Vitamin D and the Immune System

Shir Azrielant and Yehuda Shoenfeld

Department of Medicine B and Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer, Israel, associated with Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

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There is a growing interest in the effects of vitamin D on the immune system, both in its role with autoimmune diseases and in infectious diseases, especially chronic ones like tuberculosis.

The association between vitamin D and infectious diseases has been investigated for many years, albeit not always directly. As early as the 19th century, Dr. Niels Ryberg Finsen used light therapy to treat tuberculosis [1]. Although at the time the exact mechanism for the effect was not yet known, today it is mostly attributed to the synthesis of vitamin D in the skin in response to light exposure.

Epidemiological studies also support the association between the immune system's functioning and vitamin D. Deficiency of vitamin D has been previously linked to increased risk for *Mycobacterium tuberculosis (M. tuberculosis)* infection [2] and other respiratory infections [3]. The risk was attributed to compromised host defense mechanisms. Epidemiological studies also demonstrated the association between vitamin D deficiency and a risk for autoimmune diseases, including: systemic lupus erythematosus, multiple sclerosis, type 1 diabetes mellitus, inflammatory bowel diseases, and rheumatoid arthritis [4-7].

The role of vitamin D in modulation of the immune system is supported by the presence of vitamin D receptor on cells of both the innate and the adaptive immune system, including macrophages, dendritic cells, B cells, and T cells [4,8,9]. The effect of vitamin D on these cells has been studied extensively. In general, it seems that vitamin D stimulates innate immune responses and modulates adaptive immunity [10].

In the context of infectious disease, vitamin D seems to enhance chemotaxis, phagocytosis, and production of antimicrobial proteins [10]. Vitamin D was shown to enhance mycobacterial killing through a nitric oxide-dependent mechanism in mice infected with *Mycobacterium bovis* (*M. bovis)* [11]. Vitamin D also increased antimycobacterial activity against *M. tuberculosis* by inducing autophagy in human monocytes via cathelicidin, an antimicrobial peptide [12]. These findings were also supported in a newer study by Belyaeva and colleagues [13] that demonstrated reduced cathelicidin response associated with vitamin D deficiency in both infectious and autoimmune granulomatous lung disorders, including *M. tuberculosis* and sarcoidosis. All of these findings could contribute to the explanation of the above-mentioned results of Dr. Finsen's light therapy.

In the context of autoimmunity, many studies support the existence of an immunomodulating role of vitamin D, which has been shown to have an inhibitory effect on type 1 T helper cells (Th1), cells that have been previously associated with autoimmune processes, and specifically in organ-specific autoimmune diseases. Vitamin D also affects Th1 subsets of cytokines including interleukin-2, interleukin-12, interferon gamma, and tumor necrosis factor [14]. Vitamin D was shown to modulate the response of type 17 T helper cells, which also has a crucial role in various autoimmune conditions [15]. Moreover, some studies have suggested that vitamin D promotes an immunologic shift toward type 2 T helper cells (Th2), by increasing Th2 cytokines [10,14] as well as T regulatory cells [16]; however, there are conflicting reports on this matter, as some studies suggest vitamin D inhibits Th2 cytokines [17].

The effect of Vitamin D on the immune system can also be seen in B cells. In an in vitro study, vitamin D inhibited autoantibody production and secretion [18]. Finally, differentiation, maturation, and activity of dendritic cells seem to be inhibited by vitamin D treatment, resulting in increased tolerance in autoimmune conditions [19].

Based on the information presented here, it is not surprising that there is growing interest in vitamin D and its effects on different aspects of the immune system and the implications in treatment of both autoimmune and infectious diseases. Further investigations on this subject are needed and may also shed light on the role of vitamin D in the link between infection and autoimmunity.

Correspondence
Dr. Y. Shoenfeld
Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel Hashomer 5265601, Israel
Phone: (972-3) 530-8070
email: yehuda.shoenfeld@sheba.health.gov.il; shirazrielant@gmail.com

References

1. Allison RR, Mota HC, Sibata CH. Clinical PD/PDT in North America: an historical review. *Photodiagnosis Photodyn Ther* 2004;1 (4): 263-77.
2. Davies PDO. A possible link between vitamin D deficiency and impaired host defence to *Mycobacterium tuberculosis*. *Tubercle. Elsevier* 1985; 66 (4): 301-6.
3. Laaksi I, Ruohola J-P, Tuohimaa P, et al. An association of serum vitamin D concentrations < 40 nmol/L with acute respiratory tract infection in young Finnish men. *Am J Clin Nutr* 2007; 86 (3): 714-7.
4. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. *Ann Rheum Dis* 2007 66 (9): 1137-42.

