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Clinical Diagnostic News

Newsletter for the Clinician

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Vitamin D Edition

DiaSorin

The Diagnostic Specialist

Vitamin D or Hormone D ?

Vitamin D, which is essential for life in higher animals, is a unique vitamin. It does not fit the usual definition of a vitamin as "an organic compound required as a nutrient in tiny amounts by an organism."[1] Furthermore, a substance is usually referred to as a vitamin when it cannot be synthesized in sufficient quantities by an organism and must be obtained from the diet. In the case of vitamin D, sufficient quantities for health can be synthesized in the body, and in our early ancestors that was the primary source of vitamin D. In fact, there are limited natural food sources of vitamin D, primarily fatty fish and fish liver oil.

The term "vitamin D" usually refers collectively to two molecules, vitamin D_3 and vitamin D_2, which are actually secosteroids or pro-steroid hormones similar in structure to that of classic steroid hormones such as estradiol and cortisol.[2] Neither vitamin D_3 nor vitamin D_2 is known to have intrinsic biological activity. Vitamins D_3 and D_2 are converted in the body to the active form of vitamin D (calcitriol) which is actually a hormone.

Vitamin D_3 (cholecalciferol) is found in all animals, and in humans it is made in skin exposed to ultraviolet B (UV-B) radiation from the sun or artificial UV-B light. It is derived from a cholesterol precursor in the skin, 7-dehydrocholesterol. When the skin absorbs UV-B radiation, the precursor is converted to previtamin D_3, which undergoes thermally induced transformation to vitamin D_3. Vitamin D_2 (ergocalciferol) is derived from a similar plant sterol and has been frequently used in vitamin D supplements.

Vitamin D_2 and D_3, from the diet or UV-B conversion, are incorporated into chylomicrons and absorbed into the lymphatic system. (Hence, vitamin D is referred to as a fat-soluble vitamin.) They then enter the circulation where they are bound to the vitamin D binding protein (DBP) and lipoproteins. Both D_2 and D_3 are released from DBP to the liver where they are metabolized by respective 25-hydroxylase enzymes to 25-hydroxyvitamin D (25(OH) D), which is the functional indicator of vitamin D status. Then 25(OH)D proceeds along two "pathways." (See Figure) In the classic vitamin D endocrine pathway, 25(OH) D is further hydroxylated in the kidney to 1,25-dihydroxyvitamin D (1,25$(OH)_2$D or calcitriol) which is the active hormonal form of vitamin D. Calcitriol then circulates in the bloodstream where its primary role is control of calcium and phosphorus homeostasis. Important regulatory factors include 1,25$(OH)_2$D itself, which down-regulates its own production; parathyroid hormone; fetal growth factor 23; and serum concentrations of calcium and phosphate.[3]

The second 25(OH)D "pathway" is the autocrine pathway, which was discovered after scientists recognized that various cells of the immune system as well as many epithelial cell types, such as breast, colon, lung, skin, and prostate, are able to make 1α-hydroxylase and contain vitamin D receptors (VDRs). In these tissues, 25(OH)D is converted intracellularly to 1,25$(OH)_2$D which binds to the VDR.[4-8] Subsequently, in combination with tissue- and stimulus-specific proteins, 1,25$(OH)_2$D binds to one of more than 1000 vitamin D response elements on the chromosomes, inducing transcription of the corresponding proteins. These autocrine cells also produce vitamin D 24-hydroxylase which degrades excess 1,25$(OH)_2$D. This enables each cell to have the amount of 1,25$(OH)_2$D it needs when it needs it without the risk of excess 1,25$(OH)_2$D and concomitant hypercalcemia. Thus, in its autocrine mode of action, 1,25$(OH)_2$D can switch genes on or off in most tissues of the body by binding to the VDR. For the autocrine function, the principal input variable will be serum 25(OH)D, as circulating calcitriol levels are not usually high enough to elicit the full autocrine response. Instead, each tissue controls its own autocrine activation independently of other tissues, but is dependent upon an adequate circulating level of 25(OH)D.

