Vitamin D, Regulatory Hormone of Immunity and Inflammation – Implications in Chronic Infectious Diseases

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By
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What are the determinants of chronic infectious diseases

- Who gets infected? Who gets over it? Who gets exposed, but does not seem affected?
- What does a “diagnosis” of any disease really mean?
- Do treatment strategies and “protocols” have a scientific basis in individual cases with the same diagnoses?
- What defines the best approach in an individual with a given diagnosis?

Complex factors in disease expression

- Is the “primary” identified infectious agent (viral, bacterial, fungal, parasitic) the real culprit as we test and diagnose different “diseases”?

- What individual factors are un-modifiable (genetic) and what factors can we make reasonable changes in that increase success in treating, reducing, controlling or eliminating specific infections?

Common aspects that define response to infectivity or treatment success

1. Genetic variants –
   a. Polymorphisms – genetic variants in structure that affect functional expression
   b. HLA types that determine specific identities of self-non-self proteins or response to various similar proteins
   b. Genes from infectious agents incorporated into the genome that retain expression under variable conditions
2. Nutritional status of key nutrients that improve or reduce immune or endocrine functions
3. Xenotoxic compounds and environmental toxins (mold) that mimic or interfere with specific hormonal or immune receptors
4. The "Metabolome" or internal gut bacteria, viruses, yeasts and fungi and parasites
5. Past infections that have become chronic internal "load" on immune capacity
6. Mental status that may have positive or negative effects on immune or endocrine responses
7. Endocrine status

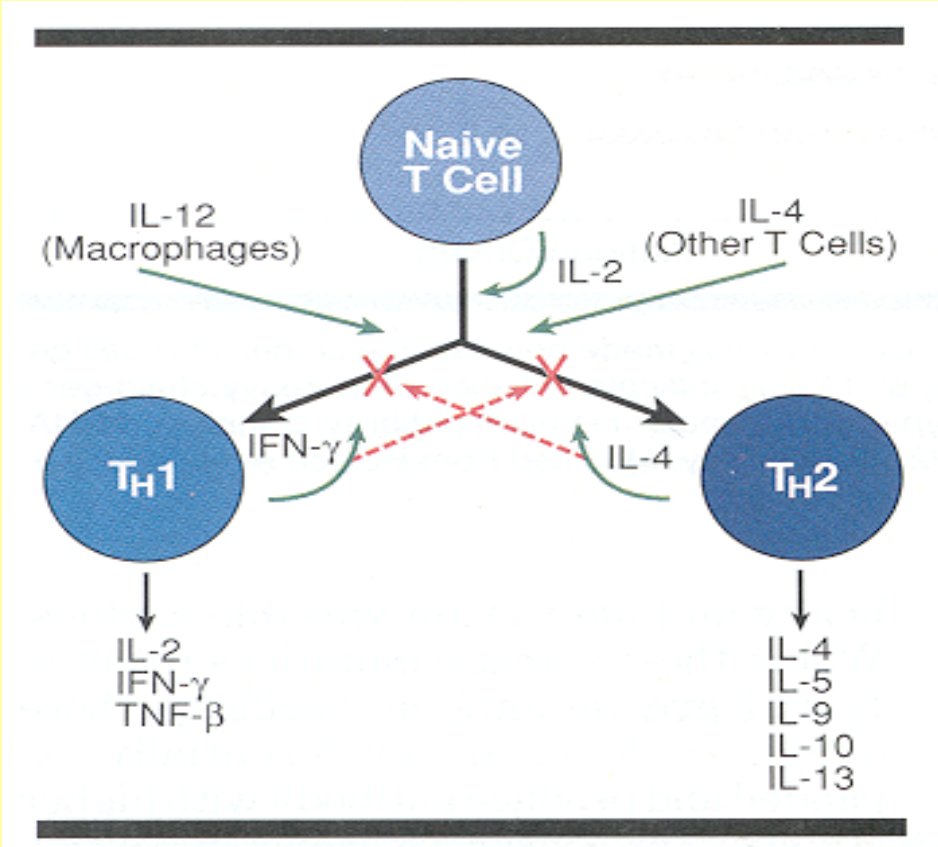
Basic responses to new infections

- Recognition of foreign invader by lymphocytes
- Release of pro-inflammatory signaling molecules – cytokines - that recruit other immune cells to attack, process and induce long term immunity
- The first response is called “Innate” immune response known as Th1 (T Helper cells) or cellular immunity
- The second response is called “adaptive” immune response know as Th2 or humoral immunity
- A third response involves auto-immune regulation to protect self from non-self invaders known as Th17 pathway