5. Agmon-Levin N, Theodor E, Segal RM, Shoenfeld Y. Vitamin D in systemic and organ-specific autoimmune diseases. *Clin Rev Allergy Immunol* 2013; 45 (2): 256-66.
6. Rosen Y, Daich J, Soliman I, Brathwaite E, Shoenfeld Y. Vitamin D and autoimmunity. *Scand J Rheumatol* 2016; 45 (6): 439-47.
7. Azrielant S, Shoenfeld Y. Eppur Si Muove: vitamin D is essential in preventing and modulating SLE. *Lupus*. 2016; 25 (6): 563-72.
8. Mok CC. Vitamin D and systemic lupus erythematosus: an update. *Expert Rev Clin Immunol* 2013; 9 (5): 453-63.
9. Bhalla AK, Amento EP, Clemens TL, Holick MF, Krane SM. Specific high-affinity receptors for 1, 25-dihydroxyvitamin D3 in human peripheral blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. *J Clin Endocrinol Metab* 1983; 57 (6): 1308-10.
10. Mathieu C. Vitamin D and the immune system: getting it right. IBMS Bonekey. *Springer Nature*; 2011; 8 (4): 178-86.
11. Waters WR, Palmer M V, Nonnecke BJ, Whipple DL, Horst RL. Mycobacterium bovis infection of vitamin D-deficient NOS2−/− mice. *Microb Pathog* 2004; 36 (1): 11-7.
12. Yuk J-M, Shin D-M, Lee H-M, et al. Vitamin D3 induces autophagy in human monocytes/macrophages via cathelicidin. *Cell Host Microbe* 2009; 6 (3): 231-43.
13. Belyaeva IV, Churilov LP, Mikhailova LR, Nikolaev AV, Starshinova AA., Yablonsky PK. Vitamin D, cathelicidin, prolactin, autoantibodies, and cytokines in different forms of pulmonary tuberculosis vs sarcoidosis. IMAJ 2017; 19 (8): 499-504.
14. Boonstra A, Barrat FJ, Crain C, Heath VL, Savelkoul HFJ, O'Garra A. 1α, 25-Dihydroxyvitamin D3 has a direct effect on naive CD4+ T cells to enhance the development of Th2 cells. *J Immunol* 2001; 167 (9): 4974-80.
15. Joshi S, Pantalena L-C, Liu XK, et al. 1,25-Dihydroxyvitamin D3 ameliorates Th17 autoimmunity via transcriptional modulation of interleukin-17A. *Mol Cell Biol* 2011; 31 (17): 3653-69.
16. Jeffery LE, Burke F, Mura M, et al. 1,25-Dihydroxyvitamin D3 and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J Immunol* 2009; 183 (9): 5458-67.
17. Staeva-Vieira TP, Freedman LP. 1,25-dihydroxyvitamin D3 inhibits IFN-γ and IL-4 levels during in vitro polarization of primary murine CD4+ T cells. *J Immunol* 2002; 168 (3): 1181-9.
18. Linker-Israeli M, Elstner E, Klinenberg JR, Wallace DJ, Koeffler HP. Vitamin D 3 and its synthetic analogs inhibit the spontaneous in vitro immunoglobulin production by SLE-derived PBMC. *Clin Immunol* 2001; 99 (1): 82-93.
19. Penna G, Adorini L. 1α, 25-dihydroxyvitamin D3 inhibits differentiation, maturation, activation, and survival of dendritic cells leading to impaired alloreactive T cell activation. *J Immunol* 2000; 164 (5): 2405-11.

Capsule

A new anti-malarial drug

Malaria continues to be a scourge in much of Africa. Paquet and co-authors screened a small-molecule library against the human malaria parasite, *Plasmodium falciparum*, and identified the 2-aminopyridine chemical class as having potent activity. An optimized compound, MMV390048, was active against multiple parasite life cycle stages, both in the mammalian host and the mosquito vector, and killed drug-resistant parasites. MMV390048 killed the malaria parasite by blocking the parasite's phosphatidylinositol 4-kinase and protected monkeys from malaria infection. MMV390048 has potential as a new anti-malarial drug that may contribute to global malaria eradication efforts.

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Eitan Israeli

Capsule

Effect of disease activity, glucocorticoid exposure, and rituximab on body composition during induction treatment of antineutrophil cytoplasmic antibody-associated vasculitis

Wallace and collaborators investigated the relationships between glucocorticoid use, disease activity, and changes in body mass index (BMI) in patients with antineutrophil cytoplasmic antibody-associated vasculitis (AAV). They analyzed AAV patients enrolled in the Rituximab in AAV trial. Glucocorticoid use, BMI, and disease activity were measured regularly during the trial period. The authors performed mixed-effects regressions to examine the associations of time-dependent cumulative average glucocorticoid use and disease activity with changes in BMI over time, while adjusting for potential confounders. The mean ± standard deviation (SD) baseline BMI of the 197 patients enrolled was 28.8 ± 6.3 kg/m^2. Patients with newly diagnosed AAV tended to have a lower mean ± SD BMI than those with relapsing disease (28.0 ± 5.7 kg/m^2 vs. 29.6 ± 6.8 kg/m^2) and higher disease activity (mean ± SD Birmingham Vasculitis Activity Score for Wegener's Granulomatosis 8.7 ± 3.3 vs. 7.4 ± 2.7). The most significant change in BMI occurred during the first 6 months of the trial (mean ± SD increase of 1.1 ± 2.2 kg/m^2; $P < 0.0001$). Disease activity improvement, glucocorticoid exposure, and randomization to rituximab were each independently associated with an increase in BMI ($P < 0.001$ for all analyses). These findings suggest that changes in BMI, as well as glucocorticoid exposure, are independently associated with improvements in disease activity in AAV. Rituximab may also have effects on BMI independent of its impact on disease activity.

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Eitan Israeli

"Open your arms to change, but don't let go of your values"

Dalai Lama (born 1935) Leading monk of the Gelug school, the newest school of Tibetan Buddhism