Understanding that 1,25$(OH)_2$D has a wide range of biologic activity in addition to the classic endocrine pathway has led to recognition of its importance for general health. Studies suggest that vitamin D insufficiency plays a role in development of cancer, viral infections, multiple sclerosis, autoimmune diseases, hypertension, tuberculosis, diabetes, cardiovascular disease, musculoskeletal disorders, and asthma, as well as schizophrenia and depression. Unfortunately, this new knowledge has not been translated into improved vitamin D status. In fact, vitamin D insufficiency is highly prevalent across all age groups, geographic regions, and seasons.[9-11] Many factors are associated with low vitamin D status, including age-related decreases in cutaneous synthesis, low oral vitamin D intakes, obesity, use of sunscreen, and high degree of skin pigmentation.[9;10;12] The major reason for the current epidemic of vitamin D insufficiency is that many people do not get as much sunlight exposure as individuals did in earlier agricultural societies. It is important to emphasize the "vitamin" aspect of D as an essential dietary factor in those who do not obtain adequate sunlight exposure and to strongly promote adequate oral intake of vitamin D through fortified and natural vitamin D foods and with supplementation.

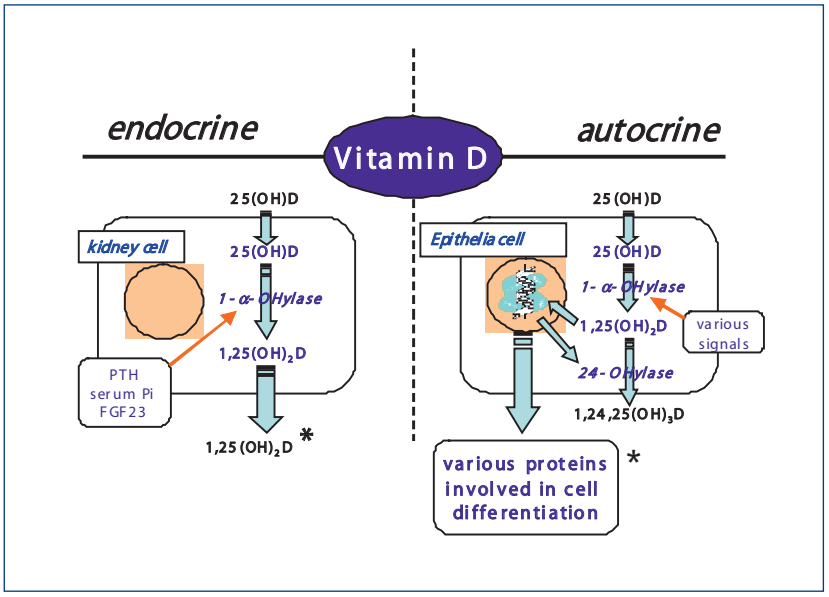

*Fig 1. Schematic depiction of the two pathways of vitamin D function. The principal outputs of each are designated by the symbol *. On the endocrine side, the stimulus to expression and action of the 1-α hydroxylase is typically PTH and FGF23, and the principal output is calcitriol (1,25(OH)$_2$D). On the autocrine side, the stimulus for expression of the 1-α hydroxylase will vary from tissue to tissue, and the principal output of the process (but not released from the cell) will be the proteins involved in signaling, e.g., cell differentiation and apoptosis.*

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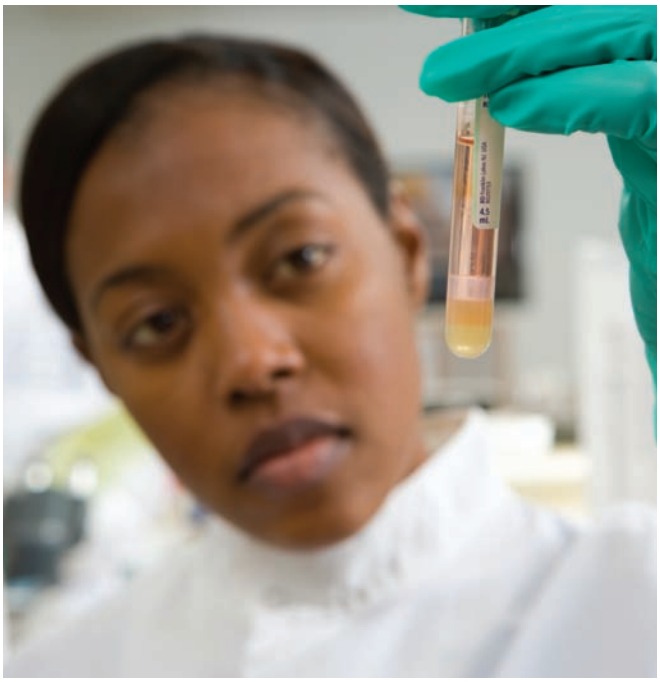
Vitamin D *The Missing Link in Automiunity*

