Vitamin D and the Magic Mountain: The Anti-Infectious Role of the Vitamin

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Vitamin D status has become a "hot topic" in human nutrition.[1-7] In part, the concept of osseous and non-osseous effects of the active form of the vitamin underlies this expanded emphasis on vitamin D nutrition.

There are 2 mechanisms by which human beings acquire vitamin D: ingestion from the diet and synthesis after exposure to sunlight. The discovery that appreciable segments of human populations are vitamin D-deficient or -insufficient,[3,8] with the finding that essentially all human tissues contain a vitamin D receptor (VDR), has led to new interest in the vitamin D system and the mechanisms of its hormonal action.[1,2,4-6,9-15] Although the role of this secosteroid hormone on skeletal status has long been recognized,[6,11,16] recent and mounting evidence suggests that it affects immune function and can protect against cancer, cardiovascular disease, infection, and autoimmune disorders such as multiple sclerosis and type 1 diabetes mellitus.[2,6,11,14,17]

Vitamin D status is best assessed by measuring circulating 25-hydroxyvitamin D (25[OH]D) values.[1,4,5,10,12-15] Large population surveys, such as the National Health and Nutrition Examination Survey, indicate that substantial segments of infant, child, and pregnant women populations are vitamin D-deficient or -insufficient.[3,7,12,13] Parenthetically, the association of infection and vitamin D deficiency has long been noted, and some of these biologic effects were described more than a century ago, even before the concept of vitamins had been surmised.

Recently, it has been hypothesized that subjects' vitamin D status can be divided into ranges of serum 25(OH)D concentrations termed deficient, insufficient, or sufficient. One study defined 25(OH)D values <15 ng/mL as deficient, those 15 to 30 ng/mL as insufficient, and those >30 ng/mL as sufficient. Traditionally, a serum 25(OH)D value <10 ng/mL has been considered the cutoff point for deficiency.[2,18] A division into "deficient" and "sufficient" with a cutoff point of 20 ng/mL has been proposed, but many people have serum 25(OH)D levels this low.[1-7] These concentrations should be viewed as approximate guides to vitamin D status and may vary slightly with the season or latitude.

There can be concern about vitamin D toxicity from overdosing. Current guidelines from the Section on Breastfeeding and the Committee on Nutrition of the American Academy of Pediatrics recommend "that all infants and children, including adolescents, have a minimum daily intake of 400 IU (10 μg) of vitamin D beginning soon after birth."[19] Because of northern latitudes, the Canadian Paediatric Society recommends increasing vitamin D intake from 400 IU/day to 800 IU/day between October and April above the 55th parallel. These doses are felt to be safe and effective in preventing vitamin D deficiency.[19,20]

Although mineral balance is regulated by the calcium-vitamin D-parathyroid hormone (PTH)-endocrine system,[6] many of the non-skeletal effects of vitamin D appear to operate outside this tight feedback-controlled endocrine loop,[5,6,18,21,22] and thus are independent of regulation by serum calcium, phosphorus, and PTH levels.

Ultimately, our understanding of the complex clinical effects of the vitamin and implications of its insufficiency rests on 3 degrees of evidence. This is especially relevant for the immunomodulation roles of vitamin D and its skeletal effects. The first is observation and association, such as children with rickets are more likely to develop pneumonia or tuberculosis (TB) than children without rickets.[2,6,11,16] Second, on the basis of epidemiologic studies of defined populations, gradations of vitamin D status have clinical implications. For example, deficiency or insufficiency can be associated with infection after dental procedures, other infections,[2,6,9,11,15] or pneumonia.[16] Third, vitamin D and its metabolites operate at tissue, cellular, and nuclear sites[6,9,22] and likely alter immune function at a subcellular level.[21,22] Again, we now know more about the anti-infectious role of vitamin D; this level of function is not under the tight feedback control of the vitamin D endocrine system.[22]

The association of vitamin D with infectious disorders has actually been recognized for more than a century, but clinicians believed that infections caused rickets.[16,23-25] It is timely to examine infections during the epidemic of rickets that occurred from 1650 to 1930. This review will examine some of the infectious complications of vitamin D

$1,25(OH)_2D$	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
AMP	Antimicrobial peptide
BCG	Bacillus of Calmette and Guerin
IL	Interleukin
INFγ	Interferon gamma
LPS	Lipopolysaccharide
PTH	Parathyroid hormone
RXR	Retinoid X receptor
STAT 1α	Signal transducer and activator of transcription
TB	Tuberculosis
TLR	Toll-like receptor
TLR2/1L	Toll-like receptor 2/1 ligand
VDR	Vitamin D receptor

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deficiency with a historical perspective and the currently understood anti-infectious mechanisms of action of activated vitamin D. This story is still unfolding and forms a fascinating chapter in the story of vitamin D.

