

## **Vitamin D Deficiency: Common, Damaging, and Simple to Remedy** *By John Matthew, M.D.*

Most physicians think of Vitamin D as necessary to building and maintaining a strong skeleton, with rickets or osteomalacia the consequences of inadequate intake. But in recent years the understanding of the role of Vitamin D in health and disease has vastly expanded. It is now known to be necessary to the transcription of hundreds of genes and to influence crucial processes in virtually every tissue in the human body, not just in bone. Understanding this aspect of physiology is important to all of us, generalists and specialists alike, as we try to do what is best for our patients.

Thyroid hormone, which has been present in the phylogeny of organisms since at least the appearance of the mollusks, is a relative youngster compared to Vitamin D, which has been part of cellular physiology since the phytoplankton. So it should not be surprising that this ancient compound has an important role in many basic cellular processes.

In addition to the old understanding of 25 OH Vitamin D made in the liver being converted by an enzyme in the kidney to 1-25 Dihydroxy Vitamin D to then play a role in calcium absorption and bone physiology, we now know that most tissues contain the enzyme for producing the 1-25 form, cytoplasmic Vitamin D receptors, and intra-nuclear Retinoid Receptors. The Vitamin D/Vitamin D Receptor/Retinoid Receptor triad then acts like an ignition key in the "Vitamin D Response Elements" that are adjacent to hundred of genes, activation of which is necessary to the initiation of transcription to produce proteins such as enzymes critical to cell, tissue and organ function.

Deficient levels of Vitamin D are surprisingly prevalent. Roughly eighty-five percent of people tested in central Vermont in 2007, and a similar percentage of persons in a practice in Boston and of adults in Framingham, Mass., have 25 Hydroxy Vitamin D levels below 40 ng/ml – the lower limit of the preferred or optimal range – with roughly 50 percent below 30 ng/ml. Some rather large subgroups of the population have very low levels, rated as severely deficient (<10) or deficient (<20). Over 40% of men and over 50% of women in the United States have levels below 28 ng/mL. The prevalence of Vitamin D deficiency in our population is very concerning when the consequences are considered. Deficient levels are roughly three times more common in the winter/spring interval than in the summer/fall part of the year. Our Vermont sunlight contains negligible UVB levels from November through March, thus there are no realistic means of achieving adequate levels except with supplements.

Mankind evolved in equatorial Africa with high levels of UVB radiation inducing formation of Vitamin D in the skin. We are now exposed to far less UVB from sunlight, with latitude, clothing, skin pigment, smog, sunscreens, obesity, and inside living and work compounding the risk of having inadequate levels of "D". A number of medical conditions and medications add to this risk, as does the substantially reduced capacity for synthesis of D in the skin as we age.

A young white person in a bathing suit in the sunlight for long enough to get

minimally pink will generate 10 to 20 thousand units of D in their skin, then begin to break down some Vitamin D, avoiding excess levels occurring with continued sun exposure. "Lifeguard levels" of 80 to 120 are by no means unsafe and are, in fact, the levels found in equatorial "primitives" and old world apes. Recommended supplement doses are by contrast very small, probably one tenth to one twentieth of optimal doses. For example, only two hundred units a day is recommended from birth, at 8 pounds or so, to age 50, when our weight might have increased twenty to thirty fold. Two hundred units will prevent most rickets, but twenty times this amount is needed to get 97 percent of our adult population's serum levels of 25-OH levels to 40 ng/ml.

There are two principles of the scientific method we all know: "correlation does not mean causation" and the plural of anecdote is not data". The development of our knowledge of this matter, like of most others, takes time, observations leading to hypotheses and testing, including double blind, randomly allocated, prospective intervention trials. There is information concerning Vitamin D deficiency that ranges from observed correlations to intervention studies. Some matters are proven, while others are at the stage of strong correlations and compelling anecdotes. But taken together, there is a large body of information developing on this topic, with more and more firm conclusions being reported in a veritable cascade of studies and publications.

Further northerly or southerly latitude, lower UVB light exposure, and Vitamin D deficiency are associated with a great number of diseases, including our most common chronic disorders and our most prevalent causes of death. There is a bimodal distribution of many of these illnesses, with progressively higher prevalence as people live further north or south away from the equator where the prevalence is lowest. Many experts in this burgeoning area of medical science believe that correction of low Vitamin D levels may lead to substantial reductions in disease and disability and great improvements in health and life expectancy.

Lack of Vitamin D is associated with neuromuscular, not just skeletal, deficits and supplementing D has been shown to improve muscle strength, balance, reaction time, and bone density as well as reducing falls in the elderly. Osteomalacia still occurs rather often and rickets has been turning up more commonly. It is not just about bones, but now evidence is stronger than ever that Vitamin D is important in bone health. Lower D levels are associated with three times the rate of progression of degenerative joint disease of the knee and increased risk of DJD progression in the hip.

