Vitamin D: shining a light on autoimmune disease

"*Future large and well-designed prospective studies are urgently required to definitively demonstrate that low vitamin D levels increase the risk of autoimmune disorders other than MS.*"

KEYWORDS: autoimmunity ■ disease prevention ■ gene regulation ■ vitamin D

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Historically, vitamin D was thought to play a restricted role in calcium homeostasis, however, a wealth of studies now suggest that this hormone exerts more widespread effects, and as such, deficiency influences susceptibility to a wide range of conditions such as cardiovascular disease, schizophrenia and cancer [1,2]. In addition, both epidemiological and functional studies have shown that vitamin D plays a central role in the immune response, and is able to modify the risk and the course of infectious and autoimmune diseases [1,3].

Vitamin D production & deficiency

Vitamin D production is initiated in the skin where ultraviolet (UV) radiation converts 7-deydrocholesterol to previtamin D_3, which rapidly becomes vitamin D_3. This is then metabolized in the liver into 25-hydroxyvitamin D (25-OH-D) and subsequently in the kidneys (but also as we now know in several other cell types) into 1,25-OH-D, the active form of vitamin D [1]. Few foods contain vitamin D and the primary determinant of vitamin D levels is UV light exposure. It has been estimated that approximately 1 billion people worldwide are vitamin D deficient or insufficient. In addition, vitamin D levels seem to be decreasing with time [4]. The reasons for this widespread vitamin D deficiency are numerous. For example, during winter at regions of high latitude (e.g., >42 N), no UV of the right wavelength is available for vitamin D synthesis. Pollution, cloud cover, skin pigmentation and sun screen also influence the UV conversion of 7-deydrocholesterol. Increasing time spent indoors, cosmetic use and obesity (fat sequesters vitamin D making it unavailable for use) are likely to play a central role in determining the increasing burden of vitamin D deficiency [1,4–6].

Vitamin D & autoimmunity

■ Epidemiological evidence

Taken together, autoimmune diseases represent one of the most common disease groups in medicine today, affecting approximately 5–10% of the population in the developed world. Moreover, the overall incidence of these disorders seems to be increasing worldwide [7]. Ethnicity and region-specific genetic and environmental factors influence susceptibility to autoimmune disease (i.e., they are complex traits) and this is likely to happen in an interactive rather than additive manner. Thus, dissecting genes and the environment in autoimmune disease is a very challenging task. However, a number of epidemiological observations strongly suggest the involvement of vitamin D in these disorders. These include the observations that the prevalence of diseases such as multiple sclerosis (MS), Type 1 diabetes (TY1D), inflammatory bowel disease, rheumatoid arthritis (RA) and Sjogren's syndrome positively correlate with latitude and reduced UV light exposure [7–11]. Furthermore, immigrants to regions of temperate climate are at a higher risk of MS and systemic lupus erythematosus than their native countrymen [7,8,12,13] and, finally, several studies have shown that the risk of MS, TY1D, narcolepsy and celiac disease is higher among individuals born during spring and early summer [14–17].

These observations are obviously only suggestive of an involvement of vitamin D deficiency in autoimmunity but further support for this hypothesis comes from studies showing low serum vitamin D levels in patients suffering from a wide range of immune disorders including MS, TY1D, RA, systemic lupus erythematosus and inflammatory bowel disease [3,18–20] . These findings may be biased by reverse causation but

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are confirmed by the fact that vitamin D intake protects against the onset of MS, TY1D and RA [21–24]. Unfortunately, vitamin D intake is not a direct measure of serum vitamin D and only the risk of MS has been directly shown to inversely correlate with vitamin D levels prior to disease onset [25]. Future large and well-designed prospective studies are urgently required to definitively demonstrate that low vitamin D levels increase the risk of autoimmune disorders other than MS.

Functional evidence

Several functional observations demonstrate that vitamin D influences the immune system. Both the vitamin D receptor (VDR) and 1α-hydroxylase (the enzyme that converts 25-OH-D into 1,25-OH-D) are expressed in several immune cell types such as monocytes, macrophages, neutrophils, natural killer cells, dendritic cells and notably both B and T cells [19,26]. The range of effects driven by vitamin D is extremely wide and involves both the innate and the adaptive immune responses.

First, vitamin D helps the innate immune system during the initial reaction against bacteria, fungi, protozoa and viruses by increasing the expression of the antimicrobial peptide cathelicidin in neutrophils, macrophages and several other cell types [19,27].

Second, this essential hormone is also able to finely regulate the adaptive immune system. The most relevant vitamin D-mediated effects for autoimmune disease include: inhibition of the activity and proliferation of both Th1 and Th17 subsets, which are thought to play a major role in autoimmunity; decreased production of the proinflammatory cytokines IL-17, IL-23, IL-12, IFN-γ and increased expression of IL-5 and IL-10, which further shifts the T-cell response towards the Th2 subset; enhanced induction and functionality of $FOXP3^+$ regulatory T cells, which have been shown to be fundamental for the maintenance of peripheral tolerance; regulation of dendritic cell-mediated antigen presentation and T-cell activation by maintaining dendritic cells in a more tolerogenic and immature phenotype; and inhibition of B-cell differentiation and immunoglobulin production [19,28,29].

How does vitamin D exert all these effects? One way vitamin D signaling occurs is through binding by 1,25-OH-D to the VDR, which then binds specific genomic sequences (vitamin D response elements) and subsequently influences gene transcription. Using chromatin immunoprecipitation followed by massively parallel DNA sequencing (ChIP-seq), we showed the presence of 2776 different VDR elements throughout the entire genome bound by the VDR. Intriguingly, a striking enrichment for VDR binding sites was found in genetic loci associated with Crohn's disease, MS, RA, systemic lupus erythematosus, TY1D and other nonimmune conditions such as colorectal cancer and chronic lymphocytic leukemia [30]. These observations are likely to represent only part of the role played by vitamin D in gene regulation as both the binding and the functionality of the VDR–DNA complex are likely to be cell and stage-development specific.

Insight into evolution & disease prevention

In order to comprehensively understand the role played by vitamin D in human health, we must consider vitamin D deficiency from an evolutionary prospective. Man evolved in Africa with copious amounts of vitamin D; indeed depigmentation as we migrated out of Africa was an adaptation to increased vitamin D production, as pelvic deformities and consequent reproductive failure resulted otherwise [31]. Based on the data from the only longitudinal study of serum vitamin D levels and MS, a large proportion (~70%) of MS (and likely all other autoimmune diseases) cases in the USA and Europe could be prevented by increasing serum vitamin D levels to concentrations commonly found in individuals in sunny regions such as Africa. These levels could only be reached in most people in temperate climates by taking 1000–4000 IU/day of vitamin D_3, which is much greater than the daily amounts recommended by most governments. Although these doses of vitamin D are considered safe, confirmation of safety and efficacy in large randomized trials are being called for before any changes to recommended daily amounts are made. However, given the enormous benefit that prevention of autoimmune disease can have, we think the time to act is now.

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