Historical Context

Circumstances in the social and geographical features of Glasgow, Scotland, in the late 19th and early 20th centuries provide a window into the full scope of rickets, which was common in Europe and North America. Not only was the prevalence of rickets high,[26] it was so common that it was actually difficult to find enough non-rachitic children to conduct clinical trials on the etiology of rickets in Glasgow.[27] In 1908, >1000 osteotomies were performed on rachitic children at the Royal Hospital for Sick Children.[26,27] The mortality rate from TB and pneumonia was approximately 30% to 40% higher in Glasgow and environs than in the remainder of Scotland.[26,28]

Glasgow sits at 55.858°N and has limited sunlight from October to April. It was also a large urban center for heavy manufacturing (iron, railway engine, and ship building), all fueled by coal and coke. Because of conditions of extreme crowding, the smog of coal fires, children living in some of the worst slums in Europe, and the high prevalence of TB and pneumonia, it was only natural to attribute rickets to infection caused by crowding.[25] However, there was also a great deal of crowding in the tiny plots and hovels (bothies) of Highland crofters in Scotland, where both rickets and lung infection rates were lower.[28] It is probable that children of crofters had greater sun exposure and ate some fish that contained vitamin D.

Why should vitamin D influence the occurrence or severity of infections? The concept of rickets as an infection was "seductive" and initially difficult to disprove.[23] The similarity of the conditions under which infections (eg, typhus and TB) occur contributed to this hypothesis.

An association between infection and the prototypical disorder of vitamin D deficiency, nutritional rickets, has its origins in observations from the 17th to 19th centuries.[6,11,18] Indeed, many clinical scholars of the 19th century postulated that infection actually caused rickets. Robert Koch sought an infectious agent as the primary etiologic factor of rickets.[16] Sir William Jenner, a founder of the Great Ormond Street Hospital for children, described the association of rickets with TB.[29] Howland and Holt, major scholars of rickets, noted that rachitic lung often was found to be interstitial pneumonitis.[30] However, by the mid 1920s, the concept of an "antirachitic factor" in cod liver oil was secure. Manville wrote that fat-soluble vitamin deficiency "leads to infections of the respiratory tract and very frequently [to] pyogenic involvement."[16] Fatal rickets often involved an infection as a factor in a downward spiral toward death. The infection hypothesis became less secure, and it was appreciated that it was vitamin D deficiency that led to infection. We need to understand how these anti-infectious effects occur.

Vitamin D as an Immune Modulator

In the past 15 years, we have sought mechanisms to account for the non-osseous effects of vitamin D. Vitamin D, particularly in its active form, $1,25(OH)_2D$, is appreciated as a secosteroid that functions as a gene transcription factor. After binding to a VDR, this complex is then translocated to an intranuclear site.[6,17] VDRs are found in >30 tissue types, including the heart, intestine, liver, kidney, lungs, and various immune cells, such as thymic and bone marrow T and B cells.[6,11,17] After binding of $1,25(OH)_2D$ to VDRs, a heterodimerization with a retinoid X receptor (RXR; eg, 9-cis retinoic acid) occurs, and after translocation into the nucleus and binding to DNA, the transcriptional regulation of >200 proteins occurs. These proteins not only influence calcium and phosphate homeostasis, but also cell proliferation, cell differentiation, and immune function.[6,17,21,31]

