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Vitamin D: the alternative hypothesis

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Abstract

Early studies on vitamin D showed promise that various forms of the “vitamin” may be protective against chronic disease, yet systematic reviews and longer-term studies have failed to confirm these findings. A number of studies have suggested that patients with autoimmune diagnoses are deficient in 25-hydroxyvitamin-D (25-D) and that consuming greater quantities of vitamin D, which further elevates 25-D levels, alleviates autoimmune disease symptoms. Some years ago, molecular biology identified 25-D as a secosteroid. Secosteroids would typically be expected to depress inflammation, which is in line with the reports of symptomatic improvement. The simplistic first-order mass-action model used to guide the early vitamin studies is now giving way to a more complex description of action. When active, the Vitamin D nuclear receptor (VDR) affects transcription of at least 913 genes and impacts processes ranging from calcium metabolism to expression of key antimicrobial peptides. Additionally, recent research on the Human Microbiome shows that bacteria are far more pervasive than previously thought, increasing the possibility that autoimmune disease is bacterial in origin. Emerging molecular evidence suggests that symptomatic improvements among those administered vitamin D is the result of 25-D’s ability to temper bacterial-induced inflammation by slowing VDR activity. While this results in short-term palliation, persistent pathogens that may influence disease progression, proliferate over the long-term.

Take-home messages

1. Prevailing theories of vitamin D are imprecise and suggest contradictory understandings of vitamin D metabolism.
2. 25-hydroxyvitamin D is immunosuppressive.
3. Supplementation of the secosteroid vitamin D temporarily alleviates signs and symptoms of chronic disease but leads to a long-term increase in morbidity.
4. Molecular biology suggests that low levels of 25-D are a result rather than a cause of the autoimmune disease process.
5. A microbiota of bacterial pathogens may survive in the human body by secreting proteins that antagonize the VDR and disable the innate immune response.
6. Elevated levels of 1,25-D exist at the site of disease and are an indication that the innate immune system is responding to an infection.

Keywords

25-hydroxyvitamin D (25-D), 1,25-dihydroxyvitamin D (1,25-D), vitamin D, antimicrobial peptides, VDR

1. Introduction

Some researchers claim vitamin D is immunosuppressive; others argue it activates the immune system. Advocates for vitamin D supplementation insist that various forms of the “vitamin” can be protective against chronic disease, but longer-term studies have failed to confirm these findings [1]. Even among those who support widespread supplementation with the substance, there is wide acknowledgement that the understanding of vitamin D metabolism is “imprecise”[1].

L.R. Karhausen wrote, "Actually, there is no experience of causation: events do not wear their causal credentials on their faces." [2] In this *Review*, we discuss how the understanding of vitamin D metabolism in chronic disease may be approaching "black box epidemiology." [2]

We hope to show that although vitamin D is currently viewed in a beneficial light, explanations for how it provides a benefit are simplistic and imprecise. We will address liabilities of the disease/deficiency model for vitamin D and summarize an alternative theory that, if valid, would necessitate rethinking systematic supplementation with vitamin D.

2. Black box epidemiology

Black box epidemiology is a focus on risk factors related to disease outcome without satisfactorily understanding pathogenesis[3]. This is the case with autoimmune disease, of which there remains widespread debate about what causes the majority of these common illnesses[4].

There are a number of examples of how incomplete understanding of the causative factors of disease can have unfortunate ramifications. Double-blind and/or randomized controlled trials (RCTs) - as recently as 15 years ago, erroneously showed women taking combined hormone replacement therapy (HRT) had a lower-than-average incidence of coronary heart disease (CHD). This led doctors to propose HRT was protective against CHD.

