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# *Sarcoidosis associated with Vitamin D deficiency?*

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One of the earliest pieces of evidence suggesting an immune-regulatory role of vitamin D came from the demonstration of 1,25-dihydroxy vitamin D ( $1,25(\text{OH})_2\text{D}$ ) production by the granulomas and activated macrophages culled from sarcoidosis patients. Later studies showed that vitamin D plays an important role in innate immune response to Mycobacteria. More recent observations reveal that hypovitaminosis D is associated with development and reactivation of tuberculosis. In addition, multiple sclerosis, autoimmune disorders and depression are associated with low vitamin D levels.

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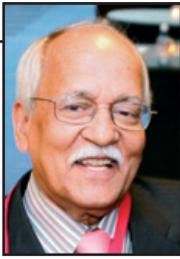
BY PROF. DR. OM P. SHARMA

**V**itamin D is abundant in nature. Vitamin D is ingested from the diet or synthesized in the skin (see figure 1). It is metabolized in the liver to a biologically inactive 25-hydroxy vitamin D ( $25(\text{OH})\text{D}$ ), the major circulating form of vitamin D. Through hydroxylation by 1 alpha-hydroxylase it is converted to biologically active 1,25-dihydroxy vitamin D ( $1,25(\text{OH})_2\text{D}$ ) primarily in the kidneys.<sup>1</sup> An immunomodulatory role for vitamin D was first proposed about thirty years ago. Adams and colleagues first showed that monocyte/macrophages from sarcoidosis patients synthesized the active form of vitamin D,  $1,25(\text{OH})_2\text{D}$  from precursor  $25(\text{OH})\text{D}$ .<sup>2</sup> About the same time, the receptor for  $1,25(\text{OH})_2\text{D}$  (vitamin D receptor, VDR) on proliferating lymphocytes was recognized. Vitamin D has two

functions: the hormonal function of regulating mineral and skeletal homeostasis and the evolutionary function of protecting the inside environment of the host. The latter is conducted by  $1,25(\text{OH})_2\text{D}$  cytokine, generated by monocyte-macrophage, interacting with VDR and modulating the innate immune system to deal with the invading microbes. Increased production of  $1,25(\text{OH})_2\text{D}$  by activated macrophages is a common finding in granulomatous inflammation.<sup>3</sup>

## **Vitamin D and granulomatous inflammation**

Throughout antiquity it was believed that patients suffering from tuberculosis improved in response to sunlight and good nutrition. In my medical school days, before the advent of isoniazid and other effective anti-tuberculosis drugs, one of my clinical duties was to make sure that every patient hospitalized on our tuberculous wards



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received a daily dose of cod-liver oil, a rich source of vitamin D, which was considered an essential part of tuberculosis therapy. This was indirect evidence of the protective mechanism of vitamin D. Liu and colleagues have offered a biochemical explanation for such a hypothesis.<sup>4</sup> These researchers have shown that the human macrophages pro-

duce large amount of the antimicrobial peptide cathelicidin (LL-37) which, when stimulated by TLR2/1L in the presence of 1,25(OH)<sub>2</sub>D, shows intense myco-bactericidal activity. Rook and colleagues observed that 1,25(OH)<sub>2</sub>D directly inhibited the growth of *Mycobacterium tuberculosis* in cultured macrophages.<sup>5</sup> Agerberth et al.