The various cells of the immune system—antigen-presenting cells (dendritic cells), macrophages, and T and B cells—express VDRs. This expression may be constitutive or induced post-stimulation.[31] Expression of 25(OH)D vitamin D 1α-hydroxylase (CYP27b1) is found in monocytic and dendritic cells after immune stimulus.[32] $1,25(OH)_2D$ appears to act on all immune-related cells.[6,22,31] This active form of vitamin D blocks dendritic cell maturation. In addition, $1,25(OH)_2D$ influences T cell gene expression of an impressive set of cytokines (interleukin [IL]1, lL2, IL I2, IL 17, interferon gamma [INFγ]) required for antigen presentation to T cells. Additional immunomodulating features include anti-proliferative and pro-differentiative actions, with both immune enhancement and suppression.[17,21] An effect of $1,25(OH)_2D$ action is to reduce activation of the acquired immune system, especially in dampening the development of or enhancement of autoimmune disorders (eg, multiple sclerosis or type 1 diabetes mellitus).[6,17,18,31,33] Treatment with $1,25(OH)_2D$ can also ameliorate either experimental or spontaneous autoimmune disorders in rodent models of experimental allergic encephalitis, nephritis, inflammatory bowel disease, and diabetes mellitus.[6,17,31,32] Epidemiologic studies in humans indicate that vitamin D intake early in life may reduce risk of type 1 diabetes mellitus, with risk reduction of 78% with 2000 IU/day.[32] Although these studies strongly suggest a role of optimizing perinatal and neonatal vitamin D status in the prevention of type 1 diabetes mellitus, randomized prospective trials are only now being conducted. However, examination of this vast array of immune disorders is beyond the scope of this review. Hence, we will focus on innate immunity and respiratory infections.

Influence on Innate Immunity

Although $1,25(OH)_2D$ action dampens the effects of activation of the acquired immune system relative to autoimmunity, this hormone has key actions that enhance the innate immune system.[6,17,21,33] The influence of vitamin D on innate immunity is dependent on tissue concentrations of

$1,25(OH)_2D$ and is regulated by 2 enzymes: the activating 25(OH)D 1α-hydroxylase (CYP27b1) and its catabolic counterpart, 25(OH)D 24-hydroxylase (CYP24).[6] The entry of 25(OH)D, the main substrate for CYP27b1 and CYP24, into the cell depends on 25(OH) binding to D-binding protein (DBP) and subsequent recognition, internalization, and intracellular release of this molecule.[17,33-35]

The innate immune system begins with the epithelial barrier between the bacteria abundant in the outside environment and the effectively sterile host. When bacterial products gain entry to the host, they are recognized by a class of receptors in the plasma membrane of macrophages known as Toll-like receptors (TLRs). These TLRs recognize a panoply of antigens, including nucleic acids, lipids, and peptides.[17,36] When bound, these TLRs recruit various adaptor proteins (eg, MyD88) that turn on signaling pathways, many of which terminate in the transaction of NFκB. This innate immune response is activated by antigens that result in up-regulation of the VDR and activation by $1,25(OH)_2D$.[37] The VDR promotes antigen processing, phagocytosis, and IL-1β and tumor necrosis factor α production,[21,36-38] which form the mechanisms by which foreign antigens are ultimately eliminated.

The macrophage is capable of accumulating 25(OH)D and locally producing $1,25(OH)_2D$. Adams and his group[21] have postulated this forms "a primitive, non-endocrine biological system designed to control immune responsiveness to invading antigens." They opine that this primitive immune system may phylogenetically pre-date the vitamin D endocrine system that controls divalent mineral balance, because $1,25(OH)_2D$ production is not feedback regulated by prevailing serum mineral concentrations.

