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Exploring the relationship between psoriasis and vitamin D

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ABSTRACT

Introduction and purpose: Psoriasis is a chronic, inflammatory skin condition that affects millions of individuals worldwide. Recent research has suggested a potential link between psoriasis and vitamin D deficiency. This review paper aims to examine the existing literature on the relationship between psoriasis and vitamin D, exploring the potential role of vitamin D in the pathogenesis and management of this debilitating skin disorder.

Materials and method: An extensive examination of articles published in scientific journals was carried out through online research platforms PubMed and Google Scholar. We searched articles by entering keywords in appropriate configuration: “psoriasis”, “vitamin D”, “obesity”.

Description of the state of knowledge: Emerging research has identified a connection between vitamin D and the development of various skin conditions, including psoriasis. Consistent findings have shown a significant association between low vitamin D levels and the presence of psoriasis. Furthermore, due to vitamin D's influence on the proliferation and maturation of keratinocytes, it has become an important local treatment option for managing psoriasis.
Summary: Although there is no clear consensus on whether sufficient dietary vitamin D or oral vitamin D supplements effectively treat psoriasis, the available evidence is still inconclusive. However, healthcare providers like nutritionists should consider recommending general vitamin D supplementation for populations at high risk of vitamin D deficiency, such as those with psoriasis or obesity.

Keywords: “psoriasis”; “vitamin D”; “obesity”

Introduction

Psoriasis is a complex, multifactorial skin condition characterized by the accelerated proliferation and differentiation of keratinocytes, leading to the formation of scaly, erythematous plaques [1] [2]. The exact pathogenesis of psoriasis is not fully understood, but it is believed to involve a combination of genetic predisposition and environmental triggers that disrupt the delicate balance of the immune system [1][3]. The estimated prevalence of psoriasis in Western countries ranges from 2 to 4% among adults, though the incidence may vary across different populations and geographic regions [4] [5]. While the condition is not life-threatening, it can have a significant impact on an individual's quality of life, with physical symptoms such as itching, scaling, and pain, as well as psychological consequences, including depression and social stig. Vitamin D (vitD) is produced in the skin when exposed to sunlight and influences many skin functions, such as keratinocyte proliferation, differentiation and apoptosis [6]. Reduced levels of 25(OH)D (calcidiol) have been shown to be associated with an increased risk of diseases such as atopic dermatitis, alopecia areata, vitiligo, and psoriasis [7]. However, the efficacy of using vitamin D supplementation as an adjuvant treatment for psoriatic patients remains a subject of ongoing debate [8]. In this review, we examine the potential bidirectional relationship between vitamin D and psoriatic disease.

The dermatological perspective on psoriasis

Patients with psoriasis display a wide variety of clinical presentations. Psoriatic skin lesions can be categorized into different types - plaque, guttate, pustular, and erythrodermic - based on factors such as the size and distribution of the lesions [9]. Psoriasis can develop at any age, including during childhood, though there are two primary age ranges when the disease typically manifests: 16 to 22 years old and 57 to 60 years old [10]. The disease course is often marked by periods of remission and exacerbation, which can be influenced by various triggers, such as stress, infections, certain medications, and weather conditions [11][12]. Psoriasis lesions exhibit hyper-proliferation and impaired differentiation of epidermal keratinocytes, as well as reduced keratinocyte apoptosis [13]. The severity of psoriasis can be evaluated using

the Psoriasis Area and Severity Index, which assigns a score ranging from 0 to 72 based on the extent and severity of skin lesions [14]. Additionally, the PASI score is useful in assessing treatment response in psoriasis patients.
Topical therapies, including vitamin D3 analogues, are valid treatment options for mild-to-moderate psoriasis, as keratinocytes in psoriatic lesions express the vitamin D receptor [15]. Oral vitamin D supplementation is also utilized, due to its role in immune homeostasis, but the results remain inconclusive [16].

