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Review

VITAMIN D IN PATIENTS WITH INFLAMMATORY SKIN DISEASES

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SUMMARY – In search for the ways to cure and improve skin condition of patients with inflammatory skin diseases, vitamin D supplementation has been shown to be useful, primarily due to its effects on a number of skin functions, e.g., keratinocyte proliferation, differentiation and apoptosis, maintenance of the epidermal barrier, and regulation of immune processes in the skin, among others. Vitamin D is essential for good general health and healthy skin, but deficiency can occur due to various factors that result in increased time spent indoors and limited sunlight exposure, such as geography (place of residence) and genetic factors. Although some results are inconsistent, previous research indicates that multiple inflammatory skin diseases can be affected by vitamin D deficiency, particularly atopic dermatitis, but also other inflammatory skin diseases. There is also evidence for an association between vitamin D deficiency and the risk of worsening of skin diseases such as psoriasis, chronic urticaria, contact dermatitis, etc. For these and several other inflammatory skin diseases, most research suggests that patients benefit from vitamin D supplementation.

Key words: *Vitamin D; Vitamin D deficiency; Atopic dermatitis; Psoriasis; Chronic urticaria; Contact dermatitis*

Introduction

Over the last few decades, various therapeutic options have been proposed for a wide range of skin diseases, among which the introduction of vitamin D supplementation has proved useful. Namely, according to the literature, low levels of 25-hydroxyvitamin D have been observed in several dermatologic diseases (as well as in patients with systemic infections and cancer); thus, its supplementation is an attempt to improve the condition of these patients[1-5].Vitamin D is synthesized in the skin, and people naturally get >90% of their needs this way, which takes place under the influence of sunlight and ultraviolet B (UVB) radiation[6]. Vitamin D regulates many cutaneous physiological processes (cell proliferation, differentiation and apoptosis, maintenance of the epidermal barrier and regulation of immune functions, etc.), which is why researchers have begun looking into the effects of supplementation in skin diseases.

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Vitamin D is fat-soluble and appears in two main forms, i.e., ergocalciferol (vitamin D2) produced by plants and cholecalciferol (vitamin D3) derived from food of animal origin[1-5]. The main source of vitamin D for humans is its synthesis in the skin in the presence of sunlight, where exposure of 7-dehydrocholesterol (7-DHC) to UVB rays (wavelengths 290-315 nm) stimulates the production of previtamin D, which under the influence of heat becomes a more stable form of vitamin D (cholecalciferol). Vitamin D, whether ingested or synthesized in the skin, undergoes double hydroxylation (with the help of enzymes), first in the liver and then in the kidneys. After synthesis in the skin, vitamin D3 is then metabolized to its active form, 1.25 (OH), by hydroxylation (using the enzymes CYP27A1 and CYP27B1). At the end of these processes, vitamin D is rendered inactive with the help of the catabolic enzyme CYP24A1, and 25 (OH) D and 1.25 (OH) 2D are metabolically inactivated by hydroxylation using the enzyme 24-hydroxylase (CYP24A1).

It is significant that vitamin D levels are affected by UVB and various other factors such as external conditions (season, latitude and air pollution), a person's skin color, lifestyle (including time spent outdoors and applying photoprotection), cultural factors (common ways of dressing), etc.[6,7]. There are heterogeneous results from research looking at 'ideal' levels of 25 (OH) D for good health and prevention of diseases (e.g., reducing the risk of allergic diseases); thus, discussion on this topic is ongoing. According to the American Endocrinological Society guidelines, vitamin D deficiency is defined as a serum 25 (OH) D level of less than 20 ng/mL (50 nmol/L), and insufficiency occurs at serum levels of 25 (OH) D between 21 and 29 ng/mL (52.5-72.5 nmol/L)[3]. Serum vitamin D values are regulated by the feedback mechanism of calcium, phosphorus, parathyroid hormone, fibroblast growth factor and vitamin D. Vitamin D toxicity can occur as 25 (OH) D levels get closer to 250 nmol/L, and although it is usually an asymptomatic phenomenon, it sometimes results in hypercalcemia, hypercalciuria, and nephrocalcinosis[6].