Vitamin D has long been known to control calcium absorption from our diet and to manage the construction and maintenance of our bones and teeth. In the last decade we have discovered that many other cells outside of our bones are influenced by the presence of vitamin D. This is true of our immune system.

Our immune system has two basic functions, recognition and response. It must recognize the difference between normal and abnormal cells or proteins in your body, then either ignore them or respond to them. When a cell becomes infected, it no longer looks normal and the immune system comes to its aide. Bacteria that the body recognizes as foreign are attacked. Cancer cells do not look normal and a healthy immune system will destroy them as well. Old, worn out, or damaged cells are cleaned up and discarded and repair is stimulated, all by the immune system.



Your immune system learns most of these two basic functions between conception and your second birthday. Your mother's womb is a protected environment in which your immune system is introduced to all the developing cells and proteins in your body. It is also introduced to many of the proteins and small molecules from your mother's diet. The cells in your immune system, which are at the heart of this recognition, are called dendritic cells or D-cells.

D-cells are heavily influenced by vitamin D. When there is sufficient vitamin D present these cells cause the rest of the immune system to behave with tolerance to a given cell or protein. If there is NOT sufficient vitamin D present these cells lead the rest of the immune system in a defensive or inflammatory response toward a given cell or protein.

If your immune system, during the late stages of pregnancy or in the first year of life, does not have sufficient vitamin D present, it may not recognize or may not develop tolerance to a variety of normal proteins and cells in your body, including some of the bacteria in your gut, on your skin, and in your airways.

A lack of tolerance begins a progressive campaign by the immune system to eliminate those cells or proteins. This inflammatory process typically takes years and sometimes decades before you develop disease symptoms. Autoimmunity is when we have an inflammatory response to normal cells or proteins in our body. There are many autoimmune diseases that we know are influenced by vitamin D. In multiple sclerosis (MS), the target of your immune system is the covering of your nerves, the myelin sheath. Inflammation destroys this covering slowing or stopping nerve impulses. Patients can develop blindness, weakness, numbness, and even paralysis.

Research has shown that the further away from the equator that you spend the first 15 years of your life, the higher the risk for developing MS. Someone born in Minneapolis, Minnesota has 3-4 times the risk of developing MS as someone born in Miami, Florida. This higher risk is maintained for a lifetime, even if you move at age 16 to Florida. This suggests that sunlight and vitamin D early in life are important for normal immune system development.

A study from Harvard University on military recruits showed a 64 percent lower risk of developing MS with vitamin D levels above 40 ng/mL and in recruits under 20 years of age the risk reduction was more than 90 percent.

Type I diabetes mellitus (type I DM) is an autoimmune disease targeting the insulin producing cells in the pancreas of young children. The risk for type I DM, as with MS, is greater the further from the equator that you were born.

In Finland 40 years ago, it was public health policy to administer 2000 IU of vitamin D in the form of cod liver oil to newborn infants through their first year of life to prevent rickets. Research in 2001 showed that children who took their cod liver oil had an 80 percent lower risk of developing juvenile diabetes. Even more striking, the children who developed vitamin D deficiency rickets were three times more likely to develop type I diabetes.

Inadequate vitamin D during immune system development shortly before birth and during childhood plays a critical role in the development of autoimmune diseases. The symptoms of many of these diseases do not show up for decades after the errors in immune system development have occurred. Persistent vitamin D deficiency as we pass through adolescence and age related changes also influence our risk for development of a multitude of health problems including autoimmune diseases later in life.