The influence of vitamin D on skin

The basal layer of the skin contains stem cells that continuously divide throughout an organism's lifetime. These cells then migrate upwards through the epidermis, undergoing differentiation and stratification to form the skin's protective barrier layer [8]. The precursor of vitamin D, 7-dehydrocholesterol, is found in the cell membranes of keratinocytes located within the basal and spinous layers of the epidermis [17]. UVB light triggers a photochemical reaction that breaks the B ring of 7-dehydrocholesterol, forming pre-vitamin D3 or cholecalciferol. This pre-cursor is then converted to 25-hydroxyvitamin D by the enzymes CYP27A1 and CYP2R1. Finally, the active form of vitamin D, 1,25-hydroxyvitamin D (calcitriol), is produced by the action of the enzyme CYP27B1[18]. Physiologically, the active form of vitamin D and its receptor modulate the differentiation and proliferation of keratinocytes, the balance of the cutaneous immune system, and the process of apoptosis. The active form of vitamin D, 1,25D, has been demonstrated to suppress the proliferation of keratinocytes [19]. Moreover, vitamin D can reduce inflammation in the skin by downregulating the expression of inflammatory cytokines and chemokines, as well as by inhibiting the antigen-presenting capacity of dendritic cells. Interestingly, in vitro studies have shown that low levels of vitamin D can stimulate keratinocyte proliferation, while higher, pharmacological doses of vitamin D exhibit a clear inhibitory effect on keratinocyte growth [20]. Additionally, vitamin D plays a role in regulating the production of glycosylceramides, which are essential for preserving the barrier integrity and permeability of the stratum corneum layer [8]. Decreased levels or deficiency of 1,25D, the active form of vitamin D, or impairment of its receptor function, have been found to disrupt the normal differentiation of the epidermis. This disruption leads to reduced levels of key structural proteins like involucrin and loricrin, as well as a loss of keratohyalin granules, ultimately resulting in excessive proliferation of the basal layer of the epidermis [8].

Table 1. Vitamin D actions on skin biology and psoriasis pathogenesis
Regulation of keratinocytes proliferation, differentiation and apoptosis
Regulation of cutaneous immune system (inhibition of T cell proliferation, Tregs induction)
Down-regulation of pro-inflammatory cytokines

Stimulation of antimicrobial peptides expression
Regulation of barrier integrity and permeability

Vitamin D's influence on the skin's immune system

Psoriasis pathogenesis involves the activation of both the innate and adaptive immune responses. Key players in this process include T cells, particularly the T-helper Th1, Th17, and Th22 subsets, which interact with various other cell types and secrete pro-inflammatory cytokines such as tumor necrosis factor-α, IL-6, and IL-17 [21] [22].

The activity of these pro-inflammatory cells, such as T-helper Th1, Th17, and Th22 cells, is regulated by a specific subset of T lymphocytes known as regulatory T cells. Regulatory T cells have the ability to suppress the immune response and maintain cutaneous immune homeostasis, thereby preventing autoimmune reactions against self-antigens [23]. Vitamin D functions as a versatile immunomodulator, suppressing the proliferation of T lymphocytes and promoting the generation of CD25+/CD4+ regulatory T cells. These regulatory T cells help maintain tolerance and inhibit immune responses following antigen stimulation.[24]. Additionally, vitamin D plays a role in enhancing the skin's defense mechanisms. It promotes autophagy, a cellular process that helps macrophages combat opportunistic infections. Furthermore, vitamin D stimulates the production of endogenous antimicrobial peptides in the resident epithelial cells of the skin, thereby reinforcing the innate skin barrier [25].

