fewer markers of inflammation.

25-Hydroxyvitamin D Levels and the Risk of Mortality in the General Population
PMID:18695076
JAMA Internal Medicine Aug, 2008

Vitamin D Supplementation and Total Mortality A Meta-analysis of Randomized Controlled Trials
PMID:17846391
JAMA Internal Medicine Sep. 9, 2007

Concerns about vitamin D deficiency arose when studies like these showed patients with autoimmune diseases have lower levels of serum 25(OH)D and study subjects given vitamin D had lower rates of autoimmune diseases and fewer markers of inflammation.



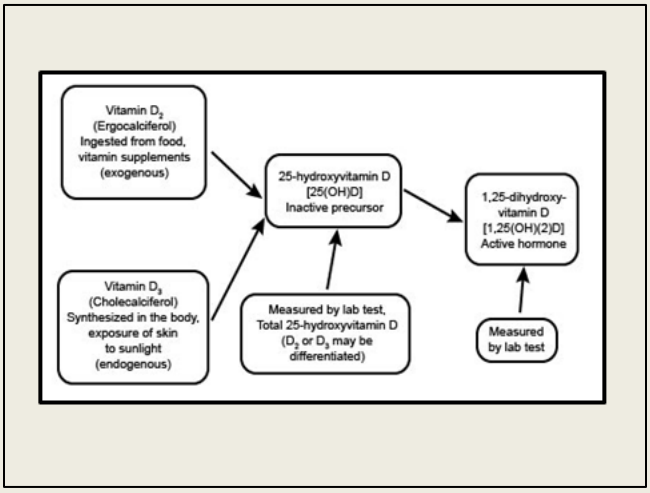
Although more people are being tested, there is no consensus on the definition of vitamin D deficiency or insufficiency and authorities haven't agreed on the significance of low 25(OH)D.

The Leading Medical Authority

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

- Established 1970 by the National Academy of Sciences
- Independent, non-government, non-profit
- Evidence-based information on science, medicine, health
- 1700 volunteer members
- Leading national & international experts
- Committees are carefully composed to:
  - assure expertise
  - avoid bias or conflict of interest
- Reports reviewed by external experts

In the U.S., the leading authority regarding medical research is the prestigious Institute of Medicine (IOM). Established in 1970 by the National Academy of Sciences, the IOM is an independent, non-government, non-profit organization with over 1700 volunteer members who provide evidence-based information on science, medicine, and health. IOM committees are carefully composed to assure expertise, avoid bias or conflict of interest, and their reports are reviewed by external experts. In a New York Times article on August 25, 2011, Gardiner Harris wrote, "The IOM is the most esteemed and authoritative adviser on issues of health and medicine, and its reports can transform medical thinking around the world."



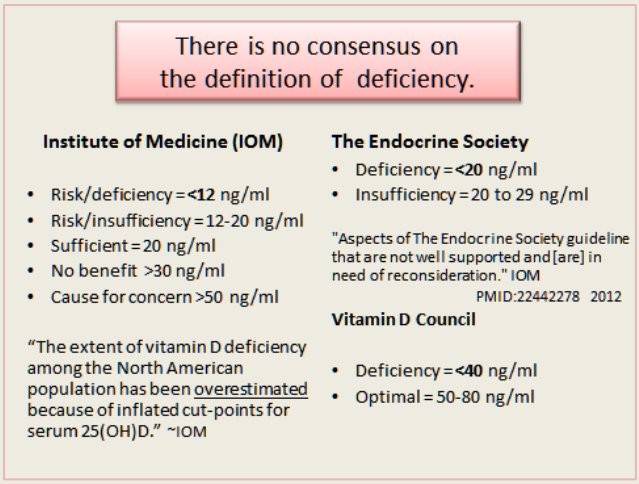
In 1997, the IOM defined serum 25(OH)D as the functional indicator of vitamin D status. It is a biomarker of exposure and, thus, a reflection of the supply of vitamin D to the body (the net incoming contributions from cutaneous synthesis and total intake). However, what is not clearly established is the extent to which 25(OH)D levels serve as a biomarker of effect.

What is vitamin D deficiency?

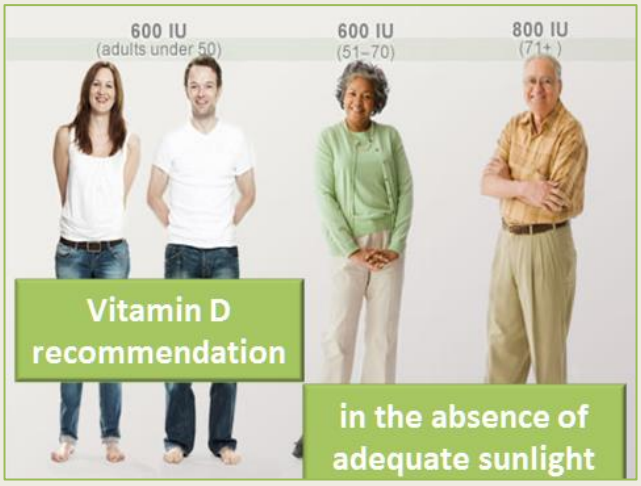
- 1997 - IOM defined 25(OH)D as the functional indicator of vitamin D status

- 2006 Merck Manual: 25(OH)D range 25- 40 ng/ml
- Current NIH normal: 25(OH)D range 30-74 ng/ml
- "25(OH)D lab ranges have been skewed high by Vitamin D supplementation" ~IOM

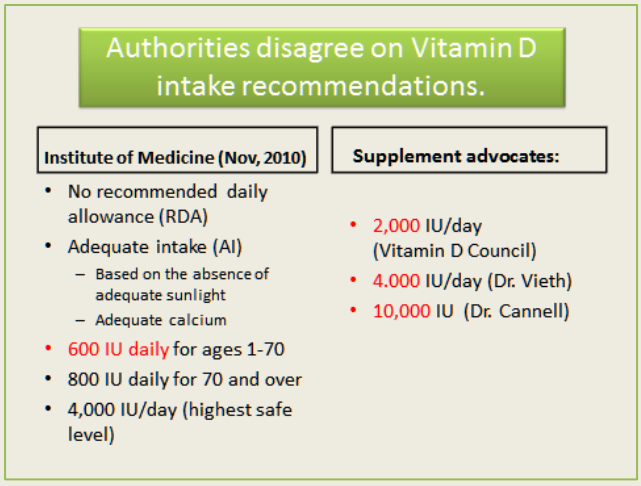
In 2006, the Merck Manual listed 25-40 ng/ml as the normal 25(OH)D range. Recently, this range has skyrocketed to 30-74 ng/ml, leading some to declare that half the U.S. non-institutionalized adult population is deficient, with 25(OH)D levels between 12–30 ng/ml. Laboratory reference ranges for serum 25(OH)D levels have long been based upon average values from populations of healthy individuals but many people are now supplementing with vitamin D. The IOM report emphasized that the current measurements, or cut-off points, of sufficiency and deficiency of 25(OH) D in use by laboratories have not been set using rigorous scientific studies. They suggest that since no central authority has determined which cut-off points to use, reports of deficiency and lab ranges may be skewed and numbers overestimated. Most importantly, 25(OH)D may not always reflect the level of 1,25(OH)2D (the active metabolite).