As it was learned, those with higher socioeconomic status were more likely to use HRT[5]. The increased incidence in CHD caused by HRT could have been mitigated by other factors also associated with elevated status: better medical care, healthier eating habits, etc. Although we don't know the mechanism by which HRT causes CHD, studies suggest, given its widespread use, tens of thousands of women died prematurely or suffered strokes or cancer. One commentary asked provocatively, “Is this the death of observational epidemiology?” [5]

RCTs are not without liabilities – especially not when an intervention generates a short-term benefit, but is harmful over the long-term. Multiple studies found the combination therapy of fenfluramine and phentermine (fen-phen) improved various physiological measures of health – raising HDL cholesterol, lowering triglycerides[6, 7] and reversing obesity over the short-term. Yet, when researchers finally gathered data on patients who had been taking the drug for longer periods of time, it became clear fen-phen caused pulmonary hypertension and valvular dysfunction[7].

The entire class of steroids seems to be especially problematic. The first-line treatment for many autoimmune diagnoses, the corticosteroid Prednisone, may temporarily reduce symptoms of disease, but long-term use dramatically increases the odds of disease relapse[8]. This finding, as we will see, may be true for the secosteroid 25-D.

3. The Vitamin D Receptor and the vitamin D metabolites

People obtain vitamin D through diet, supplements, and exposure to sunlight. Vitamin D₂ is found in plants and fungi and vitamin D₃ in meats. Vitamin D₃ is also produced endogenously when the eyes and skin are exposed to ultraviolet light. Both vitamins D₃ and D₂ are hydroxylated in the liver, becoming the secosteroid 25-hydroxyvitamin-D (25-D). Under hormonal control mechanisms, the enzyme 1-alpha-hydroxylase further hydroxylates 25-D into the main biologically active hormone/secosteroid, 1,25-dihydroxyvitamin-D (1,25-D). 25-D and 1,25-D serve as the native or endogenous ligands for the Vitamin D Receptor (VDR), a nuclear receptor found in immune and other cell types[9].

The VDR is responsible for transcribing 913 genes and probably many more[10]. Directly and/or indirectly, the vitamin D endocrine system regulates 3% of the human genome[11]. The VDR transcribes the beta-Defensin and cathelicidin antimicrobial peptides, broad-spectrum antibacterials which target pathogens[12]. When active, the VDR also transcribes TLR2, which recognizes gram-positive bacteria.

Recent vitamin D studies seem to address two broad observations regarding 25-D. First, serum levels of 25-D tend to be significantly lower in patients with autoimmune disease[13]. Second, subjects given vitamin D, even in controlled studies, often seem to have lower rates of autoimmune disease and fewer markers of inflammation[14].

These observations have led people to assume that supplemental vitamin D is beneficial, because it decreases inflammation and autoimmune disease symptoms. Therefore, many researchers suggest, some more strongly than others, that regular and systematic supplementation with vitamin D alleviates autoimmune disease[9]. We will call this view the deficiency/disease model.

However, these same observations can be interpreted differently. Low 25-D levels in autoimmune disease may be a result of the disease process itself, and the drop in inflammation among individuals taking the secosteroid may stem from its ability to slow immune function. We will call this view the alternate model. Efforts to determine which of these models is correct must examine how 25-D affects the VDR.

4. Liabilities of the deficiency/disease model

Vitamin D's mode of action at the molecular level remains a matter of debate among those who espouse the deficiency/disease model. Autoimmune diagnoses are widely explained to be illnesses in which the immune system and subsequently the VDR are overactive[15]. These researchers argue additional vitamin D calms the immune response, presumably by deactivating the VDR. Shoenfeld *et al* note, "Vitamin D has multiple immunosuppressant properties." [15]

In contrast, cancer, arteriosclerosis, and other inflammatory diagnoses are often characterized as illnesses in which the immune system fails to function adequately, suggesting decreased VDR activity. Such research theorizes that additional vitamin D activates the VDR after being converted into 1,25-D[16]. Researchers have even tried to treat cancer by inducing autoimmune disease[17].

