VITAMIN D
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VITAMIN D AND RHEUMATIC DISEASES

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Summary

Initially postulated by epidemiological studies, the existence of a relationship between vitamin D and rheumatic diseases has been broadly confirmed by many experimental and clinical studies. In general, the literature points to both a high incidence of hypovitaminosis D in patients with inflammatory/autoimmune rheumatic diseases and a correlation between disease activity/severity and vitamin D levels. Randomized controlled studies have tested the effect of cholecalciferol supplementation (versus placebo) in patients with rheumatic diseases: these have shown significant beneficial effects on both disease activity indices and some clinical outcomes. The complexity of the inflammatory/autoimmune rheumatic diseases and some methodological limitations of published studies to a considerable extent prevent us from making generalizations about cholecalciferol's therapeutic potential in these conditions. Nevertheless, data from preliminary studies, together with the safety and the low cost of cholecalciferol, strongly support the use of cholecalciferol in patients with these diseases, given also the potential beneficial effects on the bone metabolism.

INTRODUCTION

Traditionally, the two primary functions of vitamin D are regulation of calcium and phosphorus homeostasis and control of skeletal mineral metabolism, which are commonly defined as "skeletal effects" [1-3]. In this context, the effect of vitamin D on calcium homeostasis is important not only for bone health but also for some metabolic, cellular and neuromuscular functions.

In the last thirty years, some other functions of vitamin D have emerged, such its effect on the homeostasis/metabolism of many tissues and organs. These effects are usually defined as "extra-skeletal". It has been suggested that vitamin D has a role in cellular proliferation and differentiation, on the cardiovascular system and on the modulation of the immune system as well [1-3].

These "extra-skeletal effects", originally hypothesized on the basis of evidence from animal models [4], were subsequently confirmed by several epidemiological studies [5].

However, even though multiple and significant epidemiological studies have confirmed the correlation between appropriate levels of serum 25-hydroxy-vitamin D [25(OH)D] and a lower incidence of some pathologies, data from randomized controlled studies (RCTs) are quite heterogeneous and in some cases even contradictory [5].

The aim of this review is to describe the existing relationship between vitamin D and some inflammatory/autoimmune rheumatic diseases (IRDs) and to summarize scientific findings related to the benefits of cholecalciferol supplementation in IRDs.

VITAMIN D AND THE IMMUNE SYSTEM

Clinical observations and experimental data suggest that vitamin D plays a critical role in the modulation of immune system functions (6-8). Through its active metabolite – calcitriol [1,25(OH)2D] – vitamin D indeed seems to be able to affect the activity of most immune system cells.

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Conflict of interest
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Two observations support this hypothesis: [6-8]

- the vitamin D receptor (VDR) is expressed in most immune cells, including B and T lymphocytes, monocytes, macrophages and dendritic cells;
- some immune cells seem to be able to convert 25(OH)D to 1,25(OH)2D, the active metabolite that produces the final effect of vitamin D at the cellular level.

The modulatory activity of vitamin D seems to apply both to innate and adaptive immunity [6-8].

The role of vitamin D as regulator of innate immunity has been widely characterized [6-8]. Calcitriol is able to trigger the production of antimicrobial peptides from macrophages/monocytes and to increase chemotaxis, autophagy and immune system phagolysosome fusion. In addition, 1,25(OH)2D seems able to affect gut microbiota, to reduce intestinal permeability and, more generally, to "facilitate" the barrier function of tissues against pathogens [6].

Regarding the adaptive immune system, experimental data appear more heterogeneous, even while supporting an effect on the immune function [6-8]. Calcitriol seems capable of suppressing T helper 1 (Th1) activation and to modulate activity of Th2 cells (upregulation), Th17 cells (suppression) and Treg cells (function stimulation) [6]. Moreover, 1,25(OH)2D has proved to be able to reduce the proliferation and differentiation of B lymphocytes, causing less expression of autoantibodies [6-8].

In conclusion, even though available data are not always supported by solid scientific evidence, overall they seem to indicate that vitamin D may play a protective role against pathogens and in the reduction of inflammatory/autoimmune processes, phenomena that essentially require immunomodulatory action.

HYPOVITAMINOSIS D IN INFLAMMATORY/AUTOIMMUNE RHEUMATIC DISEASES

Epidemiological studies have unequivocally confirmed a high incidence of hypovitaminosis D in several IRDs. On average, patients with rheumatoid arthritis (RA), psoriatic arthritis (PA), ankylosing spondylitis (AS), systemic sclerosis (SS) and lupus (SLE) appear to have 25(OH)D values lower by at least 8-10 ng/mL compared to those of healthy control groups [9-14].