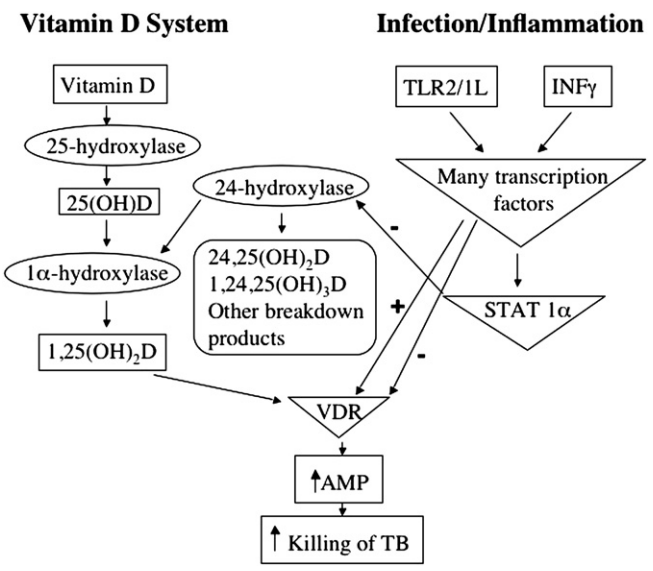

Figure. The vitamin D system in infection and inflammation. The left side shows normal metabolism of vitamin D. The right side shows the inflammatory pathways described in the text. Stat 1α down-regulates 24-hydroxylase (CYP24). After the binding of $1,25(OH)_2D$ to VDR there is an increase in AMP production (especially cathelicidin), with increased killing of *M tuberculosis*. Ligands that bind to TLR also increase AMP production. (Modified from Bouillon et al. Endo Rev 2008;29:726-76).

The metabolism of 25(OH)D to $1,25(OH)_2D$ as a local event appears to differ in the innate (macrophage) and acquired (dendritic cell) immune cells. The macrophage expresses CYP27b1, necessary for $1,25(OH)_2D$ synthesis, but not 25(OH)D 24 hydroxylase.[21] In part this is because infection/inflammation results in INFγ-induced STAT1α (signal transducer and activators of transcription-1α) activity, which down-regulates CYP24 expression (**Figure**).[17] Hence, $1,25(OH)_2D$ levels in the cell remain high. Activation of the TLR system in the macrophage can also work through this STAT1α pathway. This might explain why patients with an extrarenal macrophage or granulomatous source of active vitamin D lack the ability to down-regulate further synthesis of this molecule after exposure to exogenous $1,25(OH)_2D$. If macrophages in pleural effusions die and then leak $1,25(OH)_2D$ into the extracellular milieu (which results in increased calcium absorption by the intestine), these patients may become hypercalcemic and hypercalciuric.[39] As mentioned, there is no feedback regulation of macrophage vitamin D metabolism.

Activation by TLR type 2/1 ligand (TLR2/1L) binding results in vitamin D-dependent induction of fundamental antimicrobial peptides (AMPs). It also has been shown that IL-15 and IL-4 can stimulate macrophage differentiation, but only IL-15 can induce CYP27b1, resulting in VDR activation, and induce the synthesis of a specific AMP, namely cathelicidin.[40] It is theorized that 25(OH)D in sufficient concentrations within the macrophage can trigger IL-15-differentiated macrophages to induce specific AMPs that act against intracellular *Mycobacterium tuberculosis*.[21,38-40] IL-15 links TLR2/1-induced macrophage differentiation to the vitamin D-dependent pathway. Although IL-15 classically promotes differentiation and activation of lymphocytes (for example, NK, B and T cells) and induces T cell memory, it also activates monocytes/macrophages.[40] The picture that is emerging is that vitamin D acts through cytokine pathways to form defensins, endogenous AMPs that result in intracellular killing of organisms that have invaded the cell.[21]

As aforementioned, another aspect of inflammation and infection is that the up-regulation of CYP24 is hampered by INFγ-sustained STAT1α, which results in sustained elevated $1,25(OH)_2D$ levels and continuing production of AMPs.[17] This VDR-related action to combat infection may have an intracrine effect within the same cell or a paracrine effect on a neighboring cell.

TB is a prototypical infection that is influenced by vitamin D status[41] and by the innate immune response.[17,21,39,40] Macrophages stimulated by live *M tuberculosis* produce large amounts of $1,25(OH)_2D$. In particular, TLR1/2-primed macrophages kill *M tuberculosis*, whereas the bacterium survives inside TLR1/2-primed dendritic cells.[33] When macrophages are infected with fluorescein-labeled

BCG (tuberculosis vaccine—"bacillus of Calmette and Guerin") both cathelicidin and the organism are co-localized to the macrophage cell membrane.[22,33]

Consistent with these fundamental cellular mechanisms defining the importance of adequate 25(OH)D values is the finding that reduced serum 25(OH)D is associated with a higher risk for active tuberculosis, as discerned by meta-analysis.[41]

Vitamin D Status and Implications for Infection

The role of vitamin D status in innate immunity helps explain some of long-held views on the role of sunlight in the clinical course of TB. Both clinical observations and epidemiologic studies exist that show that *M tuberculosis* is suppressed by sunlight exposure and by habitation at higher elevations.[42] TB is more common in patients with rickets and vitamin D deficiency per se[6,22]; it is also more prevalent in dark-skinned individuals whose melanin blocks out the UV wavelength necessary for cutaneous vitamin D synthesis.[6,9] What is now understood is that innate immunity against *M tuberculosis* is influenced by serum 25(OH)D concentration, and the organism is killed by cathelicidin, synthesized after macrophage production of 1,25(OH)D.[33] Thus, in essence, the autocrine immune action of macrophages is positively influenced by vitamin D sufficiency.