Autoimmune diseases and cancers are not mutually exclusive. There is co-morbidity between the diseases, and they share some physiological biomarkers. People with the autoimmune diagnosis Crohn's disease are much more likely to get certain forms of cancer, including colon/colorectal cancer[18].

If a patient presents with both cancer and Crohn's, how can vitamin D alleviate symptoms associated with both diseases if it is expected to activate the VDR in one disease state and slow its activity in another? Thus, the deficiency/disease model for vitamin D metabolism leaves us without a clear model for how the secosteroid works at the molecular level and contradictory assumptions for how it exerts a beneficial effect.

5. Insights emerging from the molecular biology

Recent molecular and clinical research forms the basis for an alternate model of vitamin D metabolism, one that fully accounts for clinical observations in autoimmune disease. If valid, this theory significantly undermines any rationale for giving supplemental vitamin D to patients with autoimmune diagnoses. According to the alternative model, low levels of 25-D in patients with autoimmune disease are a result rather than a cause of the disease process. Secondly, the reduction in inflammation, clinical disease markers, and disease symptoms in patients taking supplemental vitamin D result from temporary suppression of the innate immune response.

As previously discussed, research indicates the VDR is ultimately a control system for the innate immune response. *In silico* simulations show that while 1,25-D possesses the residue necessary to agonize the VDR, 25-D does not (Figure 1)[19]. That the two main forms of vitamin D alternately activate or deactivate a receptor at the heart of several critical feedback pathways makes sense from an evolutionary viewpoint. Indeed, 25-D and 1,25-D share an almost identical affinity for the Receptor[19]. The body regulates the production of 1,25-D, and, in turn, the VDR, through a series of intricate and carefully controlled feedback pathways, mechanisms that belie the simplicity of the deficiency/disease model.

Understanding the alternate model for vitamin D requires an appreciation for how the human microbiota has evolved to slow the innate immune response in order to facilitate its survival. Molecular data shows certain members of the microbiota create ligands that block the transcriptional pathways set in motion by an active VDR[20].

Relatively little is known about the nine of ten non-human cells persisting in *Homo sapiens*; the genomes of only a fraction of such microbes have been sequenced. While some of these bacteria may contribute to well-

being, others may be pathogenic. Persistent and unique communities of microbes have been detected in subjects with diseases ranging from autism[21] to obesity[22].

The innate immune system responds to chronic pathogens by secreting cytokines and chemokines in an effort to clear them from the body. If it fails, the result may be a disease stalemate that accounts for the chronic inflammation observed in autoimmune disease. Furthermore, as the microbiota continues to dysregulate the VDR, transcription of key enzymes is thwarted. VDR production of CYP24A1 decreases, allowing 1,25-D to rise without a feedback system to check it. As the hormone/secosteroid rises above a normal range, it down-regulates, via the PXR Nuclear Receptor, the amount of vitamin D converted into 25-D[19]. This results in the low levels of 25-D characteristic of autoimmune diagnoses.

5.1 Explanation for effects of vitamin D supplementation

Substances capable of slowing VDR activity also reduce the innate immune response and subsequently the inflammation associated with bacterial death. Since 25-D antagonizes the VDR, it follows that as the secosteroid and bacterial ligands accumulate, the innate immune system is less able to effectively target pathogens - including those that may further dysregulate the VDR. In the short-term, cytokine and chemokine production by the innate immune system drops. Fewer endotoxins and less cellular debris are created by bacterial die-off, resulting in a decrease in inflammation and overall disease symptoms. Yet, over the long term, the pathogens at the heart of the disease process spread with greater ease. In this respect, the vitamin D in food and supplements is not unlike corticosteroids - substances that ameliorate disease symptoms in the short-term but exacerbate them over time.