“Normal” Immune Responses

- Undirected, “naïve” lymphocytes are activated to differentiate into Th1 active lymphocytes to initiate the attack
- These lymphocytes release signaling molecules or cytokines that induce influx of macrophages to attack and “ingest” pathogenic invaders
- Additionally, they signal the development of Th2 lymphocytes to start the process of antibody formation and long term adaption and protection from future attack
- Th2 signally then down-regulates the initial innate Th1 inflammatory pathway
- When healthy immune processes are working properly, there is a balance established between Th1 and Th2 arms of the immune process and down-regulating of inflammation and overall immune activities as the “battle” against the invader is won.
- In chronic disease states, both Th1 and Th2 may be over-active

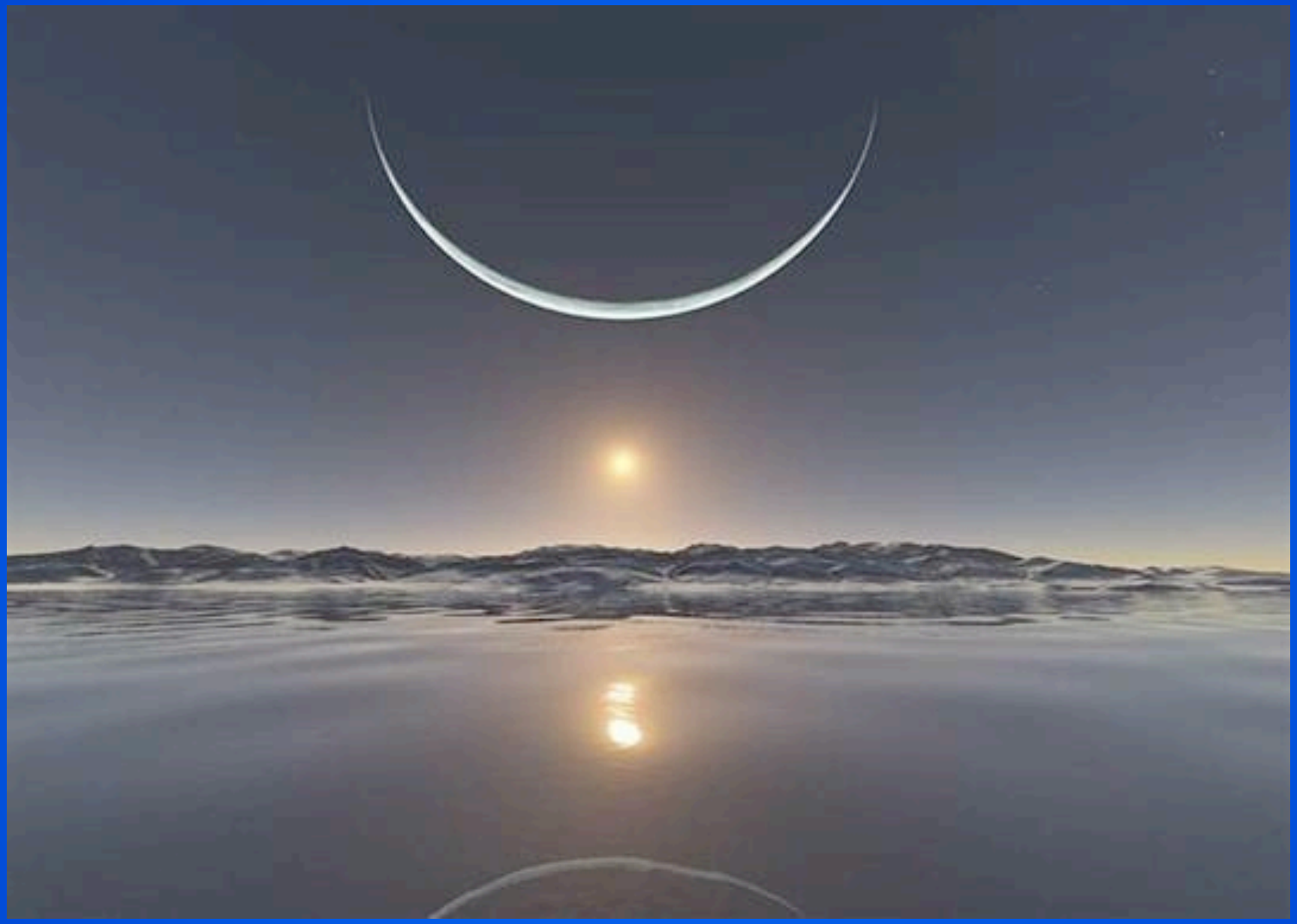
TH 1 and TH 2 Interactions



JAMA. 1997;278(22):1804-1814

Key Determinant of Immune Regulation
- Vitamin D -

- In my opinion, Vitamin D status is a major determinant for risk for infectious diseases and for successful immune response and treatment.
- It is the most powerful alterable health factor that is only now being recognized as a weapon in the treatment of many common infectious and autoimmune diseases
- I hope to shed some light on the subject, since some researchers and physicians prefer to keep their patients in the dark!



Some facts about Vitamin D

- Vitamin D is arguably the most common deficiency in populations living in the higher latitudes and it is not infrequently seen in the sunnier southern climates as well