The practice of treating subjects with TB in a sun-exposed open air mountainous location (a "sanatorium") has been impressively described in Thomas Mann's Nobel Prize-winning bildungsroman *The Magic Mountain* (Der Zauberberg).[43] A Nobel prize was given to Niels Finsen in 1903 for his observation that sun exposure was an effective treatment for cutaneous tuberculosis. We now understand the dual influence of high altitude, which has lower concentrations of ozone, an element that absorbs photons of light, and of sunlight, which results in greater photocutaneous synthesis of vitamin D. Higher serum 25(OH)D values are achieved per unit of time and more substrate is available for pulmonary macrophage synthesis of $1,25(OH)_2D$. This in turn enhances cathelicidin synthesis. In essence, the effect of sunlight exposure at higher elevation is to enhance innate immunity.

Epidemiologic evidence also suggests that vitamin D may be involved in the seasonality of influenza. In 1981, Hope-Simpson proposed that "a seasonal stimulus" for the onset of influenza was associated with a reduction in solar radiation.[44] It had long been known that clinical influenza is clustered during the winter regardless of the hemisphere. However, for the modern indoor worker, the extent of crowding does not differ by the season.[45] In experimental attenuated influenza infection in volunteers, a proof of hypothesis is that infection occurs predominantly in winter.[46] Recent epidemiologic evidence suggests that for many areas of the world, influenza occurs during the months after the winter solstice, when circulating 25(OH)D concentrations are their lowest, and disappears after the summer solstice.[47] This raises the question whether the seasonal decline in circulating 25(OH)D concentrations might represent the "seasonal stimulus factor" at latitudes above 40°, which is associated with increased case rates for influenza.[47] Recall that sunlight-related photocutaneous synthesis of vitamin D in late fall and winter is virtually absent at such latitudes.[6,9]

Vitamin D status appears to influence the risk of developing both upper and lower respiratory tract infections, including pneumonia. Clinical vitamin D deficiency was associated with a 13-fold increased risk of pneumonia in Ethiopian children younger than 5 years. [48] In Yemen, half the children admitted for lower respiratory tract infections were rachitic,[49] and 43% of children in Kuwait with rickets had pneumonia.[50] Subclinical vitamin D deficiency and non-exclusive breast feeding in the first 4 months formed a risk for lower respiratory tract infections in Indian children.[51] These reports from 1989 to 2004 are reminiscent of the high rates of pneumonia in rachitic children in Glasgow[23,25-28] and in the reports of Park and Howland.[16,30] Although it has long been presumed that vitamin D deficiency induces muscle weakness, especially of the diaphragm and intercostal muscles, which leads to impaired clearance of respiratory secretions and can lead to lower respiratory tract infections, the immunologic impairment of vitamin D deficiency is probably also important. Consistent with this idea is a recent study that showed that serum 25(OH)D levels are significantly and inversely associated with upper respiratory infection.[52] The percent of subjects with a recent upper respiratory infection and a serum 25(OH)D level <10 ng/mL was higher in winter than in summer. Controlling for all variables, serum 25(OH)D levels <10 ng/mL in patients with asthma were associated with 5.67 higher odds of upper respiratory infections compared with patients with asthma with levels >30 ng/mL.

Conclusion

The risk of respiratory infections, including TB, influenza, pneumonia, and other upper and lower respiratory tract infections, is much greater in children with vitamin D deficiency (serum 25(OH)D <10 ng/mL). This inverse relationship between vitamin D status (low in winter and high in summer) and infection is what was found when rickets was epidemic. Recent experiments have shed light on the immune-enhancing properties of vitamin D, especially involving innate immunity and localized monocyte production of vitamin D-dependent antimicrobial proteins (cathelicidin) that combat *M tuberculosis* and other infectious agents. The concept prevalent in the late 19th century that infections caused rickets can now be reversed, because mechanisms exist by which vitamin D deficiency leads to increased infection rates. ■

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