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The impact of vitamin D deficiency and microbiome in psoriasis versus non immune-mediated diseases

Abstract

Psoriasis consists of a chronic inflammatory disease with systemic character and may be associated with several comorbidities. Although its etiopathogenesis has not yet been fully elucidated, it is known that it is an immune-mediated pathology, especially by T cells. Like other inflammatory and autoimmune disorders, psoriasis is also related to changes in the cutaneous microbiome. Vitamin D deficiency is one of the conditions associated with pathologies whose microbiome is altered, although the causal relationship between these events is not precisely determined. Thus, the objective of this study was to estimate the prevalence of vitamin D deficiency in patients with psoriasis who attended the Dermatology Clinic of ABC Medical School (FMABC) and compare it to the prevalence of vitamin D deficiency among patients with non-inflammatory pathologies. 88 patients with psoriasis and 91 patients with non-inflammatory diseases (Control Group) were evaluated and had their serum vitamin D measured. It was observed that the Psoriasis Group had lower serum vitamin D levels compared to the Control Group ($p<0.001$) and It was observed that the chance of a person with psoriasis present low vitamin D levels is about seven times higher.

Keywords: psoriasis, microbiome, autoimmunity

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Introduction

Psoriasis is a chronic inflammatory disease, with a prevalence of approximately 1% in Brazil and Latin America and 3% in Europe. Although skin involvement is widely known, including the nail apparatus, it is important to mention the systemic character of this condition, that may involve osteoarticular system and present a strong association with the metabolic syndrome or its components alone, and even greater cardiovascular risk.[1]

Clinically, psoriasis mayappear itself in various forms, being classified as follows: vulgar or plaque, guttate, inverted, palmoplantar, pustular, nail, erythrodermic and psoriatic arthritis. Within the pustular category, manifestations are subclassified as localized forms: palmoplantar pustulosis and acrodermatitis continua of Hallopeau; and generalized forms: von Zumbusch type (acute generalized pustular psoriasis) and impetigo herpetiformis, which occurs in pregnant women.[1,2]

The main histological findings in psoriasis are evident in the most superficial layers of the skin, where the inflammatory process leads to uncontrolled proliferation and altered keratinocyte differentiation. In addition, it also affects the vascular network present in the dermal layer and the interaction of keratinocytes with different cells of the innate and adaptive immune system.[1]

The cutaneous microbiome plays an active role in immune regulation and defense against pathogens, stimulating the production of antimicrobial peptides and the biofilm formation. The role of bacteria and virus in triggering the inflammatory cascade may be seen as an example the breakdown of immune tolerance involved in the etiopathogenesis of Crohn's disease, characterized by changes in the intestinal microbiome and classically associated with psoriasis.[3–6] Beyond other autoimmune and chronic inflammatory pathologies, such as acne, rosacea, atopic dermatitis and vitiligo, psoriasis has also been associated with changes in the skin microbiome. There are reports describing the relative increase in Streptococcus and Staphylococcus aureus, reduction in Malassezia and Cutibacterium and also a decrease in immunoregulatory bacteria such as P. acnes and *S. epidermidis*, which could determine exacerbation of the Th17 axis. However, it remains uncertain whether the alteration of the cutaneous microbiome is the causal factor or the mere consequence of the inflammatory microenvironment.[7–9]

On the other hand, besides the regulatory action on calcium and phosphorus homeostasis classically described as the main function of Vitamin D, it has a wide range of effects, such as important role in cardiovascular protection, as an immunoregulator and even acting on the skin barrier and cell differentiation.[1,10] In this context, the complex interaction among the alteration of the cutaneous microbiome, vitamin D levels and pathologies with a chronic autoimmune or inflammatory component, such as psoriasis, becomes evident due to mechanisms that are still uncertain.

The aim of this study was to estimate the prevalence of vitamin D deficiency in patients with psoriasis who attended the Dermatology Clinic of ABC Medical School (FMABC), compared to patients without inflammatory pathologies.

Materials and methods

The study was approved by the Ethics Committee of ABC Medical School (FMABC) and the data were collected only after agreement and voluntary signature of the Informed Consent Document by the selected patients. It was an observational, cross-sectional and retrospective study, with a quantitative approach, carried out at the Dermatology Discipline Clinic of FMABC, between the months of June and September 2019, with data obtained from medical records. Psoriasis patients were recruted by observing clinical manifestations, therapeutic history, and current treatment, as well as patients without inflammatory pathologies as a control group. Patients on current vitamin D replacement or less than a year ago were excluded.