In a post-hoc analysis of the CARMA study (Fig.1) [9], the vitamin D status of 2,234 patients with RA, PA and AS was compared with that of 667 healthy subjects. Vitamin D deficiency (< 20 ng/mL) fluctuated between 40 and 41% in patients with RA, PA and AS and was found in 27% of healthy subjects (P < 0.001). These results are even more significant if we consider that the average age of the population was well below 60 years and that patients were treated with vitamin D supplements in varying percentages. In patients affected by RA – the group with the highest percentage of patients treated with cholecalciferol (42%) – the relationship between RA and hypovitaminosis D was particularly strong in the multivariate analysis as well (OR = 1.5 - 95% CI 1.1-2.0) [9].

The high incidence of hypovitaminosis D in patients with RA was clearly confirmed by a recent meta-analysis performed on 15 observational studies (1,100 RA patients and 1,000 healthy controls) [12]. The authors observed considerably lower average 25(OH)D values in RA patients compared to those in the control group and further found that deficiency was significantly higher in patients with RA (55% in RAs vs. 33% in healthy subjects; OR = 2.5 - 95% CI 1.1-5.3). Similar studies on patients with SLE or SS produced the same results [10,11,13,14].

Recently, Islam et al. conducted a review of several studies on the prevalence of hypovitaminosis D in patients with SLE [13]. In total they analyzed 34 studies (2,265 patients with SLE and 1,846 healthy subjects). The average 25(OH)D value in SLE patients was generally about 10 ng/mL lower compared to the control group. In the absence of appropriate vitamin D supplementation, the difference between SLE patients and the control group becomes particularly important in patients treated with hydroxychloroquine, corticosteroids or other immunosuppressive medications (average difference compared to healthy subjects: 16 ng/mL) [13].

Analogous results were found in another meta-analysis conducted on data regarding SS and hypovitaminosis D (6 studies, 554 SS patients and 321 healthy subjects) [14].

The standardized average difference between patients with SS and healthy subjects was about 9 ng/mL, with some variability linked to the characteristics of the SS.

HYPOVITAMINOSIS D AND INCIDENCE OF INFLAMMATORY/AUTOIMMUNE RHEUMATIC DISEASES

Even though the data described so far clearly indicate a relationship between hypovitaminosis D and some IRDs, they are unable to define a cause-effect relationship. In other words, these data do not clarify the possible pathogenetic link between prolonged 25(OH)D deficiency and disease onset.

In the case of vitamin D, it is difficult to establish a cause-effect relationship: to do so would require long-term longitudinal studies performed on the general population. In this context, then, data regarding IRDs incidence

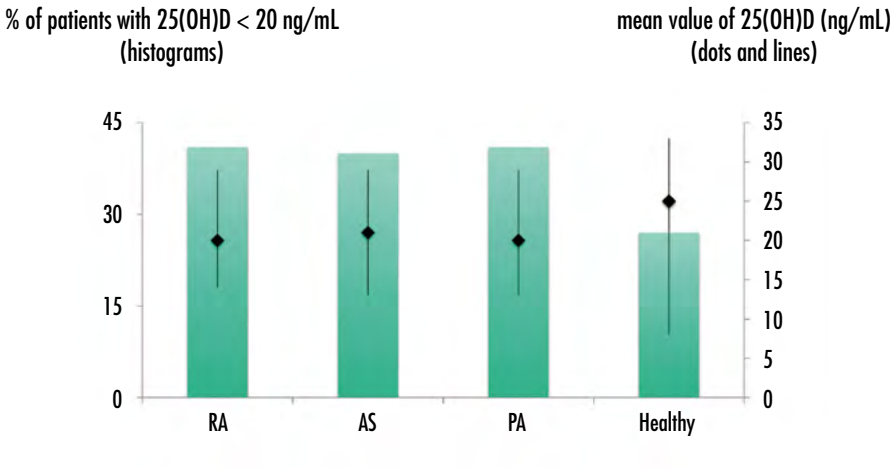

FIGURE 1.
Percentage of patients with vitamin D deficiency [25(OH)D < 20 ng/mL] (histograms) and mean value (95% CI) of 25(OH)D (ng/mL) (dots and lines) in healthy subjects and those with RA, AS and PA (CARMA study) (Urruticoechea-Arana et al., 2015) [9].

