CHAPTER 11

Role of Vitamin D in Infection

Caitlyn Lee, DPM

Vitamin D is a fat-soluble vitamin that is primarily obtained from dietary sources, supplementation, and produced endogenously through exposure to sunlight. Moreover, vitamin D plays a pivotal role in promoting calcium absorption, mineralization of bone, and metabolism. It has other essential roles in the body as well, ranging from modulation of cell growth, reduction of inflammation, and is a key substrate in the immune system (1).

Vitamin D_2 and D_3 are two forms that are of importance for humans. However, these original forms are biologically inert and must undergo hydroxylation in the liver and kidneys, respectively in order to become active. First, vitamin D is converted to 25-hydroxyvitamin D [25(OH)D], known as calcidiol, in the liver. It is then further hydroxylated in the kidneys to form the physiologically active form 1, 25 dihydroxyvitamin D [1, $25(OH)_2D$], also known as calcitriol (2). The immune system promotes the formation of calcitriol through the use of monocytes, macrophages, and dendritic cells. In addition, calcitriol can be produced in other tissues such as the skin, colon, blood vessels, and pancreas (3,4). Calcitriol works on dendritic cells by inhibiting their maturation and aids in modulating helper T-cell function (5). Calcitriol works on the innate immune system through cathelicidin, which functions in chemotaxis, cytokine and chemokine production, cell proliferation, increasing vascular permeability and wound healing (6).

In its biologically active form, vitamin D is a very potent steroid and a key modulator of DNA transcription within the cell nucleus via VDRs, or vitamin D receptors. The role of VDRs is to modulate the production of Cathelicidin Antimicrobial Peptides (CAMPs) and β-defensins, which act as chemoattractants for neutrophils, monocytes and immune response cells (3). Regarding wound healing, vitamin D also regulates the expression of β-defensin, an antimicrobial peptide, which helps to inhibit microbial colonization on epithelial surfaces (4). Vitamin D also induces autophagy, a process by which a double-membrane autophagosome surrounds the organism before fusion with the lysosome occurs. Once phagocytosed, the organism or bacteria undergoes degradation and the nutrients are recycled (2). Calcitriol also activates monocytes to release hydrogen peroxide to help oxidative burst potential to kill bacteria.

Vitamin D drives mechanisms in adaptive immune response by affecting T-cells. Calcitriol primarily works on T-cells by facilitating the differentiation of T-cells to T-helper type 2 (Th2) cells and to a lesser degree T-helper type 1 (Th1). The Th2 cells impart a protective effect to tissue damage by producing anti-inflammatory cytokines, such as interleukin 4 (IL-4) and IL-5. Th1 produces proinflammatory cytokines like interferon-gamma (INF-ϒ), which activates macrophages and induces MHC molecule expression, which presents antigens to the T-cell receptor (2).

Vitamin D is recognized as a mediator of both the innate and adaptive immunity, it is important however to determine how this vitamin affects medical management of infectious disease. Although the treatment of vitamin D deficiency and insufficiency is well understood, the definition of the parameters varies and seems unclear. Serum concentration of calcidiol, 25(OH)D, is the best indicator of vitamin D status. It reflects vitamin D produced endogenously and obtained from food and supplementation (1). For example, the Vitamin D Council defines deficiency as 25(OH)D 0-40 ng/ml, the Endocrine Society defines it as <20 ng/ml, and the Institute of Medicine defines it as <12 ng/ml. Laboratory reference ranges are typically based on population averages and Quest Diagnostics defines the upper limit of normal as 100 ng/ml (7). Although there is not a clear consensus on what laboratory values clearly indicate vitamin D deficiency or insufficiency, these values provide a rough guideline on how to assess a patient's vitamin D serum values and treatment goals.

Vitamin D deficiency is considered an epidemic and can be attributed to many factors. However, there are common misconceptions. For example, melanin has been implicated as a factor that determines the amount of vitamin D3 that is photosynthesized in the skin. However, Matsuoka et al concluded darker skin pigmentation does not prevent the generation of normal levels of 25(OH)D. It has been noted that individuals with dark skin compensate for a low 25(OH)D level by rapidly converting it to the active calcitriol metabolite (7).