The relationship between vitamin D and psoriasis

Epidemiological studies have consistently demonstrated an association between vitamin D deficiency and an increased risk of developing psoriasis [26]. Psoriasis is associated with alterations in the vitamin D receptor (VDR), which plays a role in maintaining the skin's barrier function. Multiple studies have found a link between VDR gene polymorphisms and susceptibility to psoriasis [25]. According to the findings of Richetta et al., the A-1012G promoter polymorphism of the VDR gene is linked to an increased risk of psoriasis. This is due to a reduced expression of VDR mRNA, which may contribute to changes in the cutaneous barrier and the development of psoriatic lesions [27]. Furthermore, in psoriatic skin, there is a decrease in the expression of the vitamin D receptor and a reduction in tight-junction proteins. These tight junctions play a crucial role in regulating the adhesion, permeability, and polarization of keratinocytes, as well as the extracellular calcium gradient. They also interact with nuclear and cytoplasmic proteins, thereby influencing the regulation of specific genes involved in keratinocyte differentiation and proliferation [28]. Numerous studies have investigated the potential association between vitamin D deficiency and the pathogenesis of psoriasis. The active form of vitamin D exhibits an anti-inflammatory effect by modulating the inflammatory profile of human monocytes and macrophages [39–42]. It downregulates the expression and production of several pro-inflammatory cytokines, such as TNF-α, IL-1β, IL-6, and IL-8. Additionally, vitamin D appears to dampen the differentiation,

maturation, chemotaxis, and antigen presentation of dendritic cells [29]. Numerous studies have demonstrated that low levels of the active form of vitamin D, 1,25D, are associated with the development and progression of psoriasis. Specifically, research has shown that 1,25D concentrations are significantly decreased in patients with psoriasis compared to healthy individuals [30] [31]. An additional study found that women with psoriasis had lower vitamin D levels compared to men, a distinction not present in the control group [32]. Furthermore, reduced vitamin D was negatively correlated with markers of inflammatory activation and obesity [30].

Additionally, other research demonstrated that patients with psoriatic arthritis exhibited decreased serum vitamin D, which was inversely related to disease activity. However, it is still unclear if low 25(OH)D levels represent a consequence of psoriasis or a possible contributing factor.

Topical vitamin D in psoriasis treatment

The therapeutic benefits of vitamin D, enhanced by sunlight exposure, in managing psoriasis have been recognized for many years. The effectiveness of vitamin D and its derivatives, such as calcipotriol and maxacalcitol, in treating psoriasis has been well-established since 1985, with extensive clinical trial evidence confirming their efficacy [32]. Topical therapy with vitamin D, either alone or in combination with topical corticosteroids, is one of the most commonly prescribed first-line treatments for psoriasis. Numerous studies have documented the efficacy and safety of using topical calcipotriol, a vitamin D derivative, in managing localized plaque psoriasis [33]. Vitamin D-based medications do not lose their effectiveness over time, unlike corticosteroids, and can be used topically for an extended period without significant adverse reactions. These treatments have also proven beneficial for addressing psoriatic skin lesions in both children and older adults [34]. The findings indicate that topical vitamin D derivatives have shown a favorable safety profile, with "steroid-sparing" effects, and should be considered an essential part of the current treatment options for physicians managing psoriasis [8]. The therapeutic effects of topical vitamin D are mediated through both genomic and non-genomic pathways. The genomic mechanism involves activation of the vitamin D receptor, which leads to inhibition of keratinocyte proliferation. The non-genomic mechanism induces keratinocyte differentiation by increasing intracellular calcium levels [35]. The anti-inflammatory actions of vitamin D may also stem from its ability to suppress the production of certain pro-inflammatory cytokines like IL-2, IL-6, and interferon-gamma. Furthermore, topical application of the vitamin D derivative calcipotriol has been shown to inhibit the expression of human beta defensin and other pro-inflammatory cytokines, which are typically elevated in psoriatic skin lesions [36].

The nutritional perspective on psoriasis

Severe psoriasis has been linked to nutritional deficiencies, especially in vitamin D, due to the rapid overgrowth and excessive shedding of the skin's outer epidermal layer [37]. Dietary supplements are the primary factor influencing the variability in vitamin D consumption [38]. Nutritionists should consider supplementing vitamin D in populations with a high risk of vitamin D deficiency, such as individuals with psoriasis [39]. The vitamin D compounds used

in clinical trials varied, including 1,25D (the active form) and 1αOHD (which requires only liver metabolism to become active), as well as cholecalciferol (which requires both liver and kidney metabolism). Perez et al. reported an overall 88% clinical improvement in psoriasis with oral vitamin D, accompanied by a decrease in mean PASI scores. [40]. These findings have been corroborated by other studies, demonstrating moderate to significant improvement in 25-50% of psoriatic patients receiving vitamin D supplementation [41]. A large-scale study involving 70,437 US females over 14 years investigated the relationship between vitamin D intake and the incidence of psoriasis.