A total of 18 cancers have reported increased prevalence, and some with decreased survival rates, associated with lower D levels. This is particularly noted with respect to gastrointestinal malignancies. Intervention studies of Vitamin D's influence on some of these conditions have been started. Colon cancer has been shown to be reduced with increased Vitamin D levels. One prospective study reported reduced rates of total cancers, including new breast cancers, in women given a modest dose of supplemental D for four years. There is a logical possible mechanism of action for this relationship, since Vitamin D dependent processes are involved in cell differentiation and maturation, growth arrest of cells with abnormal DNA, apoptosis, and the inhibition of angiogenesis.

As well, there is a 17 percent lower risk for all cancers, and a 43 percent lower risk of GI cancers, associated with each 10 ng/ml increase of Vitamin D serum level. One of the country's Vitamin D experts projects that if all Americans' levels were at least 55 ng/ml we would have 60,000 less colon cancers and 85,000 less breast cancers yearly.

Similarly, autoimmune and inflammatory disorders, including Multiple Sclerosis, Crohn's Disease, Rheumatoid Arthritis, Lupus, Diabetes, and Asthma, are associated with low D levels and some of these improve with correction of low Vitamin D levels. Correcting low Vitamin D levels leads to several changes in inflammation and immune mechanisms, including reducing Tumor Necrosis Factor. There are provocative studies showing reductions of MS events and of the prevalence of childhood onset diabetes with supplementation of Vitamin D. There have also been several mechanisms elucidated by which Vitamin D improves diabetic control, including increasing insulin secretion and decreasing insulin resistance.

There are also anti-infection actions of Vitamin D, which is necessary to the production of Antimicrobial Peptides needed to prevent or control infections by bacteria, yeast, fungi, and viruses. There is a long history of maneuvers, now known to increase Vitamin D levels, which reduced or controlled infections in the past, including irradiation of the blood in the 30s and 40s with the "Knott Technique" for surgical infections and the use of sanatoria for treating Tuberculosis with fresh air and sunlight in the pre-antibiotic era. We now have studies relating reduced risk of colds, influenza and TB in persons with higher Vitamin D levels.

Low Vitamin D levels are associated with increased risk of coronary artery disease and winter is also associated with worse peripheral vascular and cerebral vascular disease, perhaps exacerbated by lack of D increasing inflammation, a strong risk factor for these illnesses. Low D levels predict a substantially increased risk of dying with increasing age at all ages in a representative sample of the general population. Those twenty years of age and older with 25 OH D levels in the lowest quartile (<17.8 ng/ml) have a 26 percent higher risk of death from all causes than those in the top quartile over a mean of 8.7 years of follow-up. Whether raising the level of D will lower the risk of death has not been studied as yet. But accumulating risks, such as the doubling of risk for coronary disease at similar low levels, increased risk for a number of common cancers, and increased risk for diabetes may explain these findings.

Low D levels are also associated with decreased myocardial contractility, elevated Renin and high blood pressure, age-related macular degeneration, pre-eclampsia, elevated triglyceride levels, insulin resistance, reduced insulin production, periodontal disease and tooth loss, and reduced activity of Tyrosine Hydroxylase, the rate limiting step in the synthesis of Central Catecholamines (Serotonin, Norepinephrine, and Dopamine). Thus lack of D can cause or aggravate depression and perhaps other brain disorders.

Some researchers are concerned that low D levels affect brain development of children in utero, with summer born infants, manufactured in the winter, at increased risk of various neuro-developmental disorders. There are also correlations of mothers' D

intakes with other risks to their offspring, including wheezing when their children are three years old. It takes about 6600 units of Vitamin D a day going into a nursing mother to allow her breast milk to contain sufficient D for her nursing infant to have adequate levels. There are also intriguing reports of improved function in persons with autism when low D levels are corrected. (See <http://www.vitamindcouncil.org/> ). There are those who believe that autism itself is at least in part a consequence of inadequate vitamin D levels during gestation.

As of yet, there have been no double blind intervention trials with respect to most of the above matters. After all, the intervention is not a proprietary product with profit potential. Organizing such trials will require the action of a governmental agency, one would presume, the potential profit devolving to the public in the currency of better health, rather than to a pharmaceutical company.

There are some tantalizing reported effects of Vitamin D supplements. Finnish infants given 2000 units daily for the first year of life had, over the next thirty years, an 80-percent reduction in childhood onset diabetes. Nebraska women given 1100 units of Vitamin D daily had a 60-percent reduction in new cancers in four years. The 95 percent confidence limits for this study were 40- to 90-percent reduction. There are also reports of supplements reducing tooth loss and falls in the elderly, as well as supplements providing impressive relief to people with fibromyalgia, poor sleep, chronic pain and depression.