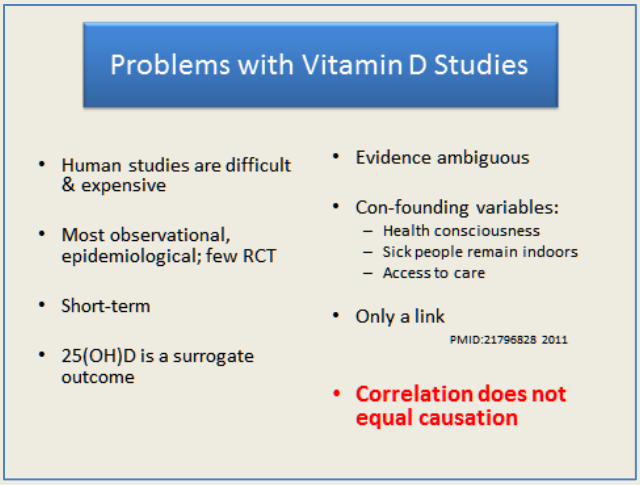
Without a consistent normal range for serum 25(OH)D, the definitions of vitamin D insufficiency and deficiency vary significantly; for example, some definitions of deficiency for adults are based on 25(OH)D levels associated with rickets in children (<10 ng/ml). Following a review, the IOM discounted the Endocrine Society data and showed it was incorrectly analyzed. In April, 2013 a paper published in Endocrine Connections reported concerns that the Endocrine Society's Clinical Practice Guideline may lead to vitamin D toxicity. "The way forward is the implementation of IOM recommendations, worldwide, especially given that the new specifications have increased two to threefold for children and young adults and increased by 33-50% for those over age 50 years compared with the last IOM report in 1997." The Vitamin D Council guideline is worrisome because it is even higher.



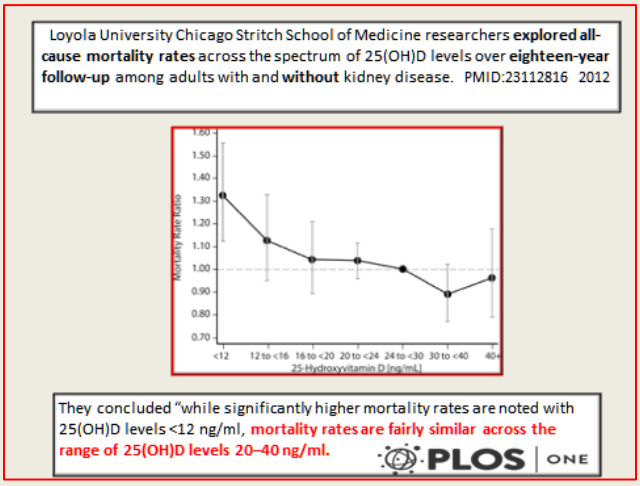
There is no recommended daily allowance (RDA) of vitamin D because it is not an essential nutrient (i.e., a substance the body can't make). Instead, the recommendation for vitamin D is stated as adequate intake (AI) and the need for an AI is based on the absence of adequate sunlight and the presence of adequate calcium. An IOM committee met in 1997 and set the AI standard of 400 IU of vitamin D per day for adults. After an extensive data review, the IOM raised the adequate intake level in 2010.



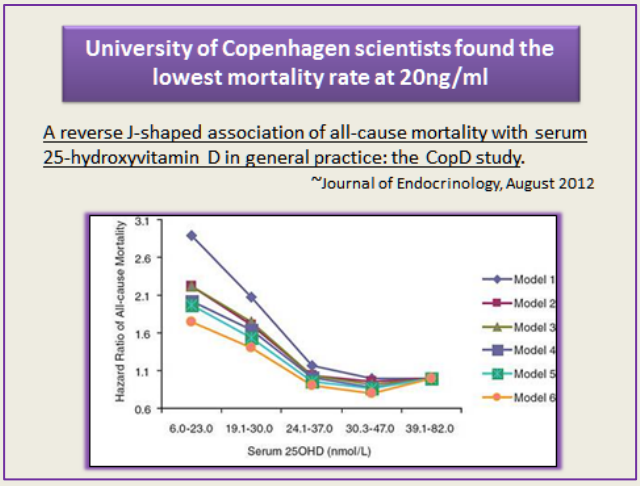
The 2010 IOM consensus report on vitamin D was endorsed by many organizations such as the American Society for Bone and Mineral Research. Hector DeLuca, one of the most respected vitamin D researchers in the world and a member the National Academy of Scientists, agrees with the IOM guidelines but support is not universal. Proponents of vitamin D supplementation lobbied the IOM, unsuccessfully, to raise the AI much higher (2,000-10,000 IU/day) but their request was denied because the IOM saw many problems with the vitamin D research they reviewed.



The IOM didn't recommend a higher adequate intake because they saw many problems with the vitamin D research they reviewed. The IOM noted that most vitamin D studies are observational; few are randomized or well-controlled. Most are short-term and serum 25(OH)D is used as a surrogate marker (i.e., not a true health outcome). No biological plausibility is given to explain study conclusions and often the evidence is ambiguous. Con-founding variables (e.g., health consciousness, sick people remain indoors, access to medical care, etc.) are often not taken into account. The studies only show a link between low 25(OH)D and illness; researchers and clinicians understand that correlation does not equal causation.



Meta-analysis statistics studies have attempted to make sense of multiple vitamin D studies. An analysis was done in 2012 by Loyola University Chicago Stritch School of Medicine, in which researchers explored all-cause mortality rates, across the spectrum of 25(OH)D levels, over an eighteen-year follow-up, among adults with and without kidney disease. They concluded that while significantly higher mortality rates are noted with 25(OH)D levels less than 12 ng/ml, mortality rates are fairly similar across the range of 25(OH)D levels 20–40 ng/ml. In other words, they found no benefit to a higher level of 25(OH)D.



A retrospective analysis of over 247,000 subjects in Denmark came to a similar conclusion; at the University of Copenhagen, scientists found the lowest mortality rate when 25(OH)D was 20 ng/ml. A 2013 study found parallel results; 25(OH)D in the 20-36 ng/ml range was associated with the lowest risk for mortality and morbidity. Blaney et. al found little association with vitamin D deficiency and autoimmune conditions, challenging the assumption that serum levels of 25(OH)D are a sensitive measure of the autoimmune disease state.

Misleading Claims

"A lack of this wonder nutrient can set the stage for no fewer than 33 disorders, including autism, cancer, diabetes and infertility."

Dr. Joe Mercola
www.mercola.com

"There's overwhelming evidence ... that increasing your vitamin D intake can make substantial improvement in your overall health and welfare. There is no downside to increasing your vitamin D intake."

Dr. Michael Holick
PMID:18550652 2008

Sensational Headlines

"Vitamin D fights Crohn's disease."
(Mercola website headline)
The lead researcher of this Crohn's tissue study said data "will have to be borne out in the clinic, which may be tricky."
PMCID:PMC2807280 2010

"Vitamin D Deficiency, the Ignored Epidemic of the Developed World"
PMCID:PMC3068797 2010

Experts Advise Caution

- "It's premature to go out and make a big deal out of vitamin D supplementation when we don't have the evidence. We've been burned before on nutrition-based interventions."
  Anastassios Pittas (endocrinologist -Tufts Medical Center, Boston)
- "There's a potentially large problem with leaping from observational studies to making decisions about interventions."
  Dr. Ethan Balk (Tufts Center for Clinical Evidence Synthesis)
- We should be mindful of previous erroneous study conclusions such as hormone replacement therapy.
  PMID:12117397 2002

Despite conflicting study results and the IOM recommendation, vitamin D proponents continue to exhort people to take vitamin D supplements. Referring to vitamin D as a nutrient is a serious error and Dr. Mercola failed to point out that evidence for his claims is inconclusive. And it's premature to claim there is no downside to taking a hormone that has not been studied long-term. Dr. Barry Kramer, Weighing Scientific Evidence, IOM workshop on vitamin D, August 4, 2009 said, "Especially when you're dealing with public health issues and millions of people, it pays you not to shoot first, because once you've shot, you can't ask the questions anymore, because your credibility is invested in your message. It pays to ask the questions before you shoot."