- 70% of US citizens are deficient or insufficient in vitamin D and the proportion in Northern Latitudes is even higher, approaching 90% in my own patients.
- Individuals with lower vitamin D status are susceptible to common infections, such as influenza, HIV, and bacterial infections, such as TB, autoimmune diseases, such as MS, Type 1 diabetes, as well as cancer, heart diseases and neurodegenerative diseases.

Adams, JS, Hewison M. J. Clin Endocrinol Metab. 2010 Feb; 95(2):471-8.

Disease prevalence in Northern Latitudes

- Do individuals living in Northern Latitudes have a higher burden of occult or chronic viral and bacterial infections than those living in the South due to lower Vitamin D levels?
- It is interesting that the largest concentrations of Lyme disease are also in the Northern states.
- Is it possible that there is a higher incidence of Lyme disease in those individuals with lower Vitamin D status?
- Does the total "load" of past and chronic infections secondary to lower Vitamin D status increase the risk of acquiring chronic Lyme disease sequelae?

Aspects of Vitamin D

- Vitamin D and the Vitamin D receptors activate or modulate over 800 genes in humans and the list is growing.
- Therefore, vitamin D adequacy is important in almost every aspect of healthy cellular function in every tissue and every organ system.
- It is not surprising that Vitamin D is associated with so many disease processes and that lower levels are associated with most common diseases in man, from childhood through aging, including overall mortality.