It may sound like Snake Oil: "fixes everything and improves the rest". But it is just basic physiology, with us since the days of phytoplankton, now finally getting its day in the sun.

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Clinical Notes:

A public health measure that would be quite safe and benefit many would be to increase the recommended daily intake of Vitamin D to as much as ten times the presently recommended levels. This would deliver quite a bit of improvement to the population.

But when taking care of individuals, testing levels and re-testing to determine response to treatment seems necessary to optimize replacement schedules and to achieve target levels for each patient. This is because it is quite difficult to predict or guess what an individual's level of 25 OH D will be. Multiple factors determine an individual's level, including wide variation in the activity of the cytochrome enzymes that metabolize the vitamin and the effect of various medications to accelerate or slow this metabolism.

One should test 25 OH levels, not 1-25 DiHydroxy levels, which are somewhat

volatile and may be misleading as to the sufficiency of Vitamin D levels in the body. Technology now allows people to measure their 25(OH)D in their home – which costs much less than commercial lab testing, especially if they lack insurance – by obtaining a home test kit from ZRT Labs. This link connects to additional information, via the Vitamin D Council: <http://www.vitamindcouncil.org/health/deficiency/am-i-vitamin-d-deficient.shtml>

Shall we wait for a series of double blind trials? Vitamin D supplements are cheap and safe. The downside risk of supplementation would appear to be minimal, with a substantial upside, even if only some of the benefits now thought possible prove to result from supplementation when further studies are done. We all take care of one person at a time and the care of each patient is often a single patient intervention trial, such as determining which medication is most effective for lowering an individual's blood pressure. These experiments with an N of one are part and parcel of practice every day. I am very comfortable with tolerating some ambiguity or lack of certainty as we try this simple and cheap approach to a number of clinical situations.

In our practice we have seen marked improvement in glycohemoglobin levels, and even hypoglycemia requiring large reductions or elimination of supplemental insulin, when adults with diabetes have deficient D levels corrected. Anecdotes, yes, but amazing to those of us who have this clinical experience. We have also seen supplements bring very impressive relief to some persons with fibromyalgia, chronic pain, and depression. Again these are anecdotes. The plural of anecdote is not data, but anecdotes are not without value.

We have developed the approach of sending off a serum level test when we admit people with infections to hospital, then going ahead with supplements of 50,000 units of D3 for three or four days, before their levels are reported. Without exception the levels have returned in the deficient range, often less than 10 ng/ml, while adequate antimicrobial peptide levels require 25-OH D levels of above 19. We have seen minor but chronic MRSA skin lesions, VRE urinary colonization, and Rosacea clear up without antibiotics when low D levels are corrected. We think supplementation has "turned around" some poorly responsive infections in patients on antibiotics in hospital. More anecdotes, but encouraging and provocative, low risk and low cost.

We aim to get 25 OH levels to at least 40 ng/ml, but prefer to achieve levels of 65 or so. The body converts all D that enters, via food, sunlight, or supplements, to the ready to use 25 OH form until it reaches levels of 50s or 60s, and then begins to store D in reserves for future use. So targeting replacement to these levels makes physiologic sense. Also the experts who study this matter project that possibly greater reductions in malignancies may be achieved with the higher levels. This information is well summarized in the [Disease Incidence Prevention by Serum Level Chart](#) found at the bottom of the page at [www.grassrootshealth.org/documentation/index.php](http://www.grassrootshealth.org/documentation/index.php), which also provides access to the slides from several experts who made presentations at April and December Diagnosis and Treatment of Vitamin D Deficiency seminars at the University of California San Diego School of Medicine.

Also, the following link connects you to videos of lectures at UCSD:  
<http://www.ucsd.tv/series/index.asp?show=show&seriesnumber=520>.

Patients can purchase Vitamin D3, which is available as 1,000 unit tablets or capsules, for about \$15 for 200 tablets in discount stores. Also there are 50,000 unit capsules of D2 and D3 available. D3 (Cholecalciferol) is preferred to D2 (Ergocalciferol), since D3 is about two or three times more biologically effective. If one takes 50,000 units Q 2 weeks, they are taking in 3,300 units a day. Taking this dose Q ten days provides 5,000 units a day. Taken weekly, one receives 6,600 units a day. Particularly in obese individuals and those with severe deficiency, these higher doses may be necessary to achieve and maintain serum levels of 25 OH Vitamin D in the target range of > 60 ng/ml.

Some insurances cover the D2 supplement when prescribed for deficiency. Otherwise, the 50,000 D3, available on the internet for about \$30 for 100 capsules, is the most economical method to replete and maintain optimal 25 OH Vitamin D levels.

My power point slides, with some additional details and illustrations, are here on the VMS web site:

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