The Centers for Disease Control and Prevention estimates that 60 percent of European Americans and nearly 100 percent of African Americans are deficient in vitamin D. A blood level of 25 hydroxy-vitamin D should be a part of all routine health examinations. For more information about testing and treatment go to www.vitamin-d.com

The Predictive Value of Vitamin D Status for Deaths due to Heart Failure, Sudden Cardiac Death and Stroke

Recently, several prominent meta-analyses have drawn attention to the benefits of maintaining adequate nutritional levels of 25-hydroxyvitamin D (25OHD). Autier et al demonstrated that daily intake of 300 to 2000 IU of vitamin D supplements was associated with lower total mortality rates[1]. Bischoff-Ferrari et al documented that maintenance of 25OHD above 30ng/ml was associated with optimal bone mineral density, lower extremity function and dental health as well as reduced risk of falls (in the elderly), fractures and colorectal cancer[2]. Both groups cautioned that the currently sanctioned intake levels of 200 IU and 600 IU for younger and older adults, respectively, are insufficient to maintain levels of 25OHD above 30ng/ml[1,3] and called for placebo-controlled randomized trials with total mortality as an endpoint to confirm their observations.

In follow up to the data regarding vitamin D status and risk of myocardial infarction in American men that were presented in the previous newsletter[4], we report here on several publications arising from the LURIC study[5], which involved a prospective cohort of German patients who were referred to coronary angiography between July 1997 and January 2000 and monitored for the subsequent eight years. This observational study was designed to investigate environmental and genetic risk factors for cardiovascular disease. In the current reports, the authors show a strong association between vitamin D status and several cardiac outcomes, findings that support the call for interventional trials of vitamin D supplementation.

The **LU**dwigshafen **RI**sk and **C**ardiovascular Health study involved 3299 patients who had been referred to a single tertiary care center in South-West Germany for coronary angiography. Inclusion was based on clinical stability (with the exception of acute coronary syndrome), availability of a coronary angiogram, and Caucasian ethnicity. Although the somewhat restrictive inclusion criteria limit this study's generalizability (excluding persons with low cardiac risk and non-white individuals), the criteria[6,7] do reduce the risk of confounding by non-cardiac factors that influence the distribution of 25OHD. Baseline parameters revealed a higher prevalence of female gender, diabetes mellitus, arterial hypertension, older age, lower physical activity, and impaired left ventricular function in groups with the lowest 25OHD levels (patients were stratified into four groups: <10ng/ml, 10 to 19.99ng/ml, 20 to 29.99ng/ml and >30ng/ml).

Prior publications from LURIC have demonstrated that low levels of 25OHD and $1,25(OH)_2D$ were independently associated with total, cardiovascular, and cancer mortality. During the 7.7 year follow-up period, there were 737 deaths, 463 of which were attributed to cardiovascular causes. Patients in the lowest quartile of 25OHD had higher risks of both all-cause mortality (multivariable-adjusted hazards ratios [HR], 2.08, 95% CI, 1.60-2.70) and cardiovascular mortality (HR, 2.22, 95% CI, 1.57-3.13), compared with patients in the highest 25OHD quartile[8]. Also, 25OHD levels were significantly correlated with markers of inflammation (CRP and IL6), oxidative stress (serum phospholipid and glutathione), and cell adhesion (VCAM1 and IAM1). These associations were independent of the presence of coronary artery disease (CAD), physical activity level, mineral metabolism variables, New York Heart Association (NYHA) functional class, and the Charlson Comorbidity Index. 95 patients died of cancer and the multivariable HR for individuals in the lowest (compared with the highest) 25OHD quartile was 2.22 (95%CI of 1.08-4.54)[9]. Levels of $1,25(OH)_2D$ were similarly associated with cardiovascular mortality, but not with cancer mortality[8,9].