After accounting for potential confounding factors, the researchers reported no significant association between vitamin D intake, whether from dietary sources or supplements, and the risk of developing psoriasis. Therefore, the authors concluded that vitamin D intake may not play a role in preventing the onset of psoriasis in this population [42]. Four randomized trials involving 333 subjects evaluated the effect of vitamin D supplementation on changes in PASI values. 173 participants received vitamin D at a dose of 80-100,000 IU/month (150 people - cholecalciferol, 23 people - ergocalciferol), while 160 patients received placebo. The average duration of supplementation was 8.4 months. PASI values were compared after 3, 6 and (for selected studies) 12 months. There were no statistically significant differences in PASI values between the groups [43]. The association between lower 25-hydroxyvitamin D (25D) levels and psoriasis has been observed in small case-control studies conducted on specific populations, even after accounting for the influence of body mass index [44]. Population-based studies have reported limited data on the relationship between psoriasis and 25-hydroxyvitamin D levels. One North American population-based investigation found no significant association between psoriasis and 25-hydroxyvitamin D concentrations [45]. Recent studies have indicated a non-linear association between 25-hydroxyvitamin D levels and psoriasis, with body composition playing a modifying role [46]. Additionally, open-label trials and case reports have described a positive response to oral vitamin D supplementation in patients with psoriasis, though the findings from randomized clinical trials have been inconsistent.

Vitamin D, obesity and psoriasis

The association between obesity, especially visceral obesity, and psoriasis appears to be bidirectional. Obesity may increase the risk of developing psoriasis, while psoriasis may also contribute to the development of obesity [47]. Specifically, research has shown that individuals with obesity were twice as likely to develop psoriasis compared to those with normal body weight [48]. In particular, obesity and psoriasis are closely associated, as both conditions involve a pro-inflammatory state characterized by an imbalance in adipokines, favoring those with a pro-inflammatory effect [49]. Increased body mass index is associated with lower vitamin D levels, and lower vitamin D levels are linked to higher mortality risk. However, this inverse relationship between vitamin D and mortality may be indirectly influenced by the presence of obesity itself [50]. The relationships between low vitamin D levels, obesity, and psoriasis suggest that vitamin D may be a connecting factor between these conditions. This hypothesis proposes a detrimental cycle where low vitamin D status, obesity,

and psoriasis interact, leading to increased cardiovascular and metabolic risks in obese individuals with psoriasis. Based on this, vitamin D supplementation could be particularly beneficial in preventing comorbidities associated with psoriasis. A team of Norwegian researchers, using data collected during the 2015-2016 Tromsø Study, which included 19,520 participants in the general population aged 40-79, analyzed them cross-sectionally for the association of plasma vitamin D levels with the course of any form of psoriasis. The above study showed that high BMI and vitamin D deficiency together increase the risk of active psoriasis more than the sum of these factors. Hence, it is in this particular group of patients that advice on prevention of vitamin D deficiency may be considered, and preferably appropriate supplementation (especially during the autumn and winter months) should be included [51].

Summary

Despite the lack of consensus on the benefits of adequate dietary vitamin D intake or oral vitamin D supplementation as an effective treatment for psoriasis, the available evidence remains inconclusive. Nevertheless, healthcare professionals such as nutritionists should consider recommending general vitamin D supplementation for populations at high risk of vitamin D deficiency, including individuals with psoriasis or obesity.

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Statement of the authors' contribution

Aleksandra Kiełczewska: Conceptualization, Writing-rough preparation
Grzegorz Szcześniak: Methodology, Investigation Resources
Anna Kiełczewska: Formal analysis, Visualisation, Writing-review and editing

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