Previous research shows that genetic factors play a significant role in vitamin D impact on skin condition and health, the vitamin D receptor gene being of particular importance. In one study, increased polymorphisms of the vitamin D receptor gene were found in atopic dermatitis (AD) patients (compared to healthy controls), meaning that AD patients have a genetic disorder associated with vitamin D metabolism. Thus, nucleotide (single nucleotide polymorphism, SNP) genes affect vitamin D status and calcium metabolism[9]. Of particular importance is the GC gene, which encodes a protein that binds to vitamin D; serum 25-hydroxyvitamin D levels depend on the concentration of that protein and on variations of its binding affinity for specific vitamin D metabolites. The GC gene contains many non-synonymous SNPs, and rs7041 and rs4588 are relatively common polymorphisms, the presence of which strongly (and independently) correlates with vitamin D levels. Rs7041 is associated with a lower risk of hypovitaminosis D, whereas rs4588 is associated with a higher risk of vitamin D deficiency[9]. Sun exposure and photoprotection are also important factors that affect vitamin D levels. Because photoprotection is highly recommended to prevent skin damage such as photoaging, cancer, and photodermatoses, vitamin D deficiency can consequently be more common in people who apply photoprotection every day. On the other hand, narrowband UVB phototherapy has been shown to increase 25-hydroxyvitamin D levels in patients with psoriasis, AD, vitiligo, and polymorphic light eruptions, thus positively influencing their disease condition. Thus, several factors should be considered when deciding on vitamin D supplementation, remembering that the ideal dose depends primarily on a person's sunlight exposure and intake of foods rich in vitamin D.

Vitamin D and Pathophysiology of Inflammatory Skin Diseases

Vitamin D status has been shown to be highly relevant in patients with several skin diseases, primarily AD, psoriasis, and chronic urticaria (CU) (Table 1), but also possibly in vitiligo, contact dermatitis (CD), mycosis fungoides, systemic lupus erythematosus (SLE), systemic sclerosis, alopecia areata, and polymorphic light eruption[4,7,8,10-15]. In addition, it is important to mention that vitamin D levels are associated with various infections and cancers. Notably, vitamin D affects proliferation and differentiation of skin cells (directly or through interaction with calcium). Because proper

Table 1. Literature data on vitamin D in patients with inflammatory skin diseases

Study authors	Subjects	Materials and methods	Results
Abdel-Rehim *et al.* (2014)	22 CSU patients and 20 controls	Case-control study: clinical assessment and routine laboratory tests	In CSU patients, low vitamin D levels more commonly seen, but it was not connected with disease severity
Benson *et al.* (2012)	Patients with AD or CU (data from various study)	Review article	Impact of vitamin D on allergic skin diseases has not yet been fully evaluated
Ehlayel *et al.* (2011)	483 Patients suffering from asthma and 483 controls	analysis of clinical manifestations, family history, physical examination and serum phosphorus, calcium and vitamin D levels	Significant vitamin D deficiency in patients with AD, acute urticaria, asthma, allergic rhinitis and food allergy
Goetz (2011)	63 Patients with pruritus, rash and urticaria/angioedema	vitamin D 50,000 IU was weekly administered for 8-12 weeks to 90% of patients with low vitamin D serum levels, followed by daily supplementation	After vitamin D supplementation, complete disease resolution in 70% of patients (mean 4.2 weeks); relapses only when vitamin D insufficiency recurred
Jaworek *et al.* (2020)	Patients with AD and CSU	Analysis of serum vitamin D levels (electrochemiluminescence); AD severity (SCORAD) and CSU (UAS 7 scale)	No significant relationship between vitamin D level and AD/CSU severity
Lugović-Mihić *et al.* (2022)	157 Patients in total; 51 AD patients, 55 CU patients and 51 CD patients: 38 with irritant CD (ICD) and 13 with allergic CD (ACD)	Prospective study: analysis of serum vitamin D values (CMIA); after 3 months of supplementation, control vitamin D values and disease status were determined	Vitamin D deficiency was often seen in patients with AD, CU and CD (most commonly in ICD and least commonly in ACD), although without statistical significance; after vitamin D supplementation, its levels increased significantly and clinical improvement in treated patients was seen somewhat more often than in the untreated group, but differences were not statistically significant
Quirk *et al.* (2016)	Patients with AD, CU and ACD; vitamin D deficient mice (data from various study)	Comprehensive review article	Improvement in AD and CU conditions was recorded after vitamin D supplementation; ACD was more common in vitamin D-deficient mice
Thorp *et al.* (2010)	25 CU patients and 25 subjects with allergic rhinitis on allergy immunotherapy	Case-control study with statistical analysis	Adult CU patients have low vitamin D serum levels, but more data are needed
Woo *et al.* (2015)	72 CU patients, 26 with acute urticaria, 26 with AD and 72 healthy controls	Retrospective review of clinical records	CU patients had more commonly reduced vitamin D concentration; negative association between urticaria severity and disease duration