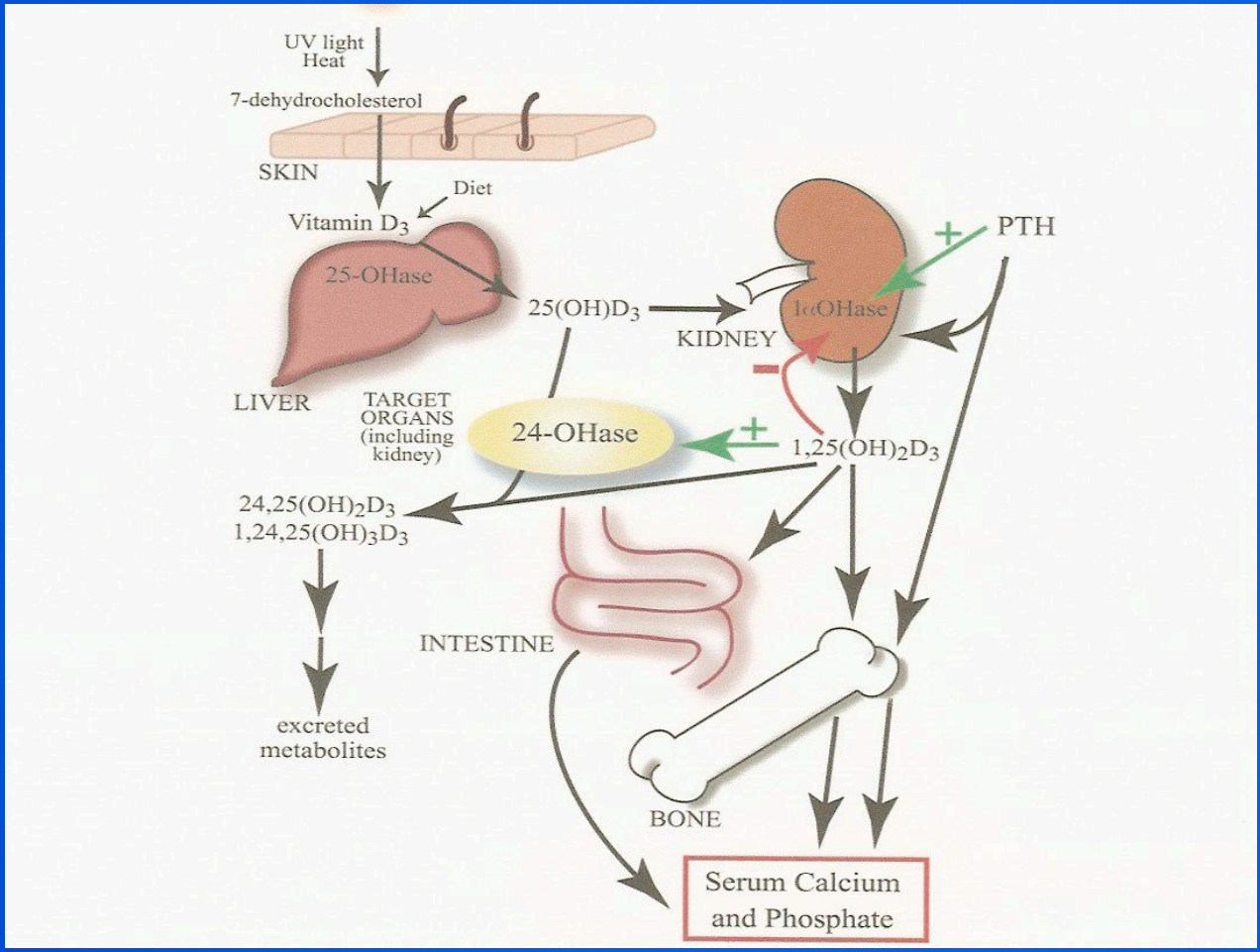
Endocrine Reviews 26(5):662– 687

Aspects of Vitamin D

- Vitamin D is not manufactured naturally in “Old World” primates, including man without sunlight (UVB) exposure.
- Many other species can produce their own Vitamin D, with or without sun exposure.
- Therefore, man is dependent on food intake or adequate UVB to keep tissue levels optimally saturated with provitamin D3 to make adequate 1,25D3, the active form in optimal amounts.
- If provitamin D3 is inadequate, optimal production of active 1,25D3 will also be inadequate.

Regulation of Vitamin D synthesis

Mol Endocrinol, May 2003, 17(5);777-791 , Sutton and MacDonald



1. UV light activates conversion of D2 to D3

2. 25 hydroxylase forms 25 (OH) D3 in liver

3. 1a hydroxylase in the kidney forms the active hormone 1,25 (OH)2 D3 (calcitriol) increased by PTH or low calcium

4. 24 alpha hydroxylase de-activates 25 (OH)D3 and calcitriol

Aspects of Vitamin D Activation

- Prohormone D3 - 25(OH)D3 is "activated" into 1,25D3 mainly in the kidney.
- Circulating levels provide adequate "active" D to tissues that may not be able to activate D locally.
- But many different tissues have the ability to activate 25(OH)D3 to make "active" 1,25D3 locally according to that tissue's immediate requirements.
- Vitamin D is metabolized both in the liver and within local tissues to "deactivate" this powerful regulator.
- Circulating 1,25 D3 levels do NOT represent full Vitamin D status or activity

Immune Regulation of Vitamin D

- Lymphocytes, macrophages, and microglia (immune and support cells in the brain) all have the ability to initiate the "Innate" Th1 immune response to invaders and to activate vitamin D.
- Interestingly, macrophages can activate, but cannot de-activate 1,25D3, sometimes seen in individuals with acute or chronic macrophage infection, (ie mycoplasma, TB) who demonstrate chronically elevated 1,25D3 levels
- Th1 lymphocytes turn on inflammatory cytokines that are integral to initiating immune processing and recruitment of other lymphocytes, macrophages and monocytes - all are involved in a successful immune defense.