in healthy subjects as a function of either the baseline levels of 25(OH)D or of cholecalciferol intake are definitely insufficient.
Two studies have shown a correlation between exposure to UVB or intake of vitamin D3 (from food or supplements) and the risk of developing RA [15,16]. The Nurses' Health Study (NHS), conducted on a population of more than 100,000 women, showed a lower incidence of RA in subjects who had a higher cumulative average exposure to UVB compared to women who had a lower exposure (HR = 0.8, 95% CI, 0.7-0.9) [15]. These results were not confirmed in the duplicate study NHSII [15].
Results from the Iowa Women's Health Study, which investigated the incidence of RA as a function of vitamin D intake in a population of more than 29,000 women, showed that higher vitamin D intake (both via diet and supplementation) was associated with a reduced risk of RA (RR = 0.7, 95% CI, 0.4-1.0) [16].
Contrary to what has just been described, it should be noted that post-hoc analysis of these two studies and of others failed to confirm the relationship between vitamin D and RA or SLE risk [17,19]. Therefore, ad hoc studies need to be designed and carried out to further investigate the cause-effect relationship between hypovitaminosis D and IRDs occurrence.

VITAMIN D STATUS AND DISEASE ACTIVITY/SEVERITY

The existence of a relationship between vitamin D status [serum 25(OH)D] and disease activity or severity has been reported in several studies that were primarily (but not exclusively) carried out on patients with RA, SLE and SS [10-12,20-23]. Most studies that examined the relationship between 25(OH)D and disease activity in patients with RA showed an inverse correlation between vitamin D status and DAS28, VAS and/or VES [12, 20-22]. In the COMORA study, for instance, performed on 1,413 RA patients, average DAS28 values in subjects with normal vitamin D levels were considerably lower compared to subjects with hypovitaminosis D (Fig. 2) [22]. A similar relation (inverse correlation) was also found for ACPAs by Wang et al. [21].
Also for SS and SLE patients, clinical data showed an inverse correlation between 25(OH)D and disease activity or clinical outcomes (scleroderma ulcers) [10,11,23]. Regarding SS patients, for example, Caimi et al. analyzed the relationship between variation of 25(OH)D values over time and the incidence of digital ulcers in 65 SS patients. They found that a 25(OH)D reduction (in 48% of patients) during a 5-year follow-up was associated with higher risk for developing digital ulcers (OR = 16.6, 95% CI, 1.7-164.5) [11]. Another study, which investigated average 25(OH)D values as a function of disease activity measured by the SLEDAI index in 199 SLE patients, found a progressive decrease of 25(OH)D in tandem with a progressive worsening of the SLEDAI (Fig. 3) [10].

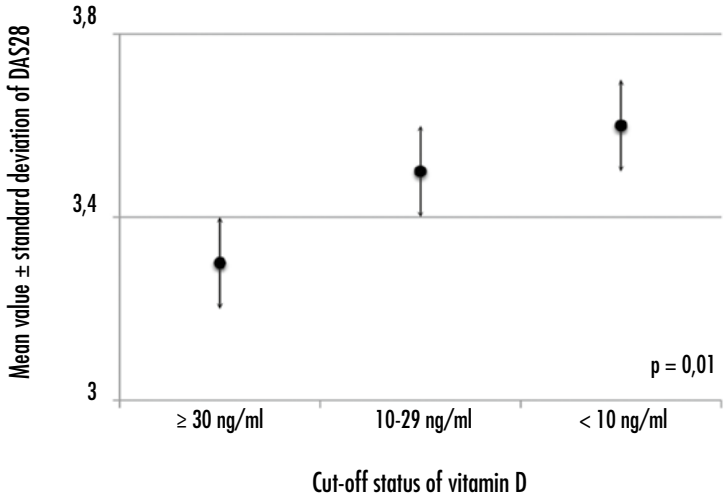

FIGURE 2.
Mean value of DAS28 ± standard deviation in patients with RA according to vitamin D status. Vitamin D cut-offs: 25(OH)D ≥ 30 ng/mL; 30 ng/mL > 25(OH)D ≥ 10 ng/mL; 25(OH)D < 10 ng/mL (Hajjaj-Hassouni et al., 2017, modified) [22].