ACD = allergic contact dermatitis; AD = atopic dermatitis; CU = chronic urticaria; CSU = chronic spontaneous urticaria; UAS = Urticaria Activity Score; CMIA = chemiluminescence microparticle immunoassay

keratinocyte proliferation and differentiation (essential for multiple dermatologic diseases) are important for maintaining proper epidermal function, the effect of vitamin D supplementation on keratinocytes (and their apoptosis) is important depending on its dose. Thus, low concentration of 1.25 (OH) 2D3 (≤10-9 M) enhances keratinocyte proliferation, and high concentration (>10-8 M) inhibits proliferation and promotes differentiation. In addition, several other factors (such as cell density, calcium concentration and its presence

or absence in serum) affect the effect of vitamin D on keratinocyte proliferation (according to *in vitro* studies). Although vitamin D (physiological concentrations) usually prevents keratinocyte apoptosis (triggered by various proapoptotic stimulants such as ceramide, UV radiation, tumor necrosis factor alpha (TNF-α), etc.), high concentrations actually induce keratinocyte apoptosis. All these factors can affect skin disease.

Vitamin D function in atopic dermatitis

The connection between vitamin D status and the occurrence of eczema in people with skin conditions is very noticeable in AD (Fig. 1). After observing that people living at high geographic latitudes, in whom vitamin D deficiency is more common, have a larger prevalence of allergic diseases, researchers have found that there is a potential correlation between vitamin D and development of allergic diseases (the so-called 'vitamin D hypothesis'). This hypothesis has been proposed after it was observed that self-initiation adrenaline injectors were less often used in areas closer to the Equator[6,16]. According to the research, there is positive correlation between the prevalence of eczema and geographic latitude and negative correlation with average annual outdoor temperature[16].