We all can appreciate that the absence of disease symptoms is not necessarily the same as the absence of disease. The adverse effects of immunosuppressants sometimes take decades to be realized. Users of anabolic steroids, which are immunosuppressive,[23] feel well being and euphoria when taking the drugs. However, researchers have documented higher rates of cardiovascular disease in former users[24]. Use of corticosteroids, a first-line treatment for many autoimmune diagnoses, significantly increases relapse by a striking margin[8]. There are no studies that show that corticosteroids improve long-term prognosis in the treatment of illness. One author writes, "Remarkably, despite over 50 years of use, there is no proof of long-term (survival) benefit from corticosteroid treatment." [25]

According to the alternative model, true recovery from autoimmune disease involves an activated immune response and a corresponding spike in symptoms due to bacterial die-off - a phenomenon known as immunopathology[26]. Symptom exacerbation in the face of an activated immune response occurs in other diseases including AIDS, in which patients exhibit Immune Reconstitution Inflammatory Syndrome after beginning antiretroviral therapy aimed at targeting opportunistic infections. Syphilis, sarcoidosis[27], and a number of additional diseases[26] also induce immunopathological-type reactions during periods where the immune system succeeds in targeting chronic pathogens.

Consequently, if patients with autoimmune disease succeed in killing bacteria associated with their disease state, their symptoms should be expected to escalate, at least in the short-term, as cytokines and endotoxins are generated[28]. Conversely, in cases in which the immune response has been suppressed by supplementation with an immunosuppressant such as the secosteroid 25-D, one would expect to see fewer clinical manifestations of disease in the short-term, yet more advanced disease in the long-term. At a certain point, depending on the clinical symptom or physiological markers of disease, patients supplementing with vitamin D would be expected to approach a "crossover point" when additional reduction of the immune response is eclipsed by the advancing disease (Figure 2). This outcome has been demonstrated in longitudinal studies, with studies on sicker or older patients taking less time to realize the effect.

The Iowa Women's Health study showed vitamin D intake seemed to protect against breast cancer in the first five years after it was taken. However, the effect began to reverse between years five and ten and was completely lost after year ten, trending towards an opposing effect[29]. Lappe *et al* published work, conducted over four years, that seemingly showed vitamin D might lower the incidence of colorectal cancer[30]. In a similar study looking at a larger cohort and over a longer period of time, Rossouw *et al* found no such effect[31].

The arc of feeling better and then worse in patients supplementing with vitamin D is one that seems to play – depending on the extent to which the VDR is already blocked by bacterial ligands – over the course of twenty

years or more. After multivariate analysis, Payne *et al* found that long-term consumption of vitamin D was strongly associated with increased brain lesions in the elderly ($p < 0.001$)[32]. In another longitudinal study, Hyppönen *et al* found atopy and allergic rhinitis were higher in 31-year-old subjects whose parents gave them vitamin D as infants and children[33].

Strong support for the validity of the molecular data forming the backbone of the alternative model comes from an open-label clinical trial in which hundreds of patients with a variety of autoimmune diagnoses are reporting improvement and recovery after taking a VDR agonist and subinhibitory antibiotics over the course of several years[34]. Subjects in the trial avoid vitamin D in an effort to increase VDR activity and subsequently the innate immune response. The strength of their resulting immunopathology indicates that lowering vitamin D intake indeed allows the innate immune system to more effectively target chronic pathogens.

6. 1,25-D and inflammatory disease

It is often assumed that administering supplemental vitamin D will stimulate 1,25-D production. Many also believe 1,25-D can be raised to very high levels in patients with autoimmune disease without exacerbating the disease state. There are several problems with these assumptions.

First, 1,25-D is generally already well above a healthy range in patients with autoimmune diagnoses due to the inability of CYP24A1 to break down the active metabolite. Unfortunately, since most researchers test only 25-D when determining vitamin D status, this elevation is frequently missed. One recent study of patients with autoimmune diagnoses residing in cloudy Vancouver found that only 15 of 100 had serum values of 1,25-D below 110 pmol/L (46.2 pg/ml)[35]. Inappropriately high levels of 1,25-D, defined in another study as greater than 60 pg/ml, were likewise observed in 42% of patients with Crohn's disease[36].