To examine the predictive value of vitamin D status for deaths due to heart failure (HF), sudden cardiac death (SCD), and myocardial infarction (MI), follow-up analyses of the LURIC data were performed[10]. The authors accounted for seasonal variation by utilizing Z-values for 25OHD levels, calculated by standardizing the log-transformed 25OHD levels within each month. Raw 25OHD levels were lowest in February (median 12.9ng/ml) and highest in August (median 22.6ng/ml).

N-terminal pro-B-type natriuretic peptide (NT-pro-BNP), a marker of left ventricular (LV) dysfunction, HF, and overall cardiovascular risk[11], was significantly correlated with 25OHD (Spearman correlation coefficient of -0.19, $p<0.001$). After multiple linear regression accounting for age, sex, BMI, physical activity level, LDL- and HDL-cholesterol, triglycerides, diabetes mellitus, smoking status, arterial hypertension, eGFR, and CRP levels, NT-pro-BNP remained significantly associated with 25OHD. 25OHD levels decreased with increasingly impaired LV function as assessed by contrast ventriculography (ANOVA, $p<0.001$). During the follow-up period, 760 patients died: 116 due to HF, 188 due to SCD and 90 due to MI. In multivariable analyses accounting for CAD, ACE-inhibitors, diuretics, and beta blockers, in addition to the co-variates listed above, adjusted HRs were 2.84 for HF and 5.05 for SCD in patients with severe vitamin D deficiency (25OHD < 10ng/ml) compared to those with optimal 25OHD levels (> 30 ng/ml). The above findings remained significant after further adjustment for physical activity, suggesting that "reverse causality" or confounding by prevalent disease status was not the primary explanation for the results.

This is the first study to indicate that low vitamin D metabolite levels are independent predictors of SCD. Several possible mechanisms might explain the association of vitamin D deficiency with HF and SCD. Several genes that are up-regulated during the course of myocardial hypertrophy are suppressed with $1,25(OH)_2D$ treatment in rats.[12] Activation of systemic and cardiac RAS, which contribute to hypertension and cardiac hypertrophy, are reduced by 25OHD[13]. VDR KO mice exhibit both RAS activation, as well as myocardial hypertrophy and aberrant cardiac function.[132] Other data derived from rat models and patients with end-stage renal failure support these observations.[14,3154] Furthermore, $1,25(OH)_2D$ partially regulates myocardial calcium homeostasis through its effect on ion channels [167].

Vitamin D also appears to have anti-inflammatory properties, and these may contribute to reduced cardiovascular risk. Schleithoff et al demonstrated the anti-inflammatory effects of $1,25(OH)_2D$ in a double blind, randomized, placebo-controlled study of congestive heart failure patients[17].

It was significant to note that low vitamin D levels were not associated with either prevalent CAD or fatal MI. Pilz et al speculated that vitamin D status may be more important for the physiology of cardiomyocytes than for the coronary circulation. In keeping with this, the risk of the combined endpoint of death due to HF and SCD was higher for study participants without CAD than for those with CAD, which led the authors to speculate 'that vitamin D deficiency might be more closely related to the pathogenesis of 'non-ischemic' myocardial disease as compared to those with an ischemic origin[10]'.

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In another analysis of the LURIC data[18], the investigators examined the association of vitamin D status with deaths due to ischemic and hemorrhagic stroke (42 events). In unadjusted logistic regression analyses, odds ratios for stroke death were 1.72 (95% CI, 1.29-2.33, p<0.001) per increment in the 25OHD z-value, and 1.61 (95% CI, 1.23-2.13, p<0.001) per increment in the $1,25(OH)_2D$ z-value. After adjustment for age, sex, LDL and HDL-cholesterol, smoking status, BMI, CRP, eGFR, arterial hypertension, diabetes mellitus, NT-proBNP, physical activity, calcium levels, and parathyroid hormone levels, the odds ratios remained significant: 1.49 (1.03 to 2.17, p=0.032) for 25OHD and 1.39 (1.01 to 1.92, p=0.047) for $1,25(OH)_2D$.

Results from the LURIC study support the hypothesis that maintenance of optimal vitamin D status could reduce the risk of death due to myocardial disease. Vitamin D deficiency was associated with death due to HF, SCD, and stroke in patients referred to coronary angiography, even after adjustment for numerous potential confounders. Prospective, placebo-controlled studies of vitamin D supplementation certainly appear to be warranted.