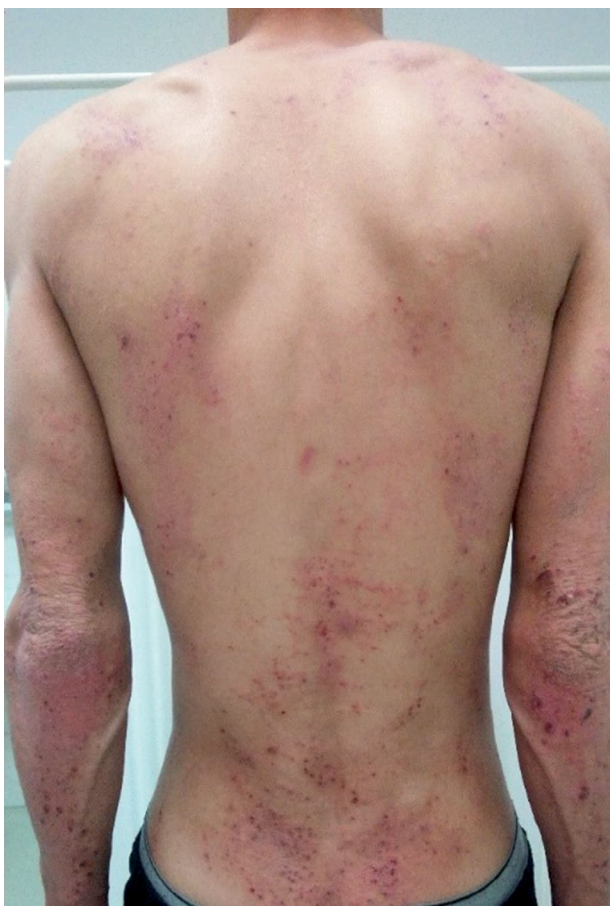

Fig. 1. Atopic dermatitis.

Also, according to study results, there is a lower prevalence of eczema in children living in regions with higher average annual humidity, higher temperatures, and higher UV index[1-3,6,7]. The impact of climatic conditions on the manifestations of eczema has been confirmed by randomized controlled studies. Namely, after a group of children changed their places of residence (from latitude 63°N to latitude 28°N), their eczema improved, i.e., children from Norway were sent to Gran Canaria, Spain (latitude 28°N) for a longer stay during the spring and autumn, which significantly improved their eczema[17]. Such geographical factors (latitude) and climatic/environmental effects on the prevalence and severity of eczema support the 'vitamin D hypothesis' theory. Observational studies have shown an association between vitamin D status and AD/eczema outcome and between lower serum vitamin D values and increased eczema incidence in children, which is even more pronounced in adults[6]. Epidemiological studies have also shown an increased AD prevalence in populations living at higher latitudes, i.e., in populations exposed to less sunlight, who thus produce less vitamin D[16,18,19]. Thus, more frequent AD development has been observed in persons with deficient/insufficient vitamin D levels.

However, there are inconsistent results concerning the relationship between vitamin D status and severity of AD/eczema symptoms. While some studies have found a correlation between lower vitamin D levels and severe forms of AD, others have not. Likewise, Akan *et al*. and Lee *et al*. noticed a relationship between allergic sensitization and vitamin D levels in patients with proven allergic sensitization, i.e., a negative correlation between eczema severity and vitamin D levels was observed, while the same impact was not observed in those without allergic sensitization[20,21]. It has also been noticed that eczema phenotypes are associated with multiple vitamin D gene pathways, indicating that vitamin D deficiency is an important factor that increases susceptibility to eczema. Overall,

few observational studies (including meta-analyses) noticed lower serum vitamin D levels in AD patients (than in controls) or a correlation between vitamin D deficiency and AD risk[22,23]. Also, according to research results, the occurrence of eczema in adults has been associated with lower bone mineral density (femur and spine) and osteoporosis (trochanter), while it has not been associated with vitamin D status, so further research is needed[6].

There are several biological/pathogenetic pathways that can be affected by vitamin D, e.g., vitamin D affects regulation of the immune system and skin barrier function, which is an important factor in eczema[6]. It also influences skin sensitivity to bacterial and viral infections[24]. According to research, individuals with eczema do not adequately produce innate immune activators, including antimicrobial peptides such as cathelicidin. Therefore, in cutaneous keratinocytes, vitamin D metabolites have been shown to encourage cathelicidin induction, which enhances cutaneous antimicrobial (anti-*Staphylococcus (S.) aureus*) activity[25]. Vitamin D also directly suppresses skin inflammation and increases the production of interleukin (IL)-10 in the skin mast cells, and has an effect on systemic immune responses that contribute to a person's allergic phenotype[6]. Vitamin D-receptor agonists also affect multiple cells and their actions/activities, i.e., Th1 cells and Th2 cells inhibit maturation of dendritic cells, induce tolerogenic dendritic cells, and induce regulatory CD4+/CD25+/Foxp3+T cells. Vitamin D also affects the skin barrier by acting on various epidermal structural cells, i.e., vitamin D and its receptor participate in the regulation and control of epidermal cell proliferation (in the basal layer), protein regulation in the spinous layer (K1, K10, involucrin) and granular layer (filaggrin and loricrin) and in the synthesis of lipids necessary for the function of the corneal layer[6].

