VITAMIN D
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Vitamin D in autoimmune diseases

Davide Gatti, Francesca Pistillo, Giulia Bonasera, Giulia Zanetti, Valeria Messina
University of Verona, Rheumatology Unit

INTRODUCTION

That vitamin D cannot be considered as merely a vitamin related to bone metabolism is by now an established fact. Certainly, everyone knows that exposure to sunlight improves our state of well-being. The explanation for this cannot simply be reduced to the production of endorphins by keratinocytes exposed to UV radiation [1].

There is a great deal of historical evidence for the efficacy of heliotherapy, starting with the Nobel Prize awarded to Niels Ryberg Finsen in 1903 for showing the extraordinary and rapid therapeutic efficacy that exposure to sunlight had on tubercular skin lesions [lupus vulgaris] [2]. Therefore, vitamin D goes far beyond bone metabolism alone, which is also confirmed by the observation that essentially, the vitamin D receptor (VDR) is nearly ubiquitous in our bodies being particularly well represented in extra-skeletal tissues [3]. Furthermore, this receptor has also been found in yeasts and in animals with no skeletal or dental apparatus at all, such as lampreys [4]. Among the extra-skeletal actions of vitamin D, this review will focus on that relating to the modulation of the immune response.

The VDR is expressed by diverse cells of the immune system (both innate and adaptive). However, many of these cells (especially macrophages and dendritic cells) possess the full enzyme apparatus required to transform vitamin D into its active form, which will then act on the same cell (autocrine activity) or on neighbouring cells (paracrine activity) [5].

VITAMIN D AND IMMUNE CELLS

In recent years, the effect of vitamin D on immune cells has been studied a great deal. This research is summarised in Table I. Monocytes/macrophages play a key role in protecting against infection by producing proinflammatory cytokines. The binding of pathogenic components (bacterial, viral, or fungal) to toll-like receptors expressed on the surface of monocytes and macrophages induces the overexpression of VDR and of the CYP27B1 cytochrome, which is essential for the activation of vitamin D inside the cell. The intracellular binding of activated vitamin D [$1,25(OH)_2D$] with the VDR forms a heterodimer, which, binding to the DNA, induces the production of cathelicidin and β-defensins. Once these antibacterial peptides have been released at the extracellular level, they act by directly destroying the cell membranes of bacteria and viruses or by activating other innate defence mechanisms such as autophagy [6]. Dendritic cells act as antigen-presenting cells to T cells, thus triggering the adaptive immune response.

In the presence of the active form of vitamin D there is a downregulation of the Major Histocompatibility Complex Class II (MHC Class II) molecules and costimulatory molecules (e.g., CD40, CD80 and CD86), expressed on dendritic cells, resulting in less T-cell activation. This is also associated with an inhibiting effect on the production of the IL-12 and IL-23 proinflammatory cytokines (and thus also on IL-17) as well as stimulating the production of IL-10, which has an anti-inflammatory effect [6]. Once the T-cells are activated by antigen-presenting dendritic cells, they induce an antigen-specific immune response. Even T lymphocytes express both VDR and CYP27B1. It is interesting to note, however, that there are low levels of VDR in naïve T lymphocytes, with values that progressively increase, after their cellular activation. The effect of activated vitamin D [$1,25(OH)_2D$] is to:

- reduce Th1 differentiation
- reduce the production of inflammatory cytokines (IL-2, IFNγ and TNF-α)
- reduce Th17 differentiation
- promote Th2 differentiation
- promote the secretion of anti-inflammatory cytokines (IL-4, IL-5 and IL-10)
- promote the differentiation of regulatory T lymphocytes.

All these actions ensure careful modulation of the immune response and the prevention of its exaggerated activation [6,7], which is always possible, and which is the basis of autoimmune diseases.

Correspondence
Davide Gatti
davide.gatti@univr.it

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B lymphocytes in the immune system are the key players in the production of autoantibodies. These cells also express VDR and CYP27B1. In their case as well, vitamin D activation appears to have a predominantly regulatory role, which is achieved by both direct and indirect mechanisms.
The indirect mechanism occurs through the suppression of B-cell differentiation, proliferation, and antibody production by $1,25(OH)_2D$-treated T helper cells. Whereas the direct mechanism occurs through vitamin D's effect of suppressing B-cell differentiation and/or their maturation to memory cells and plasma cells [6].
If we consider the general action of vitamin D (in its active form) on the immune system (Table I) it becomes quite clear how the innate destructive capacity of the various pathogens is stimulated, whilst at the same time there is also a consensual modulation of the antigen-specific adaptive response. In fact, the role of the Th1 response is to amplify the inflammatory response which must in turn be somehow controlled by the Th2 response. It appears that vitamin D acts in favour of this type of "control". Interestingly, though the action of $1,25(OH)_2D$ is always inhibitory to lymphocyte cells, the degrees of inhibition are very different. There appears to be a marked inhibition of the cells that support and amplify Th1, Th17 and B cells, whilst the inhibitory effect seems be much milder on the cells that regulate the immune response (Th2 and T-reg cells). Hence, the end result, in the presence of adequate vitamin D levels, would be a "relative stimulation" of these latter cells resulting in an immunomodulatory action [7] (Fig. 1).