USE OF VITAMIN D TO TREAT INFLAMMATORY/AUTOIMMUNE RHEUMATIC DISEASES

Overall, the epidemiological and clinical findings described here have opened the way toward the hypothesis that reduction of disease activity and perhaps even improved clinical results can be attained by using cholecalciferol supplementation in IRDs patients with vitamin D deficiency [7].
A recent literature review describing the main RCTs performed on patients with SLE, RA, Crohn's Disease, multiple sclerosis and type I diabetes has highlighted the therapeutic potential of cholecalciferol and its metabolites with regard to IRDs [7].
In the case of SLE patients, studies were conducted using cholecalciferol doses between 2,000 IU and roughly 7,000 IU daily for 3 to 12 months versus placebo. Two of these studies, namely that with the greatest duration (12 months) and that in which the highest doses of cholecalciferol were given (50,000 IU per week), clearly showed beneficial effects of cholecalciferol on disease activity (SLEDAI and ECLAM), on VES and on clinical symptoms. The only study which did not confirm these results was compromised by various shortcomings, such as the short period in which supplementation was given and the inclusion of patients in which the disease was not active [7].
Less solid though very promising data were obtained from RCT studies that used cholecalciferol supplementation or its metabolites in RA patients. The weakness of the data in these cases is probably due to several limitations of the RCTs (number of patients, duration of the follow-up and relatively high baseline 25(OH)D values) [7].
In general, these RCT studies highlighted positive trends regarding DAS28, VES and clinical symptoms; yet these did not achieve statistically significant results [7].
On the other hand, a more recent prospective study that administered cholecalciferol 100,000 IU per month in RA patients showed beneficial effects on VAS and DAS28 [24]. The most important point of this study is that it demonstrated different effects of cholecalciferol on DAS28 and VAS depending on baseline 25(OH)D levels: the most beneficial effects of cholecalciferol on

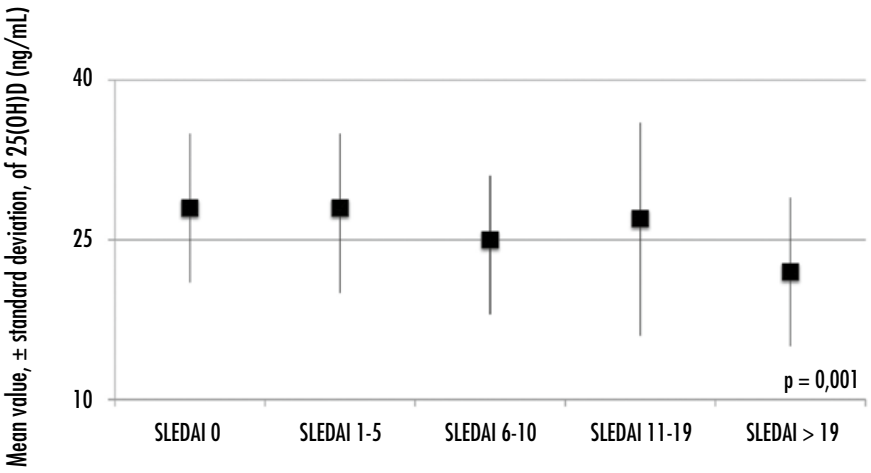

FIGURE 3.
Mean values of 25(OH)D (ng/mL ± standard deviation) in patients with SLE classified on basis of disease activity measured by SLEDAI (Eloi et al., 2017) [10].

DAS28 were found in patients with baseline 25(OH)D > 20 ng/mL, while its greatest effects on VAS were in patients with baseline 25(OH)D < 20 ng/mL [24].

CONCLUSIONS

Within the limits dictated by the complexity and heterogeneity of the IRDs, data from the literature appear to unambiguously confirm a role of vitamin D in diseases such as RA, SS and SLE. Its effect with regard to other IRDs (PA and AS) seems less clear, mainly because of the scarcity of published studies and their modest quality. It is therefore possible that vitamin D plays a relevant role in these diseases as well [20]. In general, we can state that serum 25(OH)D levels seem to influence the activity and severity of some IRDs and can possibly also have an effect on certain clinical outcomes; less clear is the cause-effect relationship in IRDs pathogenesis.

Based on data from RCTs, cholecalciferol supplementation should be offered to all patients with IRDs who do not have optimal 25(OH)D baseline values. Meanwhile, for IRDs patients with normal vitamin D values, well-designed RCTs conducted on specific populations will be necessary to determine the possible use of cholecalciferol, with the aim of improving the clinical evolution and outcome of the disease.

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