The evidence does not yet support vitamin D supplementation but proponents often oversell study findings. For example, Mercola's website headlined an item on a new study this way: "Vitamin D fights Crohn's disease". But the lead researcher, Dr. John White of the Research Institute of McGill University Health Center in Montreal, said the data came from a lab study that "will have to be borne out in the clinic, which may be tricky. Data is coming, but there's a good reason to be skeptical — people have been on this bandwagon before. When it gets into the clinic, it often doesn't work out quite as well."

Thankfully, some experts are advising caution regarding recommendations made based on observational studies. In his August 4, 2009 presentation "Weighing Scientific Evidence" at the IOM Information Workshop, Dr. Barry Kramer (Office of Disease Prevention, NIH) urged caution by quoting the Scottish philosopher David Hume (1711-1778) "A wise man proportions his belief to the evidence". In a Journal of the National Cancer Institute editorial Davis and Dwyer concluded, "While vitamin D may well have multiple benefits beyond bone, health professionals and the public should not, in a rush to judgment, assume that vitamin D is a magic bullet and consume high amounts of vitamin D. More definitive data on both benefits and potential adverse effects of high doses are urgently needed."

Vitamin D Proponents

Vitamin D Council

- John J. Cannell, M.D. (psychiatrist)
  - History of activism
  - Website markets vitamin D_3 as a nutrient
  - Authored vitamin D book
  - Sells:
    - Vitamin D tests
    - Vitamin D supplements

Commercial interests:

- Robert Heaney, M.D. (endocrinologist, Omaha)
  - Board/ Dairy Association
  - Speaker for P & G
  - Funded by Smith/Kline/Glaxo
- Dr. Reinhold Vieth (biochemist, Toronto)
  - Co-author study /Vit D lobbyists
  - Wife sells vitamin D
- Dairy farmers associations
  - Fund vitamin D studies
- Food manufacturers
- Supplement industry
  - 1/3 supp. increase = $2 billion

The Vitamin D Council founded in 2003 by John J. Cannell, M.D., a practicing psychiatrist with a history of activism in various causes. His website markets vitamin D3 as a nutrient and enables him to sell vitamin D products. Dr. Len Lichtenfeld (Deputy Chief Medical Officer for the American Cancer Society) countered Vitamin D Council claims with this statement, "When we succumb to making every medical decision solely on the basis of the strongest advocate's voice, we run the risk of moving medical practice back into an era similar to that from which we are trying to emerge. If the review and research studies confirm Dr. Cannell's position, that will be welcome. But we need to once and for all establish the science-based evidence that will conclusively answer the question one way or the other, rather than relying on advocacy to establish dietary and medical practice recommendations for the world."

Vitamin D is Big Business

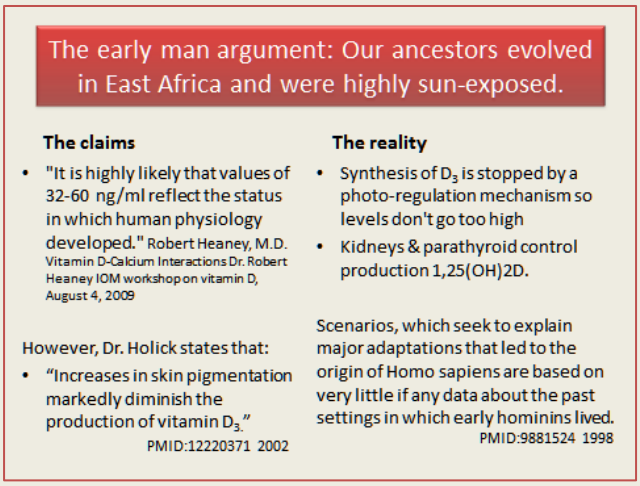
- In 1925, the first vitamin D patent made the U of WI the richest chemistry department in the world.
- The Wisconsin Research Foundation holds 162 vitamin D patents, which contribute $45 million per year to the University.
- Americans spend $20 billion annually for dietary supplements.
- 1,000 patent entries for vitamin D analogs or testing.

Vitamin D is big business; in 1925, the first vitamin D patent made the University of Wisconsin the richest chemistry department in the world. The Wisconsin Alumni Research Foundation now holds 162 vitamin D patents, which contribute about $45 million per year to the University. Many others are eager to share in the profits; the U.S. patent office has over 1,000 patent entries for vitamin D analogs or vitamin D testing.

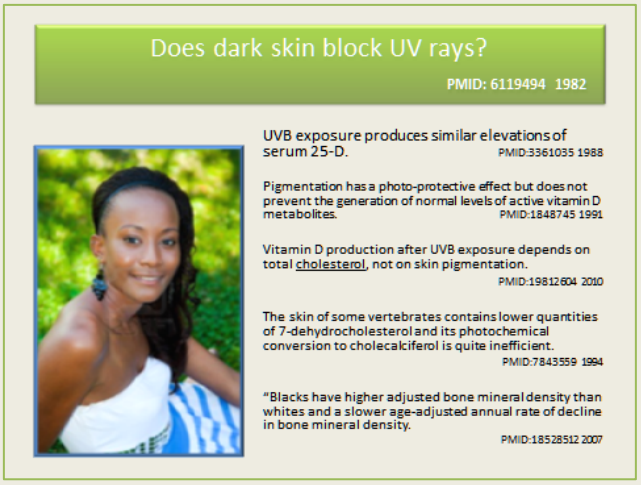
Putative Causes of Low Vitamin D

- Our ancestors were highly sun-exposed
- Living in the Northern hemisphere
- Clothes
- Sunscreen use
- Pollution
- Urban environment
- Cloud cover
- Dark skin pigmentation
- Diet limited in vitamin D foods

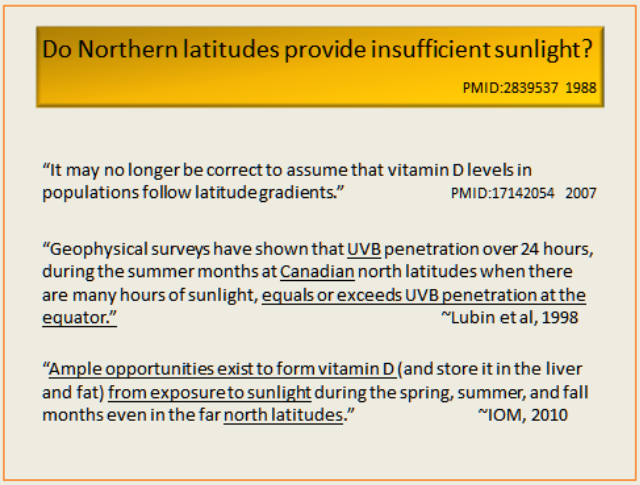
Vitamin D proponents reiterate many reasons why they believe the general population is unable to obtain enough vitamin D without the aid of supplementation. These beliefs are often based on outdated or limited studies and can be challenged with more recent research. Some authorities claim that most humans can't photosynthesis adequate vitamin D and they've convinced a lot of people. Let's take a closer look at their reasoning.