VITAMIN D AND AUTOIMMUNE DISEASES

Results from numerous epidemiological studies leave no doubt as to the high prevalence of vitamin D deficiency in subjects with autoimmune rheumatic diseases! Patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), systemic sclerosis (SS) and systemic lupus erythematosus (SLE) have circulating levels of 25-hydroxy-vitamin D [25(OH)D] at least 8-10 ng/mL lower than healthy controls [8].
The CARMA study [9] compared the vitamin D status of 2,234 patients affected by RA, PsA and AS with that of 667 healthy subjects with similar ages and found vitamin D deficiency [serum 25(OH)D < 20 ng/mL] in 40-41% of the patients compared to 27% of the healthy subjects ($p < 0.001$).

TABLE I.
Immunological effects (autocrine and paracrine) relating to the activation of vitamin D at the level of immune cells.

TYPE OF CELL	ACTION ON THE CELL	ACTION ON RELATED CYTOKINES
Dendritic cell 	– Inhibition of maturation – Inhibition of antigen presentation	– Inhibition of production: IL-12, IL-23, IL-17 – Stimulation of production: IL-10
Monocytes/macrophages 	– Increased differentiation – Increased bactericidal activity – Increased production of bactericidal substances	
T lymphocytes 	– Th1 response inhibition – Th17 differentiation inhibition – Th2 response induction – T-regs differentiation induction	– Inhibition of production: IL-2, IFNγ, TNF-α, IL-17 – Stimulation of production: IL-4, IL-5 and IL-10
B lymphocytes 	– Inhibition of proliferation – Inhibition of differentiation into plasma cells – Inhibition of antibody production	

Moreover, a correlation also emerged from the statistical analysis (albeit at the limits of significance) between vitamin D deficiency and the RA severity indicator (higher risk of ACPA positivity in RA patients with an OR = 1.45; 95% confidence interval (95% CI) 0.99-2.12 and p = 0.056) and with functional impairment from AS (higher risk of disease-related functional impairment with an OR = 1.08; 95% CI 0.99-1.17; p = 0.07) [9]. Despite the data available, it is still difficult to establish a cause-and-effect relationship between vitamin D deficiency and autoimmune diseases with any degree of certainty. In some animal models of autoimmune diseases, vitamin D was found to slow down their development and/or progression [10]. Instead, results from some observational studies in humans appear to be contradictory, whilst those concerning vitamin D supplementation of subjects with confirmed autoimmune diseases have been generally disappointing [10].
Hence at present, there is insufficient evidence supporting the possible efficacy of vitamin D supplementation in preventing the onset of autoimmune diseases. Long-term longitudinal studies performed in the general population would be required. Finally, this type of study has become available, and the results appear to be truly encouraging. The recently published VITAL study set out to investigate if vitamin D (whether or not associated with long-chain omega-3 fatty acids) can reduce the risk of autoimmune diseases.[10] This was a randomised, double-blind, placebo-controlled clinical trial conducted in the United States that involved 25,871 subjects (12,786 men ≥ 50 years and 13,085 women ≥ 55 years) who were followed for an average of more than 5 years. The randomised subjects were to take 2,000 IU of vitamin D (or placebo) and omega-3 fatty acids (1,000 mg/day) or placebo daily. By the express admission of the researchers who conducted it, the aim of the study was not to analyse the effects of vitamin D supplementation on a cohort of vitamin D-deficient subjects, but rather on a representative sample of elderly Americans in the general population. Then, the fact that subjects with a history of chronic kidney or liver disease, with hypercalcaemia, malignant tumours, cardiovascular disease, or other serious illnesses were excluded from enrolment, meant that only substantially healthy subjects were selected. Hence, it was no surprise that the number of subjects who developed