Immune Regulation of Vitamin D

- 1,25 D3 down-regulates VDR and inflammatory cytokines in Th1 lymphocytes, but does not down-regulate ability to fight infection, rather it improves it.
- 1,25 D3 increases production of cathelecidins that improve intracellular destruction of pathogens
- Additionally, 1,25D3 activates the Th2 antibody producing lymphocytes, that through active feedback signaling turn down the Th1 lymphocytes balancing the response.
- All arms of the immune system, Th1, Th2 and Th17, may be up-regulated if vitamin D deficiency is present

The paradoxical effects of vitamin D on type 1 mediated immunity. Mol Aspects Med. 2008 Dec;29(6):369-75. Epub 2008 May 4. Cantorna MT, et al

Vitamin D induces natural intracellular antibiotics

- Throughout most live species, including many micro-organisms, natural antibiotics are produced to protect from other bacteria, viruses and fungal organisms.
- There are of two major types: the cathelecidins and the defensins; both are highly preserved throughout evolution.
- Interestingly, "Old World" primates, including man are the only species that require Vitamin D to induce production of these powerful protective defense mechanisms

Human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25-dihydroxyvitamin D3.
Gombart AF, et al. FASEB J. 2005 Jul;19(9)1067-77.

Immune Regulation of Vitamin D

- Without adequate prohormone D3, source for active 1,25D3, full immune response is reduced and Th1 inflammation may remain increased leading to a chronic "pro-inflammatory" state.
- Additionally, when 1,25D3 is activated, it increases activity of 24 hydroylase that increases metabolism of both prohormone D3 and 1,25 D3 to regulate activity
- In cases where prohormone D3 is already deficient, this makes deficiency worse!

Vitamin D and inflammatory Cytokines

- 1,25D3 down-regulates major controlling cytokines that activate the inflammatory cascade.
- Decreased Th1 lymphocyte production of TNFa,
- The major central regulating enzyme pathway is through NFKappaB that is modulated by many factors, including 1,25D3.
- Most inflammatory diseases have up-regulated NFKappaB activity.

Vitamin D Deficiency activates the autoimmune pathway

- Vitamin D is also a major regulator of the autoimmune system through Th17 signalling.
- With deficiency, regulatory T cells (Treg cells) cannot balance the activity of these active cells increasing autoimmune activity
- It is not surprising that in individuals with chronic lyme disease sequelae, that there is frequently the appearance or reactivation of common autoimmune diseases