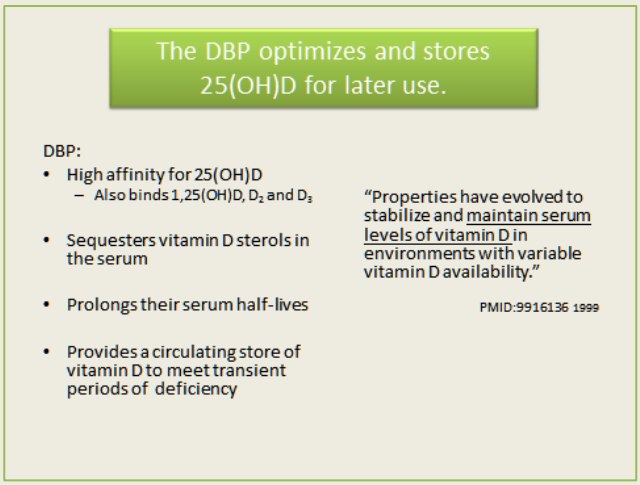
The evolutionary rationale for low serum 25-D levels is highly speculative. An analysis by Greaves concludes that early humans may have evolved black skin to protect against a very high risk of dying from ultraviolet light (UV)-induced skin cancer. Critics of this hypothesis point out there are no reported cases of hypercalcemia secondary to vitamin D toxicity as a sole consequence of prolonged sun exposure (i.e., photosynthesis of D3 is stopped at normal levels by a protective regulation mechanism in the skin). Many factors (e.g., protection of sweat glands, sunburn, frostbite, skin cancer, defense against microorganisms, etc.) may have played a role in the evolution of skin color.



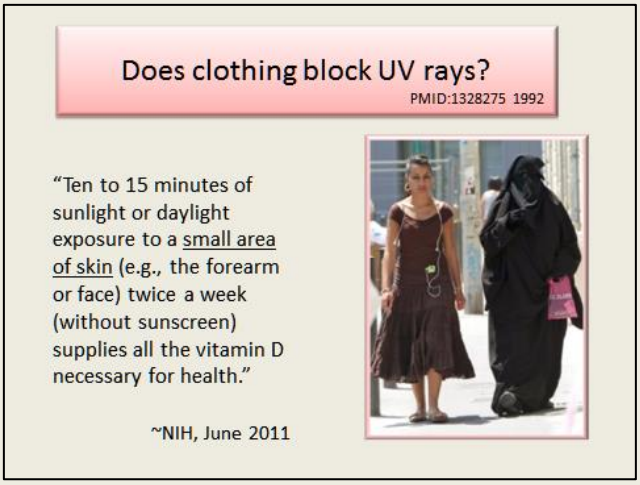
Researchers in Denmark measured the baseline serum 25(OH)D and total cholesterol levels of 182 fair-skinned and dark-skinned subjects; and studied the effect of UV radiation on their serum 25(OH)D levels. They found the amount of serum 25(OH)D produced was determined by the amount of cholesterol in the skin, not on skin pigmentation. Most importantly, skin pigmentation doesn't negatively affect vitamin D status. Persons with dark skin compensate for low 25(OH)D by rapidly converting it to the active 1,25(OH)2D metabolite, thus allowing them to maintain adequate vitamin D status. Matsuoka et al concluded that while racial pigmentation has a photo-protective effect, it does not prevent the generation of normal levels of active vitamin D metabolites. The concern about dark skin and vitamin D deficiency appears to be misplaced.



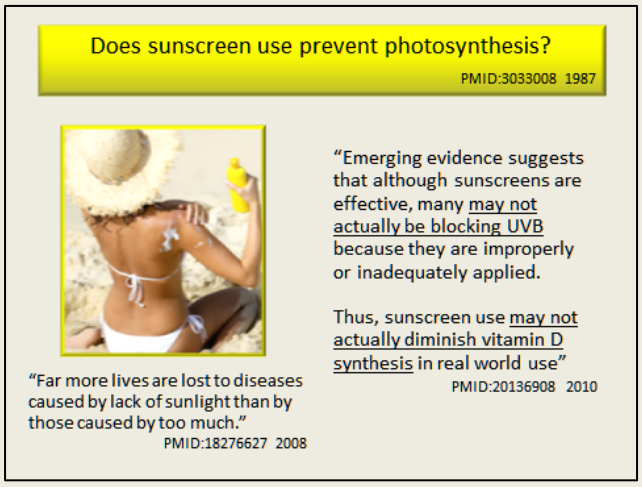
Recent studies refute the latitude hypothesis. Kimlin concluded, "It may no longer be correct to assume that vitamin D levels in populations follow latitude gradients." And Lubin stated, "Geophysical surveys have shown that UV-B penetration over 24 hours, during the summer months at Canadian north latitudes when there are many hours of sunlight, equals or exceeds UV-B penetration at the equator." A review by Ross et al. reports that ample opportunities exist to form vitamin D (and store it in the liver and fat) from exposure to sunlight during the spring, summer, and fall months even in the far north latitudes.



Our bodies have mechanisms for preserving the vitamin D we acquire during the summer; which have evolved to stabilize and maintain serum levels of vitamin D in environments with variable vitamin D availability. The DBP optimizes and stores 25(OH)D for later use; it also binds 1,25(OH)2D, as well as the parental vitamin D itself. DBP sequesters vitamin D sterols in the serum, prolongs their serum half-lives, and provides a circulating store of vitamin D to meet transient periods of deficiency. In so doing, DBP helps to prevent the development of severe vitamin D deficiency.



Clothing is a barrier to ultraviolet radiation but this is an issue only for people who cover themselves from head to toe (e.g., woman who wear a burka may not be exposed to sufficient sunlight). It takes relatively little sunlight exposure to acquire adequate stores of vitamin D and few people wear enough clothes to prevent that from happening. Ten to 15 minutes of sunlight or daylight exposure to a small area of skin (e.g., the forearm or face, etc.) twice a week (without sunscreen) supplies all the vitamin D necessary for health.



The belief that sunscreen lotion blocks vitamin D production is based on a 1987 study funded by the ultraviolet foundation, which is supported by the tanning bed industry. Contradictory information was provided by a 2010 study which concluded that although sunscreens are effective, many may not actually be blocking UV-B because they are improperly or inadequately applied. Thus, sunscreen use may not actually diminish vitamin D synthesis in real world use. As reported by ABC News on May 21, 2009, (according to a survey of 1,000 adults by the Consumer Reports National Research Center) 31 percent of Americans reported not using sunscreen, while 69 percent were occasional users.

Does pollution block UV rays?

In urban areas of high pollution, 50% of UV rays reach the ground.

Reductions in atmospheric ozone, due to pollution, are expected to result in higher amounts of UVB radiation reaching the earth's surface.

PMID:9894350 1998

Although pollution can block some ultraviolet radiation, even in urban areas of high pollution 50% of UV rays reach the ground. One study concluded that reductions in atmospheric ozone, due to pollution, are expected to result in higher amounts of UV-B radiation reaching the earth's surface.

Do tall buildings and clouds block UV rays?

- Tall buildings provide shade but shade gives up to 50% of UV rays
- Bright surfaces reflect 25% of UV rays
- 90% of UV rays may penetrate clouds

A significant amount of UV radiation exposure can be obtained in dense metropolitan areas; tall buildings provide shade but shade gives up to 50% of UV rays. Indoor workers receive 10% to 20% of outdoor workers' yearly UV exposure; and for many, this may be adequate, especially if sunlight exposure is higher when they are not working. UV radiation is reflected or scattered to varying extents by different surfaces. For example, fresh snow can reflect as much as 80% of UV radiation, sand about 25% and UV radiation is still 40% as intense at half a meter under water.