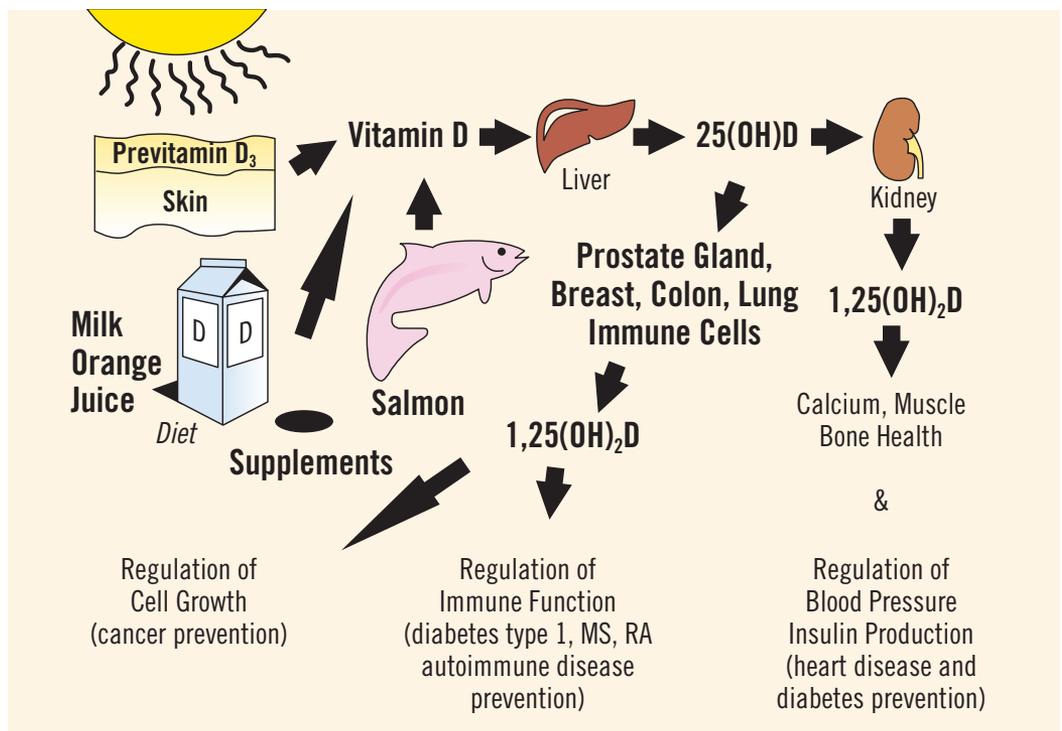


Figure 1. The process by which vitamin D is produced and exerts its biological effects is complicated, involving several vitamin D-related molecules.

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contend that the presence of cathelicidin mRNA in innate immune system may be relevant in persons who are susceptible to vitamin D deficiency.<sup>6</sup> Multiple studies now show that hypovitaminosis D is a risk factor for the development and reactivation of tuberculosis.<sup>7-10</sup>

### **Seasonal variability of tuberculosis**

Fares analyzed the current knowledge about seasonal variability of tuberculosis. The evidence suggests that the immune cell function and the number of some peripheral blood leukocytes subsets vary through the year. In this context, it is significant to know that seasonal variability in tuberculosis shows a peak notification rate in spring and summer. The natural killer cells and CD4 T-cells increase in winter associated with an increased level of Interleukin-6. This could be a reason for a better immune response against Mycobacteria in winter compared to summer, obviously not preventing infection, but allowing to control it in winter, whereas the infection later progresses to disease.<sup>11</sup> Moreover, these findings are consistent with the observation showing that the morbidity of tuberculosis is high in summer compared to winter. In contrast, in Western Africa, CD4 cells count were low in children in the rainy season (winter). That may give an explanation for a peak of tuberculosis notification in Cameroon during the winter season. These observations, however, remain controversial. Control of tuberculosis worldwide depends on our understanding of human immune mechanisms, which combat the infection. Acquired T-cell responses are critical for host defense against microbial pathogens, yet the mechanisms by which they act in humans remain unclear. T-cells, by the release of interferon- $\gamma$  (IFN- $\gamma$ ), induce autophagy, phagosomal maturation, the production of antimicrobial peptides such as cathelicidin, and generate antimicrobial activity against Mycobacterium tuberculosis in human macrophages via a vitamin D-dependent pathway. IFN- $\gamma$  induces the antimicrobial pathway in human macro-

phages cultured in vitamin D-sufficient sera, but not in sera with lower amounts of vitamin D. In vitro supplementation of vitamin D-deficient serum with 25(OH)D restores IFN- $\gamma$ -induced antimicrobial peptide expression, autophagy, phagosome-lysosome fusion, and antimicrobial activity. Thus vitamin D helps to overcome the ability of intracellular pathogens to evade macrophage-mediated antimicrobial responses.