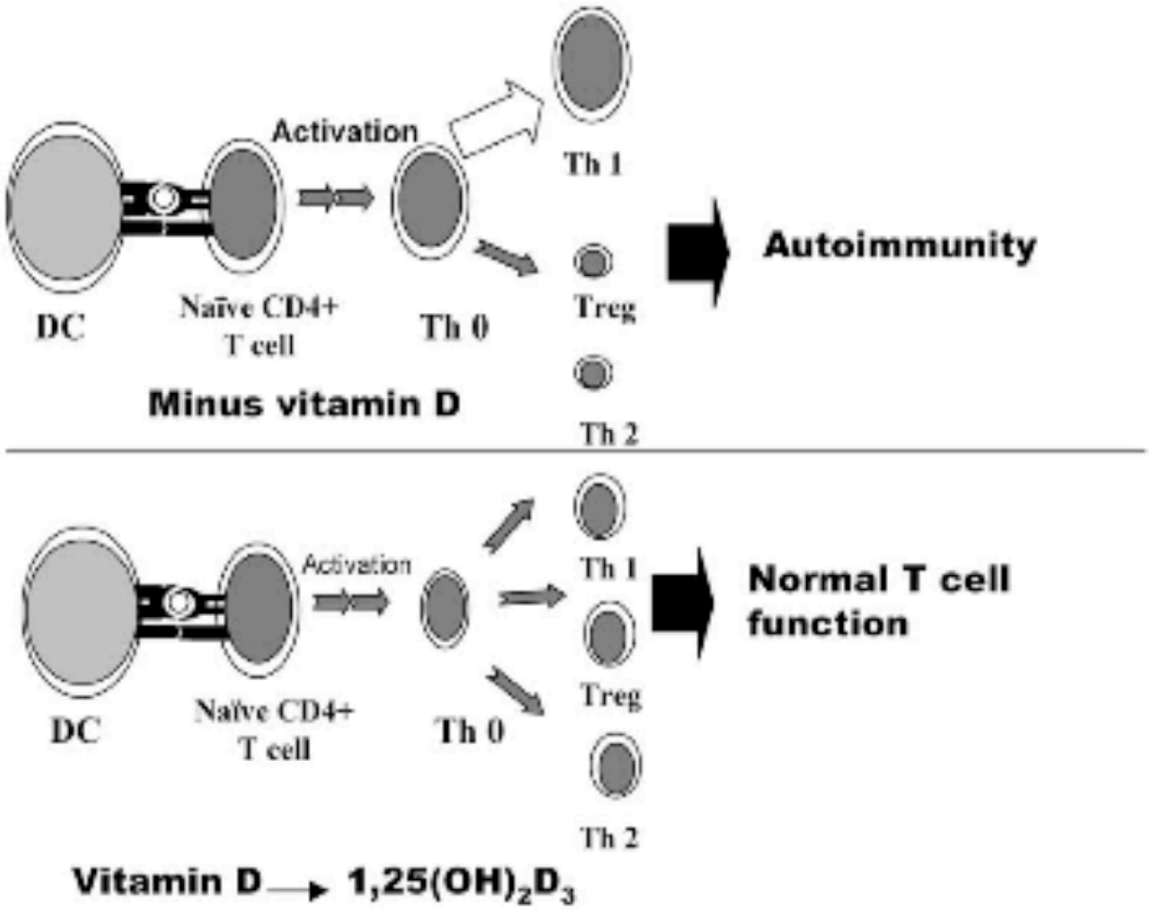


Figure 1. A model for the effects of vitamin D and 1,25-dihydroxy vitamin D_3 ($1,25[OH]_2D_3$) and T-cell development and function. The hypothesis is that vitamin D and $1,25(OH)_2D_3$ regulate T helper cell (Th1) development by inhibiting Th1 and inducing other CD4+ T cell populations, including regulatory T cells and Th2 cells. In the absence of adequate vitamin D, the immune system favors the development of self-reactive T cells and autoimmunity.

Cantorna & Mahon; Minireview - Mounting Evidence for Vitamin D as an Environmental Factor Affecting Autoimmune Disease Prevalence, Society for Experimental Biology and Medicine 2004

Complex infections may make things worse

- In some chronic infections, like TB and granulomatous diseases (Sarcoidosis), activation of 1,25D3 exceeds the limit for vitamin D Binding protein to “buffer” the circulating 1,25D3 and toxicity begins to be seen with elevated serum calcium levels.
- In these cases, additional prohormone D3 may add to the increased levels and worsen toxicity.
- If hypercalcemia is absent, additional prohormone D3 may increase effective immune response and lower 1,25D3 levels will be seen over time.

Genetic factors complicate the picture

- 1,25D3 is bound by Vitamin D Binding Protein (VDBP) that "buffers" its activity as it travels throughout the blood stream.
- 1,25D3 binds to Vitamin D Receptors (VDRs) in the membranes and nucleus of the cells to activate immediate or gene controlled activities
- Once activated, VDR triggers Vitamin D Response Elements (VDRE) that direct genes to be activated
- All of these activating factors have genetic variants that affect their efficiency and activities

Tissue-specific effect of VDR gene polymorphisms on the response to calcitriol. Alvarez-Hernandez D, et al; J Nephrol. 2008 Nov-Dec;21(6):843-9.

Genetic factors complicate the picture

- Since all functions of Vitamin D are mediated through these activating receptors, all functions of Vitamin D may be altered in individuals with weakened polymorphisms.

- Therefore, these individuals may be more susceptible to Vitamin D deficiency and require higher levels well above the “normal” intake of provitamin D3 to maintain optimal Vitamin D status.

What evidence is there that Vitamin D supplementation may be helpful in chronic infections

- Hippocrates recommended sun exposure as a treatment for many chronic diseases.
- Sun exposure in “Solariums” have successfully been used to treat TB before the development of anti-tuberculosis drugs.
- The Swedish government sends severe Psoriasis and arthritis patients to bath in the sun and float in the mineral rich Dead Sea in Israel.
- Sun exposure treatments have been recorded throughout medical history.

Treatment of TB with Vitamin D

- Rabb published results of direct anti-tuberculous antibiotic effects of Vitamin D in culture tubes.