Elderly Skin

As the skin ages, there is a decline in the cutaneous levels of 7-dehydrocholesterol, resulting in a marked reduction of the skin's capacity to produce vitamin D3. However, Vanderschueren et al. concluded that renal capacity to synthesize 1,25(OH)2D, in addition to 25(OH)D production in the skin in response to sunlight, may be relatively well conserved, even in elderly community-dwelling men. Despite the up to fourfold reduction in vitamin D3 production in a 70-year-old compared to a 20-year-old, the skin has such a high capacity to make vitamin D3, elders exposed to sunlight will produce an adequate amount of vitamin D3 to satisfy their vitamin D requirement.

Are modern diets deficient in vitamin D?

Foods naturally high in D_3

Foods fortified with D_3

Source	Amount	Vitamin D Content
Fortified milk	8 oz	100 IU
Fortified orange juice	8 oz	100 IU
Infant formulas	8 oz	100 IU
Fortified yogurts	8 oz	100 IU
Fortified butter	3.5 oz	50 IU
Fortified margarine	3.5 oz	430 IU
Fortified cheeses	3 oz	100 IU
Fortified breakfast cereals	1 Serving	100 IU

Natural processes favor photosynthesis but, in many developed countries, it's possible to obtain the recommended vitamin D AI, or a substantial portion of it, from food. A typical Western diet contains many foods that are fortified with vitamin D and some that naturally contain vitamin D (e.g., eggs, fatty fish, cheese, etc.), making it relatively easy to ingest a significant amount. For example, food commonly consumed in one day (e. g., 3 cups of milk, 1 serving of fortified cereal, 1 cup of fortified juice and 3 ounces of cheese) supplies 600 IU of vitamin D. This is the AI for those who are not exposed to sunlight in the spring or summer.

Is low 25(OH)D normal?

In a meta-analysis of studies on healthy subjects *worldwide*, the mean 25(OH)D was 21.62 ng/ml.
PMID:18458986 2009

80% of healthy *Bangladeshi* women had a 25(OH)D level under 16 ng/ml.
PMID:16500882 2006

Healthy young female hospital employees in *Oman* had 25(OH)D levels below 20 ng/ml.
PMID:21509209 2011

Among healthy young adults in *India*, the average levels of 25(OH)D was 17.4 ng/ml.
PMID:21508424 2011

Healthy full-term infants in *China* had 25(OH)D levels of 5 to 14 ng/ml. (none developed rickets)
PMID:1578308 1992

Healthy young adult surfers in *Hawaii*. 25(OH)D was 31.6 ng/ml.
PMID:17426097 2007

Saudi medical students, 25(OH)D level was 10.74 ng/ml in males and 6.42 ng/ml in females.
PMID:22870413 2012

The average 25(OH)D levels of a cross-section of healthy *Calgary* citizens was 23 ng/ml.
PMID:12074117 2002

Vitamin D levels that are considered deficient have even been found in healthy persons and those who are exposed to abundant sunlight. The finding in surfers is a good illustration of the action of regulatory mechanisms in the skin which prevent overproduction of vitamin D3. It's clear that low levels of 25(OH)D are found in both healthy persons and those with diseases. Opposing reasoning can be used to explain this contradiction. One explanation reasons that healthy persons with low 25(OH)D will become sick; however, studies don't support this hypothesis. The correct explanation may be that, in the absence of disease, low 25(OH)D is normal.

Other facts also suggest low 25(OH)D may be normal.

Breast milk (the perfect food) remains very low in Vitamin D even when lactating mothers take high levels of vitamin D_3.

PMID: 17661565 2006

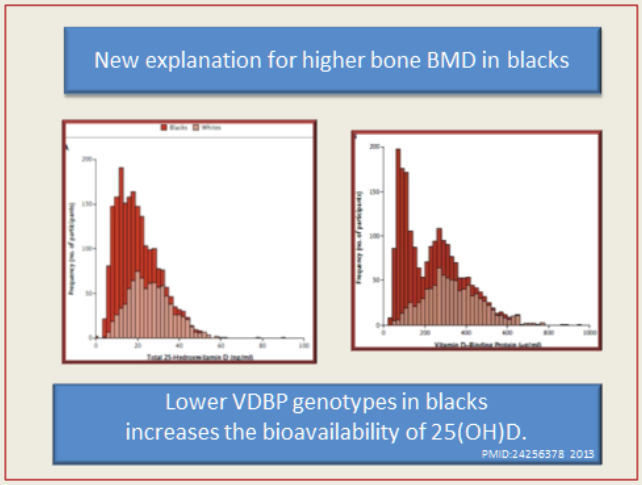
Vitamin D is low in black kids, compared to Caucasians, yet they have greater bone strength and muscle mass.

"Using the threshold of 15ng/ml, very few Caucasian kids 1-12 yrs are vitamin D-deficient.

In contrast, 10% black kids 1-6 yrs & 30% 7-12 yrs are vitamin D-deficient."

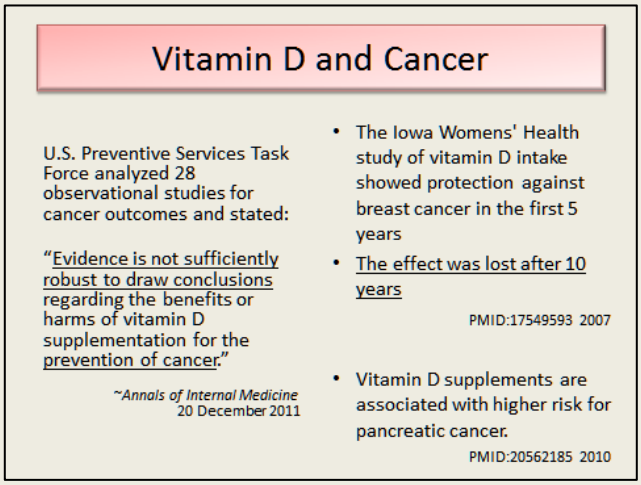
~ Pediatrics, Sept.2009

A few conundrums also support the thesis that low 25(OH)D is normal in healthy persons. The biological activity of vitamin D in breast milk may be higher than the analyzed values, because human milk contains small amounts of 25(OH)D in addition to vitamin D3. Lower serum 25(OH)D concentration was associated with an increased risk of incident coronary heart disease events among participants who were white or Chinese but not black or Hispanic. If vitamin D deficiency is rampant in blacks, why do they have greater bone strength and muscle mass, on average, than whites?



Recent research has found one explanation for the higher bone mineral density (BMD) observed in blacks. This study showed that vitamin D–binding protein (VDBP) genotypes result in lower concentrations of circulating VDBP in black Americans which seems to increase the bioavailability of 25(OH)D. Perhaps the answer to these low 25(OH)D puzzles is that low vitamin D is not a sign of deficiency in healthy individuals.

In recent years, dietary supplements containing vitamin D have been more frequently consumed. In the United States, vitamin D can now be found in multi-vitamin/multi-mineral formulations as well as a single supplement in a range of dosage levels; including 1,000 to 5,000 IU of vitamin D3 per dose and even up to 50,000 IU of vitamin D2 per dose. The impetus for the upsurge in supplementation is the hope that it might protect against a broad range of chronic diseases; including cancer, cardiovascular disease, osteoporosis and autoimmune disease. However, that hope is driven mostly by epidemiologic data, which should be viewed as hypothesis-generating rather than definitive.



Evidence for a beneficial effect of vitamin D supplementation in cancer is lacking. The findings of a large prospective study in 2008 do not support the claim that vitamin D is associated with decreased risk of prostate cancer; in fact, higher circulating 25(OH)D concentrations may be associated with increased risk of aggressive disease. The Women's Health Initiative (WHI) Calcium plus Vitamin D Supplementation Trial, published in November 2013, concluded that after an average of 11 years, calcium and vitamin D supplementation did not decrease colorectal cancer incidence.