The serum dosage of 25-hidroxyvitamin D [25(OH)D] was requested for both groups and the classification was established according to the reference values: deficiency (less than 20mg/dL),

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insufficiency (between 20 and 29mg/dL) and within the normal range (higher than 30 mg/dL). The data obtained were organized in an Excel® electronic table and interpreted with Descriptive and Analytical Statistics (using the SPSS statistical software, version 15.0.1).

Results

A total of 196 individuals were included in the study, being 144 (73.4%) female and 52 (26.5%) male. The Psoriasis Group included 88 patients (44.9%), with 53 female (60.2%) and 35 male (39.7%) patients. The individuals were classified according to age: up to 60 years (group 1), which represented 54.5% (n = 48), and over 60 years (group 2), which represented 45.4% (n=40) of the total. Psoriasis vulgaris was identified in 56 patients (63.6%), psoriatic arthritis in 17 patients (19.3%) and other forms of psoriasis (pustular, erythrodermic, palmoplantar, inverted and guttate) were found in 15 patients (17 %), being regrouped in the category "Other Types of Psoriasis", in order to allow statistical analysis (Table 1). Regarding the therapeutic modality, 22.7% of patients (n=20) were using topical drugs, 57.9% (n=51) were using non-biological systemic drugs and 19.3% (N=17) were in systemic immunobiological therapy.

Table 1 Study description – Clinical manifestations in the Psoriasis Group

	Frequency	Porcentage
Psoriasis vulgaris	56	63,6%
Psoriatic arthritis	17	19,3%
Other types of psoriasis	15	17,0%
Total	88	100,0

There were 91 female (84.2%) and 17 male patients (15.7%) in the Control Group. Moreover, 82 patients were up to 60 years old (75.9%) and 26 patients aged over 60 years (24%).

The dosage of vitamin D in Psoriasis Group showed deficient or insufficient values in 76 patients (86.4%). In addition, the dosages were also related to the type of psoriasis: 47 patients with psoriasis vulgaris (83.9%), 13 patients with other psoriasis manifestations (86.6%) and 16 patients with psoriatic arthritis (94.1%) had vitamin D values below normal. Therefore, low serum vitamin D levels were significantly more frequent in arthropathic form (p=0.06).

The Control Group had 52 patients (48.1%) with insufficient or deficient serum vitamin D levels. In other words, it was observed that the Psoriasis Group had lower circulating vitamin D concentrations compared to the Control Group (p<0.001) and that the chance of a person with this disease having low vitamin D is about 7 times higher than a person without psoriasis.

Regarding therapeutic forms, vitamin D insufficiency or deficiency was observed in 18 (90%) patients with topical treatment for psoriasis, 15 (88.2%) of those undergoing systemic biological treatment and in 43 (84.3%) patients undergoing non-biological systemic treatment. However, the difference in prevalence between them was not significant (p=0.8).

Discussion

Vitamin D plays a key role in inhibiting and modulating the immune system. It is able to prevent the pathological inflammatory response by suppressing inflammation mediated by Toll Like Receptors (TLR) in dendritic cell. Futhermore, it contributes to the maintenance of the dermoepidermal junction, through distribution of integrins, such as CD26 and ICAM-1, which are commonly altered in psoriasis.

Disorders in the response of the cutaneous immune system (innate and adaptive) are responsible for the development and maintenance of the inflammatory process of psoriasis. The kernel of the pathophysiology is the hyperactivation of the innate immune system, caused by certain triggers, culminating in the hyperproliferation of keratinocytes and production of cytokines and antimicrobial peptides in response to IL-22, IL-6, TNF-α and IFNγ. Although there is consensus on the fundamental role played by T lymphocytes, especially Th1, Th17 and Th22, in the complex etiopathogenesis of psoriasis, the participation of a series of triggers in the onset and aggravation of the condition remains nuclear. However it should be noted that in psoriasis, T lymphocytes play an important role, both in the production and activation of cytokines.[11,12] Among other multiple factors mentioned in the literature, environmental factors stand out, such as alcohol, smoking, use of certain medications, trauma (Koebner phenomenon), infections and the participation of microorganisms acting as a trigger.[13–16]