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Q&A

Q: How long does it take to get enough vitamin D from the sun?

A: It depends on skin color, time of day and the season. A fair-skinned person getting sun exposure between 10:00 AM and 2:00 PM in summer months will get between 10,000 to 20,000 IU in 15 to 20 minutes.[1] This requires full torso exposure with no sunscreen. Someone with dark skin will need to spend six times that amount of time to get the same amount of vitamin D.

Q: My vitamin D test result came back with a number for D_2 and another number for D_3. How do I interpret those numbers?

A: If your vitamin D results are reported as a D_2 number and a D_3 number, they need to be added together to make a total value. The sum is your serum 25-OH vitamin D number.

Q: I drink milk everyday. What other ways can I get vitamin D?

A: Milk is fortified with 100IU of vitamin D per 8 oz glass. Key opinion leaders are recommending 4000IU to 5000IU a day for adults, which would require a great deal of milk consumption. Vitamin D can be found naturally in some foods like egg yolks and fatty fish. Sufficient vitamin D levels can be best met with appropriate sun exposure. Use of vitamin D supplements is strongly recommended in the winter months for people in northern climates.

Q: Where can I go to find some studies or articles regarding vitamin D and all the various impacts it has on disease? I asked my physician about getting tested, but she thinks it only important for bone health. Is there someplace I can go to find credible information I can show my doctor?

A: You can go to www.vitamin-d.com to find over 64 recent scientific studies and articles all in the area of vitamin d. Go to the "Vitamin D Resources" section.

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Are you D-Deficient?

NEW vitamin D website* helps you find out!

A new on-line quiz can help determine if you may be at risk for vitamin D deficiency. www.vitamin-d.com was recently launched to help fully understand this important hormone and its impact on overall health. Find the quiz at the bottom of the home page under the heading "What's your risk of deficiency?"

There is a plethora of media attention regarding vitamin D. Scientists and researchers have published literately hundreds of studies, all showing vitamin D's tremendous overall impact on the human body. It has become obvious that vitamin D goes way beyond the scope of preventing bone-related diseases.

www.vitamin-d.com was designed for clinicians, patient and laboratory professionals to provide a single, comprehensive source for information and updates regarding vitamin D. The section, "Vitamin D Resources", provides more than 64 links to current peer-reviewed articles on vitamin D's role in preventing cancer, autoimmune diseases and cardiovascular diseases. More and more, patients today are interested in the how's and why's of their own health and in working with their own doctors to determine the best course of individual treatments. The newly published data underlines the importance of testing vitamin D levels in their blood.

Physicians and patients can visit the "Vitamin D Forum" to join blog discussions and receive feedback from key opinion leaders in vitamin D research. Vitamin D topics include multiple sclerosis, cancer prevention, cardiovascular health, deficient populations, supplementation, daily intake levels, causes of deficiency, vitamin D testing, health benefits and vitamin D for infants and children.

Visit www.vitamin-d.com for the most comprehensive and up to date information on vitamin D along with the recent discoveries of its vast impact on our health. Use the "Spread the Word" link to pass this valuable information along to your friends, family and co-workers.

* Website contents subject to change.

TOTAL-D™, Total Me

Think you know the 'total' vitamin D story?

You probably know vitamin D is important for healthy bones, but did you know it is not actually a vitamin at all? In fact, it's a hormone that plays an important role in supporting our body's endocrine system, which helps regulate our metabolism, growth and development, tissue function, and mood.

Current research continues to recognize vitamin D for its ability to help prevent conditions like cancer, cardiovascular disease, autism, and diabetes. Vitamin D's health benefits come from its ability as a hormone to regulate over 200 genes in the body that assist in the prevention of disease.

Vitamin-D.com was created to help you fully understand this important nutrient and its impact on overall health. You can also find out more about LIAISON® TOTAL-D™, the only fully automated and FDA-cleared blood test that measures the two primary forms of vitamin D - your 'total-D' storage levels - in a single analysis.

To get started, take our quiz to determine your risk of vitamin D deficiency.

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