Vitamin D and Cardiovascular Disease

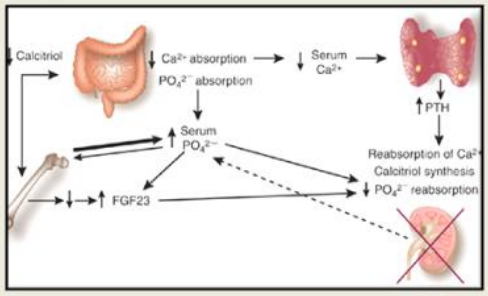
"The potential benefit of supplementation must be weighed against the current absence of definitive outcomes studies."
PMID:22654467 2011

Vitamin D supplementation failed to improve lipid profiles.
PMID:22947589 2012

"Some of the extra calcium, promoted by boosting vitamin D, may actually be taken up by atherosclerotic plaque, increasing the risk of cardiovascular events."
PMID:20061416 2010

There's no conclusive evidence vitamin D supplementation affords protection against heart disease. Dr. Lenore Buckley commented: "One of these concerns is that not all of the extra calcium absorption promoted by boosting vitamin D is going into bone to prevent fractures. Some of it may actually be taken up by atherosclerotic plaque, increasing the risk of cardiovascular events. The question we have to ask is: What does that low serum vitamin D level mean? Is it the thing that predisposes, or is it somehow a byproduct of illness?" Regarding supplementation to prevent cardiovascular disease, Dr. Whayne (Professor of Medicine-Cardiology, Gill Heart Institute, University of Kentucky, Lexington, KY) concluded, "…potential benefit of supplementation must be weighed against the current absence of definitive outcomes studies."

Vitamin D and Rickets



- Rickets occurs in sunny countries due to malnutrition.
  PMID:9483661 1997

Rickets is a softening of bones in children due to deficiency or impaired metabolism of vitamin D, phosphorus, or calcium. Hypophosphatemia is the common denominator of all rickets; low calcium intake leads to hyperparathyroidism, which leads to high phosphorus excretion and, thus, phosphorus deficiency.

Both adequate calcium and vitamin D are necessary to prevent rickets.

Calcium deficiency is the underlying cause of rickets & osteomalacia.
PMCID:PMC2740674 2008

In rural South Africa "the etiology of the rickets is related to low calcium intake"
PMID:202688 1978

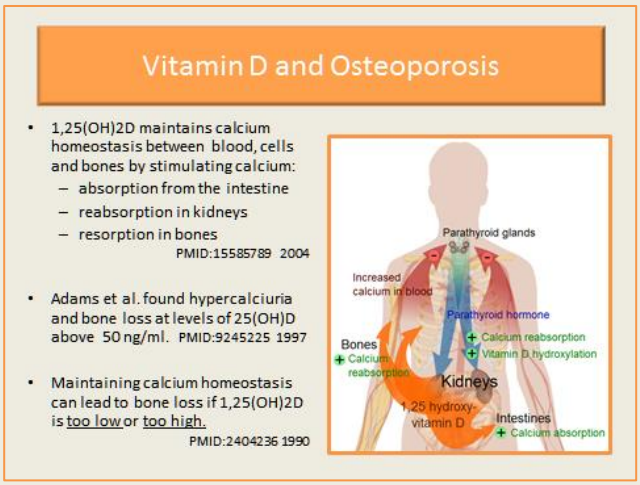
"Calcium supplementation alone effected healing of rickets…"
PMID:12937108 2003

"Low calcium intake leads to hyperparathyroidism, which leads to high phosphorus excretion and thus phosphorus deficiency."

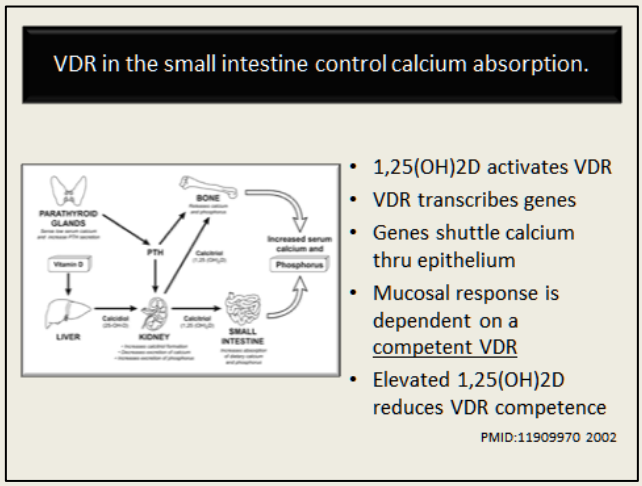
Hypophosphatemia: the common denominator of all rickets.

PMID:19504043 2009

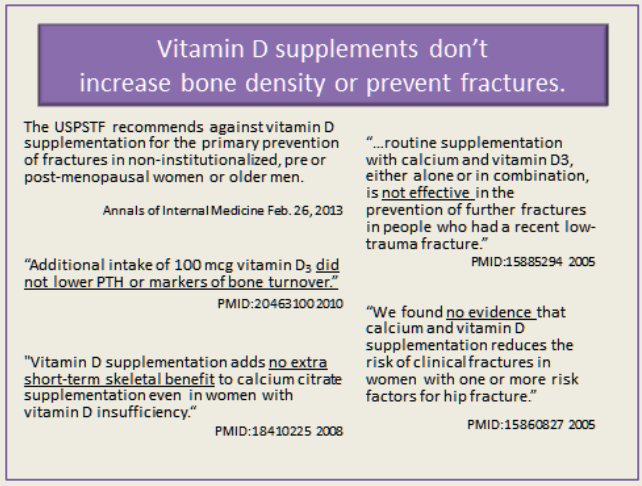
Adequate vitamin D is essential to prevent rickets, but adequate calcium is equally important; if either calcium or vitamin D is deficient, bone health suffers. Rickets is rare in the developed world; however, children in developing countries, who usually photosynthesize enough vitamin D from sunlight, develop rickets if poverty prevents them from eating enough calcium rich food. Studies found rickets occurs in sunny countries due to poor calcium intake and is cured with increased calcium ingestion.



Osteoporosis is a bone disease characterized by a decrease in bone mineral density and the appearance of small holes in bones due to loss of minerals. Vitamin D is an important factor in maintaining bone health to avoid osteoporosis. Precise maintenance of the physiologic levels of both extracellular and intracellular ionized calcium is essential to life; 1,25(OH)2D maintains calcium homeostasis between blood, cells and bones by stimulating calcium absorption from the intestines, reabsorption in the kidneys, and resorption in bones.



1,25(OH)2D up-regulates VDR in the small intestine, which then transcribes genes that shuttle calcium and phosphorus through the intestinal epithelium. However, mucosal response and calcium/phosphorus absorption is dependent on a competent VDR and elevated 1,25(OH)2D reduces VDR competence. Thus, calcium and phosphorus absorption may be inhibited if VDR function is impaired by elevated 1,25(OH)2D. This is illustrated by a study of Crohn's patients with elevated 1,25(OH)2D and low bone mineral density which concluded that treatment of the underlying inflammation would improve metabolic bone disease.



A study published in October 2013 in The Lancet found little evidence supporting the use of vitamin D supplements. Results from the Women's Health Initiative (WHI) Calcium plus Vitamin D Supplementation Trial, published in November 2013, came to the same conclusion. Vitamin D supplementation is ill-advised above a threshold of 30ng/ml 25-D. Inflammatory processes involved in disease occurrence and clinical course would reduce 25(OH)D, which would explain why low vitamin-D status is reported in a wide range of disorders. It would be wiser to seek reasons underlying the low vitamin-D level, such as inflammatory processes.