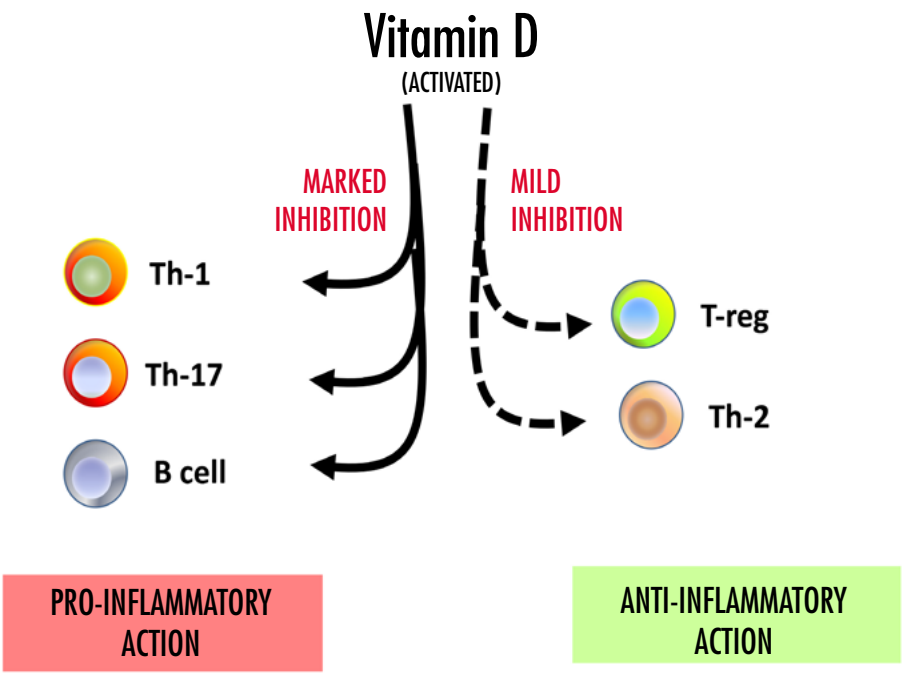

FIGURE 1.
Effect of vitamin D on adaptive immunity. Since the inhibitory effect is much more pronounced on the pro-inflammatory side, the final effect will be one of response control and modulation.

the autoimmune diseases considered in the course of the study was in any case small in absolute numbers (278 cases, which in practice, represents an incidence of new cases of just over 1%, over the five years of observation). The diseases considered were rheumatoid arthritis, polymyalgia rheumatica, autoimmune thyroid diseases, psoriasis, and inflammatory bowel diseases. However, there was in any case a field where clinicians could write in all other new-onset autoimmune diseases. The results showed that daily supplementation with vitamin D (for 5 years) with or without omega-3 fatty acids ensures a statistically significant 22% reduction in the occurrence of autoimmune diseases (with confirmed diagnosis).
The large amount of data made available by this study has permitted us to propose some very interesting considerations:

- compared to the placebo reference arm (placebo with vitamin D and placebo with omega 3 fatty acids) the significant risk reduction (again considering only cases with confirmed diagnoses) that emerged was only among those who had received vitamin D and omega 3 fatty acids together (OR = 0.69 with 95% CI 0.49-0.96: p = 0.03), or who had received vitamin D alone (OR = 0.68 with CI 95% 0.48-0.94: p = 0.02), but was not among those who had received omega-3 fatty acids alone (OR = 0.74 with CI 95% 0.54-1.03, p = 0.07 not significant);
- since autoimmune diseases develop slowly over time [11], an additional analysis was also included in the study, which excluded events that occurred during the first two years and considered only the last three years of the study. Even in this case, the group treated with vitamin D had a 39% reduced incidence of confirmed autoimmune disease compared to placebo (p = 0.005). Whereas the group treated with omega-3 fatty acid showed only a 10% reduction in new cases of confirmed autoimmune disease compared to placebo, which did not even achieve statistical significance (p = 0.54).

CONCLUSIONS

My conclusions are very much in line with those of the authors of this extraordinary study that I just presented here and with whom I agree completely. It is well known that autoimmune diseases are a group of heterogeneous disorders that often present similar pathogenetic mechanisms, accompanied by severe consequences in terms of both morbidity and mortality. Having for the first time clearly demonstrated how in a population of essentially healthy elderly subjects, constant daily supplementation of 2,000 IU of vitamin D (alone or in combination with omega-3 fatty acids) is able to reduce the incidence of autoimmune disease with more pronounced effects after two years, is of no small import. After all, this supplementation bears no risk of toxicity and is well-tolerated in the face of the total lack of treatments that are currently effective in reducing the incidence of autoimmune diseases.
I would hope that there shall soon be studies of similar quality investigating this preventive opportunity among younger subjects and perhaps among subjects at a higher risk of developing this type of disorder.

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