Furthermore, even if 1,25-D levels could be elevated by supplementation in autoimmune disease, the hormone/secosteroid would be unable to effectively bind the VDR since receptor binding pockets are already blocked by bacterial ligands. The inability of 1,25-D to activate the VDR in patients with autoimmune illness is supported by data showing that many subjects with autoimmune disease who present with higher than normal levels of 1,25-D do not develop hypercalcemia[35]. Of the aforementioned cohort of 100 patients with autoimmune disease, 85 of which had high 1,25-D, none had signs of hypercalcemia. Oncologists have noted a similar effect in cancer. An active VDR has been shown to inhibit growth of cancerous cells and induce apoptosis in tumors[37]. However, some cancer researchers have suggested the VDR loses sensitivity to 1,25-D as the disease progresses[37].

Third, up-regulation of 1,25-D in disease, even without additional vitamin D supplementation, already interferes with transcription by other receptors. Molecular research shows that excessively high concentrations of 1,25-D interfere with numerous hormonal pathways by displacing native ligands from nuclear receptors such as PPAR-gamma and alpha, the glucocorticoid receptor, and the androgen receptor[38]. Since these receptors also express antimicrobial peptides, when 1,25-D reaches unnaturally high levels, the innate immune system's ability to eliminate pathogens is further thwarted.

7. Conclusion

Uncertainties resulting from epidemiological studies underscore the danger in recommending use of a substance when the exact manner in which it works to ameliorate disease is not fully understood.

Ioannidis wrote, "...for many current scientific fields, claimed research findings may often be simply accurate measures of the prevailing bias." [39] The literature has been nearly unequivocal in its support for vitamin D supplementation in autoimmune disease, but the factors dictating the autoimmune disease process are not empirically self-evident. In this case, it is possible that the statistical analyses and studies on which they are based are misleading, and a reassessment may be warranted.

Definitive mechanisms by which vitamin D protects against autoimmune disease have yet to be identified. Some argue that low levels of 25-D exacerbate disease and can be remedied by additional consumption of vitamin D. This explanation may be overly simplistic. Researchers are recommending vitamin D supplementation at historically unprecedented levels. Yet, by most measures, rates of chronic diseases that ought to be reduced by such supplementation continue to escalate.

A reconsideration of the deficiency/disease model is warranted. The alternative model is based on the growing possibility that persistent bacteria drive autoimmune disease. Under such circumstances, 25-D, which

inactivates the VDR, palliates symptoms over the short-term, but allows chronic pathogens to proliferate over time. If so, low 25-D in patients with autoimmune diagnoses is the result, rather than cause, of the disease process - further undermining any therapeutic benefit from vitamin D supplementation.

Fig. 1 The secosteroids 25-hydroxyvitamin D (yellow) and 1,25-dihydroxyvitamin D (purple). Note that although the secosteroids have nearly identical structures, 25-D lacks the extra hydroxyl group, serving to stabilize the helices of the VDR and activate it[40]. The two metabolites have nearly identical affinities for the VDR: 1,25-D has an estimated K_d of 8.48 while that of 25-D is 8.36.