Elevated 1,25(OH)2D leads to bone loss.

"Levels above 42 pg/ml, 1,25(OH)2D stimulate bone osteoclasts. This leads to osteoporosis, dental fractures and calcium deposition into the soft tissues: lungs, breasts, muscle bundles, kidneys."
PMID:15225795 2004

"Vitamin D is a toxic compound, and excessive amounts can cause soft-tissue calcification."
PMID:6350405 1883

"A combination of high 1,25(OH)D and low 25-D is associated with the poorest bone health."
PMID:23386642 2013

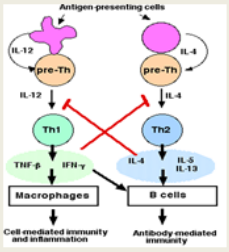
"Elevated 1,25(OH)D induces increased production of osteoclasts from stem cells."
PMID:20813899 2010

"...elevated levels of 1,25(OH)2D were strongly associated with decreased bone mineral density and content, and increased bone turnover."
PMID:10363752 1999

There is ample evidence that elevated 1,25(OH)2D leads to bone loss. When levels are above 42 pg/ml 1,25(OH)2D stimulates bone osteoclasts. This leads to osteoporosis, dental fractures and calcium deposition into the soft tissues: lungs, breasts, muscle bundles, kidneys. An earlier study warned, "Vitamin D is a toxic compound, and excessive amounts can cause soft-tissue calcification. There is a narrow leeway between the amount required and that initiating tissue damage." The EMAS study found that a combination of high 1,25(OH)2D and low 25(OH)D is associated with the poorest bone health. This significant evidence regarding bone loss should motivate medical practitioners and researchers to measure both 25(OH)D and 1,25(OH)2D to determine vitamin D status.

Autoimmune Disease

- Popular hypothesis: an overactive immune system produces auto-antibodies
- Alternate hypothesis: CWD bacteria invade phagocytes, causing a cytokine release
- Signals to T cells and B cells indicate something is wrong
- Antibodies include some that attack human proteins, as well as target pathogens
  PMID: 19716269 2010
- Antinuclear antibodies (ANA) are created in response to infectious agents
  PMID: 17894023 2007
- Molecular mimicry contributes to auto-antibody production
  PMID: 16126512 2005



The cause of autoimmune disease is unknown; the prevailing theory states that an overactive immune system produces auto-antibodies against self. An alternate hypothesis posits a bacterial etiology in which a persistent intracellular infection causes a cytokine release that induces signals to T cells and B cells, and the antibodies they produce (to the intracellular invader) include some that attack human proteins, as well as target the pathogens. In other words, when an innate immune system is forced to respond to a persistent infection, the resulting cascade of chemokines and cytokines will also stimulate an adaptive response.

Vitamin D reduces autoimmune disease symptoms.

- via immune suppression.
- Inflammation, clinical disease markers and symptoms reduced
- "Vitamin D inhibits pro-inflammatory processes by suppressing the enhanced activity of immune cells that take part in the autoimmune reaction."
  PMID: 17557889 2007
- Relapse is common
  PMID: 20182397 2010

Vitamin D appears to have a positive effect on autoimmune disease because it reduces symptoms via immune system suppression. For example, abnormal T cell reactivities in MS patients were reduced with vitamin D supplementation; serum 25(OH)D levels after 12 months were increased to 71.7 ng/ml ± 39 ng/ml. Vitamin D inhibits pro-inflammatory processes by suppressing the enhanced activity of immune cells that take part in the autoimmune reaction.

Vitamin D suppresses the immune system.

- Khoo et al. found that, in the summer when vitamin D_3 is highest, 1,25(OH)D down-regulated the immune system.

  PMID:21148505 2011

- "Exposure to ultraviolet light, especially UVB wavelengths, can impair immune responses in animals and humans."

  PMID:10447774 1999 (murine study)

- Some researchers think that immuno-suppression is a good thing.

  PMID:19491064 2009

Exposure to ultraviolet light, especially UV-B wavelengths, can impair immune responses in animals and humans. Thus, seasonal variation can have an impact on the immune response; in the summer, when vitamin D3 is highest, 1,25(OH)2D down-regulates the immune system. Reduced immunity following exposure of skin to UV radiation may explain the positive latitude gradient measured for a number of autoimmune diseases (decreased incidence of disease with residence at lower latitudes). Unfortunately, some researchers believe immunosuppression is the best form of treatment for autoimmune disease.

25-D has been found to have multiple immunosuppressant properties.

"On the whole, vitamin D confers an immunosuppressive effect."

PMID: 17557889 2007

25-D can be indirectly immuno-suppressive by being converted to excess 1,25-D.

PMID: 10769431 2000

Study:

- Low levels (below 30ng/ml) failed to inhibit the LPS inflammatory cascade
- Higher levels (30ng/ml) inhibited inflammatory signaling
- Highest levels of inflammatory inhibition occurred at 50ng/ml

PMID: 22301548 2012

Vitamin D proponents have failed to recognize the immunosuppressive effect of elevated 25(OH)D and to acknowledge that immunosuppression is contraindicated in the presence of infection. As a result of vitamin D immunosuppression inflammation, clinical disease markers and symptoms of autoimmune disease are reduced but this doesn't treat the underlying cause and relapse is common. Verway et al. wonder, "Is a specific pathogen responsible for disease or rather is a dysregulated immune response generated against a complex microbial population? Why would immune-suppressive drugs be efficacious if the primary defect is an immune deficiency?"

Despite vitamin D supplementation chronic diseases have increased.

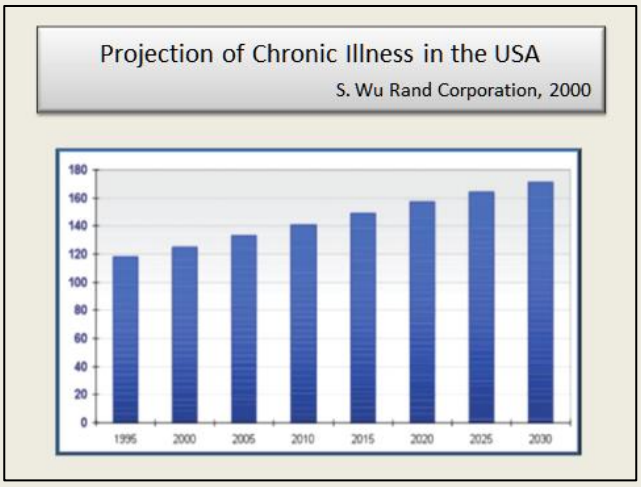
- More foods than ever are fortified with Vitamin D; dairy, bread, pasta, orange juice and soy products
- Sales of vitamin D supplements grew 116.5%, from $108 million to $234 million, from 2007 to 2008

  Nutrition Business Journal

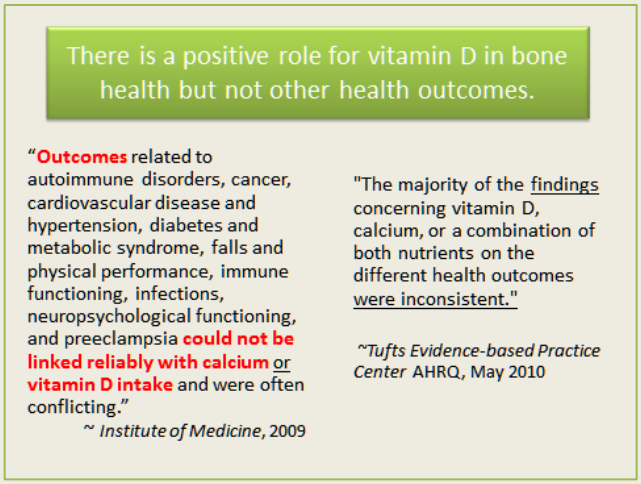
- Supplement proponents promised double digit declines in disease
- "Between 2000 and 2010, the percentage of adults aged 45–64 and 65 and over with two or more of nine selected chronic conditions increased for both men and women, all racial and ethnic groups examined, and most income groups. "