### **Vitamin D and sarcoidosis and other interstitial lung diseases**

How do the findings observed in tuberculosis relate to sarcoidosis? Sarcoidosis occurs most frequently in the winter months, when vitamin D levels are low. Sarcoidosis is more prevalent in areas that are farther from the equator. The disease is also common in dark pigmented individuals, and is particularly high in African-Americans living in the southeastern United States, who have a higher incidence of vitamin D deficiency.<sup>12</sup> The factors that favor mycobacteria cause of sarcoidosis include the histological similarity between sarcoidosis and tuberculosis granulomas, reports of mycobacterial disease either existing before, during or after sarcoidosis, and the finding of mycobacteria in occasional granulomas of sarcoidosis. Passage experiments have also suggested that mycobacteria with the characteristics of Mycobacterium tuberculosis may be the incriminating agent.<sup>13</sup> It has been shown that mycobacterial ESAT-6 and kat-G are recognized by sarcoidosis CD4+ T-cells when presented by known sarcoidosis susceptibility allele, DRB1\*1101.<sup>14-16</sup> Drs. Drake and Bradley have summed up the prevailing knowledge of hypovitaminosis D as a risk factor for the development of sarcoidosis.<sup>17</sup> Kanchwala et al. report that cathelicidin mRNA is present in lower amounts in the bronchoalveolar lavage fluid (BALF) of sarcoidosis patients; it is much lower in patients with severe sarcoidosis as compared to patients with mild disease.<sup>18</sup>

## Management of hypovitaminosis D in sarcoidosis

Vitamin D deficiency is worldwide. In the United States alone vitamin D inadequacy occurs in about 36% of otherwise healthy adults and in up to 57% of general medicine patients, with even higher numbers in Europe.<sup>19</sup> Many of these patients are also likely to have sarcoidosis. Symptoms of vitamin D deficiency include muscle weakness, fatigue, and non-specific bone and body pains. Many of these features are common to patients with sarcoidosis with or without associated chronic fatigue and depression. As a constitutional symptom, fatigue is not reflected in lung function test results or other clinical parameters, but working in daily practice with sarcoidosis patients, it is important to take this symptom seriously. One way of assessing fatigue in clinical practice may be completion of the Fatigue Assessment Scale (FAS) in regular terms. Although many fatigue scales have been used, FAS is the only fatigue questionnaire validated in sarcoidosis patients.<sup>20</sup>

In a large population based study, depression and severity of depression were strongly associated with low serum 25(OH)D levels. It is essential to the overall general health and well being of sarcoidosis patients to have their serum 25(OH)D levels measured. Hypo vitaminosis D needs to be promptly corrected. Recently, Hagman et al. have reported a high prevalence of vitamin D deficiency in patients with interstitial lung diseases (ILD), particularly those with connective tissue associated ILD, and it is associated with reduced lung function. They suggest that vitamin D may have a role in the pathogenesis of connective tissue associated ILD.<sup>21</sup> Vitamin D seems to have a more likely role in granulomatous inflammation of sarcoidosis. While we wait for research on the topic, it is important for physicians to counsel sarcoidosis patients to ensure adequate intake in order to avoid chronic debilitating and harmful effects of Vitamin D deficiency.<sup>22</sup>

I routinely screen my patients with sarcoidosis for serum 25(OH)D and 1,25(OH)<sub>2</sub>D levels. The patients with serum 25(OH)D lesser than <30 ng/ml are offered vitamin D supplementation. Sarcoidosis patients who have hypercalcemia should be treated first for their high calcium levels and then their vitamin D levels be cautiously corrected (see also table 1).

*Table 1. Suggested therapeutic regimen.*

1. Ergocalciferol (vitamin D2) 50,000 units weekly for eight weeks
2. Serum 25(OH)D levels are rechecked at eight weeks with a target of 40 ng/ml
3. Once the targeted serum 25(OH)D levels are achieved, change to cholecalciferol (vitamin D3) and continue at 2000 IU per day
4. Levels of 25(OH)D are rechecked every four months

### Final reflections

Vitamin D is an important environmental factor in modulating innate immunity in tuberculosis, autoimmunity, multiple sclerosis and most likely in sarcoidosis. It is not known whether supplemental vitamin D will prevent or change the course of sarcoidosis. What is known, however, is that symptoms of vitamin D deficiency resemble many of the systemic manifestations of sarcoidosis. It is important to measure serum levels of 25-hydroxyvitamin D (25(OH)D) and 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) levels in all patients with sarcoidosis and then correct vitamin D deficiency when found.

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