- He described cases of TB empyema, the worst fatal form of TB given from 20,000 to 40,000 units of Vitamin D by injection into the lung empyema areas weekly with resolution of the empyema.
- Some patients were given 1.1 million units weekly without side effects

Vitamin D - Its Bactericidal Action

WALTER RAAB; 1946;12;409-415Chest

Chronic infection may inhibit Vitamin D activities on the immune response – a model for Lyme Disease

- Vitamin D increases macrophage phagocytosis of live M. tuberculosis bacteria in normals and increased the lymphoproliferative response.
- Individuals with chronic TB showed poor response to Vitamin D compared to normal controls.
- This inactivation of VDR is seen in many other infections.
- It is possible that higher doses of Vitamin D may over-ride this resistance?

Effect of vitamin D3 on phagocytic potential of macrophages with live Mycobacterium tuberculosis and lymphoproliferative response in pulmonary tuberculosis. *J Clin Immunol. 2004 May;24(3):249-57.Chandra G, et al*

VDR can be activated by higher levels of provitamin D3

- In tissue cultures, prostate cancer cell lines show down-regulation and differentiation with 1,25D3 and synthetic analogues, but achieving high enough doses runs risks of Vitamin D excess and toxicity.
- High concentrations achievable with high doses of D3 have equal effectiveness in controlling similar effects, but without the potential for toxicity.

Treatment of TB with Vitamin D

- In meta-analyses, some studies show little or no benefit from Vitamin D administration where others showed significant improvement.
- In the studies at higher doses (10,000 units daily), complete clearing is seen when used in conjunction with anti-TB antibiotics.
- In one study, the addition of L-arginine enhanced the beneficial effects of vitamin D

L-arginine and vitamin D: novel adjunctive immunotherapies in tuberculosis.
Trends Microbiol. 2008 Jul;16(7):336-44. Epub 2008 May 29. Ralph AP, et al

Vitamin D and Borrelia

- "Infection of mice with Borrelia burgdorferi (the causative agent of human Lyme arthritis) produced acute arthritic lesions including footpad and ankle swelling."
- "Supplementation with 1,25-dihydroxycholecalciferol of an adequate diet fed to mice infected with B. burgdorferi minimized or prevented those symptoms."

1,25-Dihydroxycholecalciferol inhibit's the progresssion of arthritis in murine models of human arthritis.
Cantorna MT, Hayes CE, DeLuca HF. J. Nutr. 1998 Jan; 128(1):68-72

Summary

- Vitamin D deficiency is frequently seen in Lyme disease and sequelae
- Genetic factors and infection itself may make individuals more resistant to Vitamin D treatments and require higher doses.
- Vitamin D is involved with all the major aspects of initial and chronic infections and inflammatory sequelae, including autoimmune diseases seen in these settings.
- There are no long term controlled studies yet done to establish effective Vitamin D doses and benefits, but anecdotal reports and my own experience and those of some of my colleagues suggests that higher doses, given in gradually increasing amounts improve patient status and disease outcomes.

Summary

- Vitamin D has many other benefits on healthy physiology beyond the immune enhancing aspects.
- Doses of Vitamin D3 should start at 1000 units daily and be increased with patient tolerance to 10,000 units and higher if needed.
- Some patients are intolerant to large dramatic increases in dose and require special care in adjusting doses.
- Some physicians are increasing doses to as high as 50,000 units daily for limited periods.

Summary

- Testing of 2(OH)D3 and 1,25D3, PTH and serum calcium should be performed before and during treatment in chronically ill patients to insure toxicity does not occur.
- Vitamin D toxicity requires both elevated 1,25D3 PLUS hypercalcemia; elevation of 1,25D3 alone is a normal response to chronic macrophage infection and may appear in cases with deficient levels of prohormone D3!
- Individuals with elevated serum calcium should NOT be given additional Vitamin D until other treatment lowers these levels to normal since VDBP is already saturated.
- Elevated serum calcium may reflect adrenal insufficiency that is frequently seen in these chronically ill patients.
- Other hormones should also be assessed and corrected with all patients, as endocrinopathies are frequently present.

Addendum

- All interested in key new information should join: “Vitamin D Council” for free e-mail updates run by John Cannell, M. D.

- See Lyme Times for Harold Smith’s, M. D. and my article on Vitamin D and Lyme Disease for more extensive discussion and references (coming soon)