  ~CDC

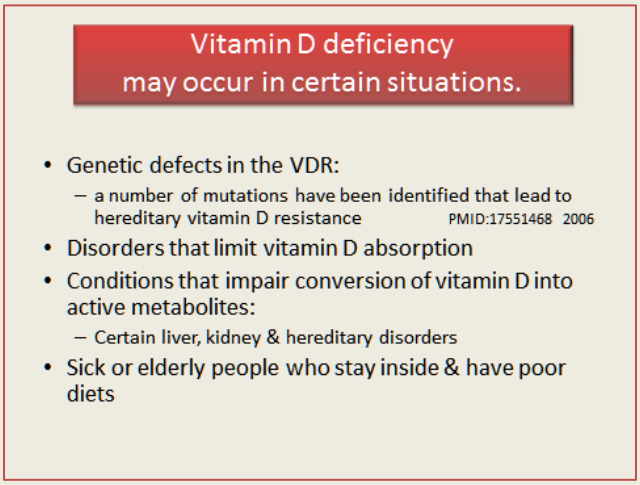
The suppressed immune system enables chronic infection and inflammation. Intracellular bacteria are able to persist and proliferate in host phagocytes, successfully compete for nutritional resources and displace commensal organisms from their niche. The result is chronic illness.



As reported by the Partnership to Fight Chronic Disease, more than one in four Americans lives with multiple chronic conditions, including one in 15 children. Almost $2 out of $3 spent on health care in the U.S. is directed toward care for the 27% of Americans with multiple chronic conditions and chronic illness is expected to continue increasing worldwide.



There is a positive role for vitamin D in bone health but not in other health outcomes. Genetic findings in those predisposed to longevity cast doubt on whether low levels of vitamin D cause age-related diseases and mortality. A study concluded that vitamin D supplementation did not reduce knee pain or cartilage volume loss in patients with symptomatic knee osteoarthritis. Subjects supplemented with high doses of vitamin D saw no improvement in serum lipids, HbA1c, or HS-CRP. Supplementation did not significantly reduce the incidence or duration of upper respiratory tract infections. In a study of older adults, the decline in physical performance and strength was not associated with 25(OH)D.



Vitamin D deficiency or insufficiency can occur in certain situations. Genetic defects in the VDR may result in vitamin D deficiency; a number of mutations have been identified that lead to hereditary vitamin D resistance. Disorders that limit vitamin D absorption and conditions that impair conversion of vitamin D into active metabolites may cause deficiency. Sick or elderly people who rarely go outdoors and have poor diets are also at risk.

Many experts are now doubtful about vitamin D supplementation.

- Low 25(OH)D did not cause age-related diseases and mortality.
  PMID:23128285 2012
- High vitamin D levels in pregnancy and at birth may contribute to a higher risk for food allergy in their children
  PMID:23253182 2013
- Depressive symptoms are not associated with low vitamin D
  PMID:19249103 2009

More vitamin D experts are beginning to reconsider vitamin D supplementation among the general population. In the Leiden Longevity study, low levels of 25(OH)D cast doubt on the causal nature of previously reported associations between low levels of vitamin D and age-related diseases and mortality. Amer, M.D., an assistant professor in the division of general internal medicine at the Johns Hopkins University School of Medicine, says "People taking vitamin D supplements need to be sure the supplements are necessary. Those pills could have unforeseen consequences to health even if they are not technically toxic."

Excess Vitamin D may cause toxicity.

- Excessive vitamin D can be toxic:
  - humans (supplements)
  - Animals
    - rodenticides (e.g., True Grit Rampage & Ortho Rat-B-Gone)
    - Plants
      - Solanum malacoxylon
        PMID:3077267 1988

People with the following conditions are at highest risk:

- High blood calcium or phosphorus levels
- Heart problems
- Kidney disease
- Sarcoidosis
- Tuberculosis

In fact, excessive vitamin D can be toxic to humans and to animals. It is difficult to ingest too much vitamin D from food, and natural mechanisms regulate the amount of vitamin D3 photosynthesized from sunlight; within about 20 minutes of ultraviolet exposure in light-skinned individuals (3–6 times longer for pigmented skin), the concentrations of vitamin D precursors produced in the skin reach an equilibrium, and any further vitamin D that is produced is degraded. However, elevated 25(OH)D and hypervitaminosis-D can occur due to vitamin D supplementation.

There are potential adverse effects from regular excess oral intake of vitamin D.

Immediate

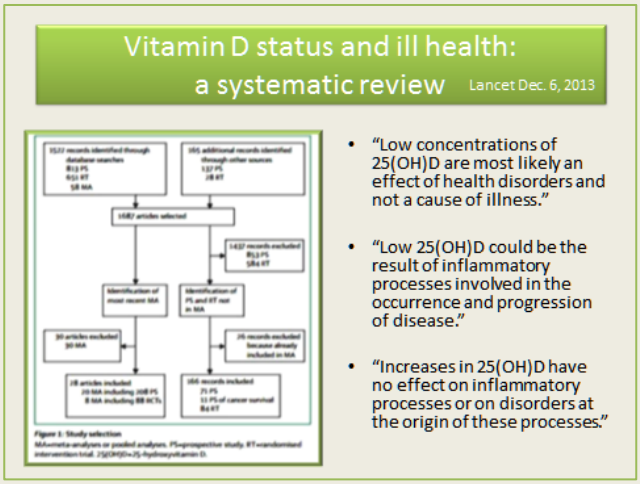
- Hypercalcemia
- Hypercalciuria
- Bone resorption
- Calcification of soft tissues
  PMID:20965147 2010

"Since high concentrations of 25-hydroxyvitamin D can bind the vitamin D receptor and can induce transcription, 25-hydroxyvitamin D is likely responsible for toxicity of vitamin D excess."
PMID:20965147 2011

Long-term

- Adverse effects may take decades to be realized
- First, do no harm
  - Previous erroneous nutrient study conclusions:
    - Lung cancer
    - Beta carotene
- Immune system suppression may be detrimental

Muhammad Amer, M.D., said "People taking vitamin D supplements need to be sure the supplements are necessary. Those pills could have unforeseen consequences to health." The IOM has challenged the notion that harm should be viewed in terms of vitamin D toxicity such as hypercalcemia, hypercalciuria, or metastatic calcification. It has advanced the concept of 'harm' in terms of chronic disease outcomes and mortality. Because adverse effects of vitamin D supplementation may take decades to be realized, clinicians (mindful of the medical ethics precept "First, do no harm") should err on the side of caution; follow the IOM guideline and wait for the results of long-term vitamin D studies.



Commenting on the Lancet findings in a press statement, Autier explained that "that decreases in vitamin D levels are a marker of deteriorating health." The authors postulate that inflammation is the common factor between most non-skeletal health disorders and low 25(OH)D concentrations. They state. "Increases in 25(OH)D have no effect on inflammatory processes or on disorders at the origin of these processes." They add that ongoing trials will provide more information, but in the meantime they advise against vitamin-D supplementation. A 2014 meta-analysis on the effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes concluded that vitamin D supplementation with or without calcium does not reduce skeletal or non-skeletal outcomes in unselected community-dwelling individuals by more than 15%. The authors stated that future trials with similar designs are unlikely to alter these conclusions.