In addition, there is a misconception that clothing and the use of sunscreen can act as a barrier to vitamin D absorption. However, just a small area of exposed skin, such as the face or forearm for 10-15 minutes twice a week without the use of sunscreen supplies an adequate amount of vitamin D (7). Age also plays a role in the risk of developing vitamin D deficiency. The amount of the vitamin D3 precursor, 7-dehydrocholesterol, in the skin decreases up to 75% at 70 years old (8). Since vitamin D is fat soluble, and is sequestered in large body fat pools, obesity is associated with vitamin D deficiency (9). The Endocrine Society recommends treating vitamin D deficient patients with 6,000 IU of vitamin D2 or D3 daily until a serum level of > 30 ng/ml is achieved, then maintaining that level with 1,500-2,000 IU per day thereafter. Obese patients and patients

who suffer from malabsorption a higher dose of 6,000-10,000 IU per day is required, as well as an increase in maintenance dose of 3,000-6,000 IU per day (10).

Vitamin D deficiency has been shown to be a modifiable risk factor for Methicillin-resistant *Staphylococcus Aureus* (MRSA) infection and chronic ulcers. In a study conducted by Matheson et al, individuals with vitamin D deficiency had a statistically significant increased risk of MRSA nasal carriage compared to individuals with sufficient vitamin D levels when analyzed using an adjusted logistic regression controlling for age, race, sex, poverty, health status, hospitalizations within the past year, and antibiotic use in the past month (11). It has been shown that nasal carriage of MRSA increases the risk of invasive MRSA infection by 4 times (11).

Chronic ulcers have been found to have low levels of LL-37, the C-terminal fragment of cathelicidin, which plays a role in inducing epithelial proliferation as well as its antimicrobial activity. This antimicrobial property, unlike antibiotics, maintains broad-spectrum and resistance to most antimicrobial strategies. As stated before, a sufficient amount of vitamin D is essential for the production of adequate cathelicidin.

On a practical standpoint, achieving a replete state of vitamin D can decrease costs of treating infection. A study by Youssef et al, showed an increase in health care utilization and costs associated with MRSA and *Pseudomonas aeruginosa* infections with veterans who were vitamin D deficient compared to veterans who had sufficient vitamin D levels (12). It should be noted that it did not significantly affect the amount or duration of inpatient stays. Although the data support that sufficient vitamin D levels may be beneficial in fighting infection and lower cost of treatment, there needs to be more research studying how the treatment with vitamin D supplementation affects the outcomes and treatment of infection.

One study performed by Coussens et al investigated the immunomodulatory actions on vitamin D supplementation during the treatment of pulmonary tuberculosis (13). Individuals who took vitamin D as an adjunct supplement to anti-tuberculous therapy had accelerated sputum smear conversion, increase in lymphocyte count, and enhanced the suppressive effect of treatment on monocytes, inflammatory markers, and circulating concentrations of chemokines, AMP and Th1 cytokine responses. However, it also was found to weaken the suppressive effect of antimicrobial therapy on antigen-stimulated secretion of IL-4, leukocyte recruitment, and IFN-α secretion. More studies are needed to determine the effects vitamin D has on other infectious diseases and if the adjunctive supplementation of vitamin D would also be beneficial for treatment.

In conclusion, vitamin D deficiency is easily treatable with oral supplementation and sun exposure. Vitamin D in its active form, calcitriol, is a key modulator of both innate and adaptive immune processes, which may have a role in providing adjunctive therapy in infectious processes from systemic bacterial or viral infections to local wounds (14). While the role of vitamin D in the immune response is known, the use of supplementation as part of treatment has not been widely studied enough to prove its efficacy in treatment. However, research has shown that patients with normal vitamin D levels have better health outcomes, specifically lower cost of treatment as well as higher immune response rates, compared to vitamin D deficient patients. Thus, simple prophylactic measures such as assessing vitamin D levels yield better therapeutic outcomes for the patient as well as a decrease healthcare utilization costs for the physician and hospital.

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