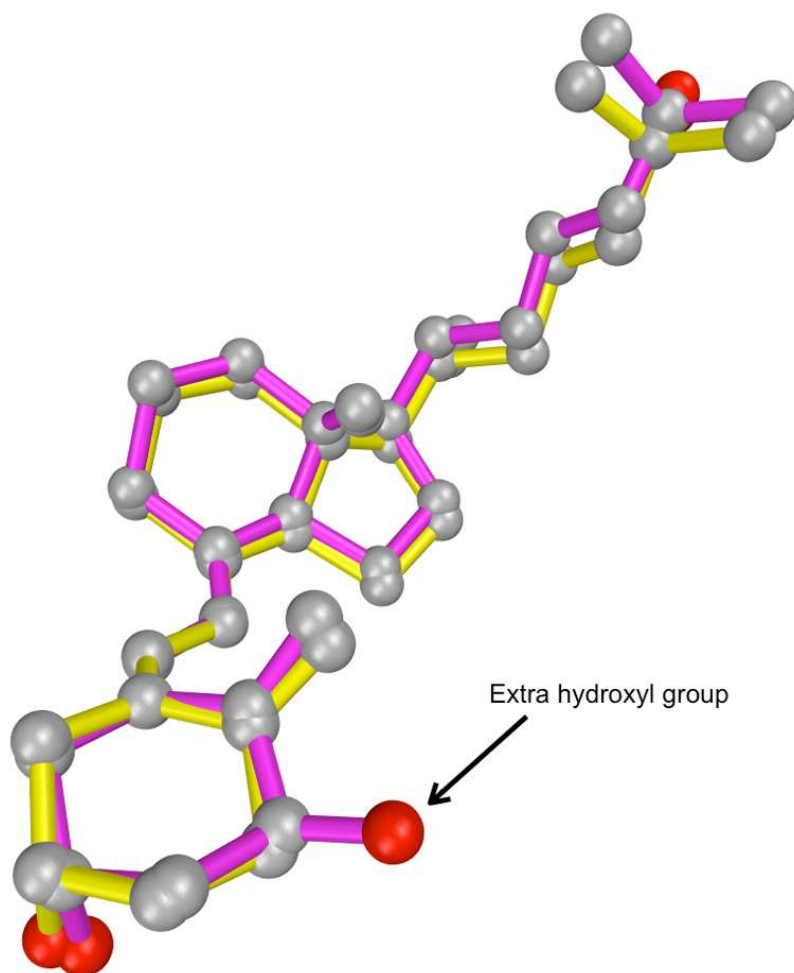
Fig. 2 *see attachment*

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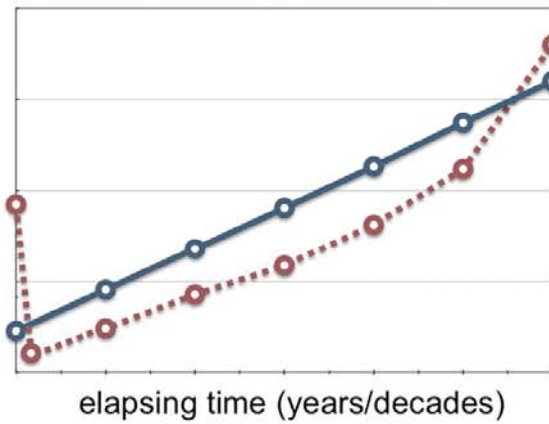
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1,25-D and 25-D as positioned when bound into the VDR ligand binding pocket



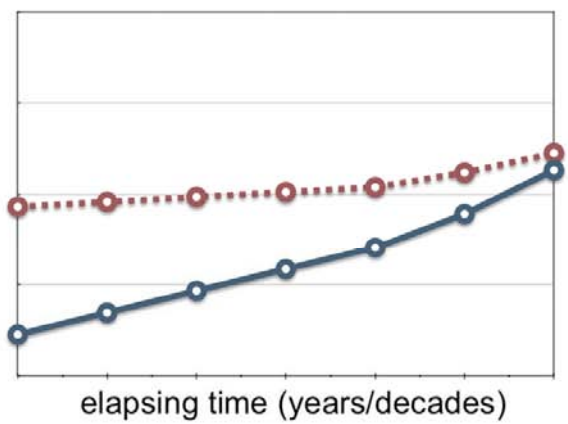
Depiction of effect of vitamin D on chronic disease

Regular supplementation w/ vitamin D



— Actual disease state
 - - - Symptoms & serum markers for disease

Without supplementation



Note: the more advanced the chronic disease, the less time it will take to show a negative clinical effect of vitamin D supplementation (years instead of decades).

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