On the other hand, literature associates vitamin D with the regulation of cutaneous immunity, by the suppression of proliferation of T cells, preferential development of auxiliary T cells (Th2), induction of regulatory cells, induction of activated B cell apoptosis, modulation in the activation of cytokines and dendritic cells. In the skin, vitamin D promotes differentiation and inactivates the proliferation of keratinocytes, selectively induces apoptosis, promotes the formation of a permeability barrier, regulates the immune system and induces the follicular cycle. This occurs through interaction between the activated metabolite 1,25-dihydroxyvitamin D3 [1,25 (OH) 2D3] and the cell membranereceptor for vitamin D (VDR).[17-23]

Correale *et al* reported that vitamin D presents a greater immunomodulatory effect in women due to estrogen action. In this group, the inhibition of cells proliferation is greater, there is less production of INF-γ and IL-17 and a greater amount of IL-10 secreting cells.[24,25] Another relevant aspect involves the association between low vitamin D serum levels and autoimmune diseases, mediated by Th1 response, such as rheumatoid arthritis, type 1 diabetes, inflammatory bowel disease and multiple sclerosis, as described in a series of publications.[26]

The relationship between vitamin D levels and psoriasis has been extensively explored and documented in literature through last years, in order to establish a possible pathophysiological mechanism.[7-9,12,13] Bearing in mind that psoriasis is an autoimmune disease, mediated by Th1-Th17-Th22 response, it is possible that its manifestation consists, among other factors, consequence of vitamin D deficiency.[24,25]

In the present study, we observed that reduced levels of vitamin D were noticeably more frequent in the Psoriasis Group compared to the Control Group, with an estimated risk of having vitamin D deficiency or insufficiency seven times higher in patients with psoriasis. Psoriatic arthritis was more likely to be associated with reduced levels of vitamin D, which supports the hypothesis that there is an interaction between this micronutrient and the arthropathic form.[27]

In general, insufficient levels have been attributed to several factors, including ethnicity, age, reduced sun exposure and reduced consumption of fish, eggs and liver. The minimum amount of vitamin D is hardly supplied by diet and the endogenous production from sunlight corresponds to 80-100% of the total amount needed. Sun protection, using sunscreen, hat and clothes that block UV rays, can

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contribute to reduction of the endogenous synthesis of vitamin D. In addition, the modern lifestyle with less time away from home or work further reduces daily sunlight exposure.[17,18,28,29]

The results obtained in this study can be justified in several ways, from disturbances in the hydration of the stratum corneum with reduced lipid content[31,32] and the use of immunosuppressive drugs that interfere with the metabolism of vitamin D, to the psychosocial repercussion of the disease in the patient with psoriasis, leading to less sunlight exposure precisely because of the habit of covering the affected body segments, which further decreases the synthesis of this vitamin in the organism.[13,26]

Vitamin D necessity can be suppressed in two ways: oral supplementation and skin synthesis through ultraviolet B (UVB) irradiation.[31,32] It is known that phototherapy with UVB light is able to activate vitamin D synthesis in keratinocytes, increasing its serum concentration, promoting activation of regulatory T cells.[33–36] Furthermore, some antimicrobial peptides, including catelicidin, participate in adaptive and innate immune regulation, play an important role in controlling skin inflammation in patients with psoriasis and depend on UVB-induced vitamin D.[37,38] In this regard, further studies are needed to assess the correlation between vitamin D levels and its possible interaction in therapeutic evolution. On the other hand, the use of vitamin D analogues in psoriasis topical treatment has been reported since the 1980s, demonstrating satisfactory results and comparable efficiency to potent corticosteroids.[39,40]

Conclusion

Normal levels of vitamin D can prevent variations in immune homeostasis, modulate keratinocytes proliferation, regulate microbial flora and host's response to infectious diseases. In this context, the complex interaction - due to mechanisms that are still uncertain - between alteration of the cutaneous microbiome, vitamin D levels and chronic pathologies with autoimmune or inflammatory component becomes evident.

Therefore, we can infer that the maintenance of serum vitamin D levels above 30mg/dL could contribute to a better evolution when it comes to autoimmune and inflammatory diseases, such as psoriasis. Finally, serum dosage of 25-hydroxyvitamin D3, in addition to instituting careful vitamin replacement with laboratory control and periodic clinical evaluation is recommended.

Conflicts of interest

There are no conflicts of interest.

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