So, with such numerous effects, vitamin D can alter/modulate the outcomes of allergic conditions by acting on altered epidermal barrier function, impaired immune regulation, and inadequate antibacterial defenses[6]. The association between vitamin D and infection is also important, i.e., a correlation between vitamin D status and growth of mycobacteria has been observed, as have correlations to other infections as well (e.g., hepatitis C infection, respiratory infections, HIV patients, acute infectious mononucleosis, and eczema herpeticum). Vitamin D has multiple antimicrobial functions because it inhibits mitogen-activated protein kinases (MAPK) and nuclear factor (NF)-kB signaling, and therefore inhibits IL-1b, IL-6, IL-8, IL-12p40, IL-23, interferon (IFN)-γ and TNF, yet inducing anti-inflammatory cytokine IL-10. At the same time, vitamin D inhibits chemokines CXCL9 and CXCL10. Considering the association between vitamin D status and infection, vitamin D supplementation may contribute to reducing the burden of *S. aureus* in the skin of AD patients. Clinical follow-ups of AD patients taking oral vitamin D supplementation (2,000 IU over 4 weeks) showed a reduction in *S. aureus* skin colonization and improvement in disease severity[26]. However, other reports exist that suggest either no role of vitamin D or even an inverse correlation between serum vitamin D levels and risk of developing AD[27]. Thus, while Di Filippo *et al*. suggest that vitamin D supplementation exerts a positive effect on AD by normalizing altered cytokines Th1 and Th2 (such as IL-2, IL-4, IL-6, and IFN-γ) in these patients, according to a study by Drozdenko *et al*., vitamin D supplementation increases the incidence of CD38+ B cells, enhances B cell receptor-mediated response, and decreases response *via* the T cell cytokines IFN-γ and IL-17[28,29]. The role of vitamin D supplementation in AD patients continues to be explored with the aim of gaining new insights

The role of vitamin D in psoriasis

Results of many studies indicate an important role of vitamin D in psoriasis, especially since deficiency and insufficiency are more often recorded in these patients[30-32]. According to a number of case-control studies, serum 25(OH)D levels were significantly lower in patients with psoriasis than in control group subjects. Also, serum 25(OH)D levels and disease severity were negatively correlated[33,34]. However, not all research led to the same conclusion; according to screening of one population in which vitamin D deficiency is not common, there was no significant difference in serum 25(OH)D levels between patients with psoriasis and those without it. Also, it has been observed that 25(OH)D levels depend on several factors including race, food intake and UV radiation (exposure), so it is important to carefully interpret the results.

In psoriasis, vitamin D inhibits IL-2, IL-6, IL-8 and IFN-γ secretion, and stimulates IL-10 production, which then reduces T cell proliferation and induces regulatory T cell differentiation. Vitamin D controls skin inflammation by influencing antimicrobial peptide production through inhibition of two antimicrobial peptides (psoriasin and koebnerisin/cathelicidin) and increase in LL-37 and HBD2 expression. These anti-inflammatory and antiproliferative effects of vitamin D led clinicians to use topical vitamin D analogs in the treatment of psoriasis. Different clinical studies have confirmed that vitamin D treatment can be effective in patients with psoriasis, especially a combination of vitamin D (or its analogs) and corticosteroid treatment. The inhibitory effect of vitamin D in patients with psoriasis has been established in different ways, including connection to plasmacytoid dendritic cells (pDCs). These pDCs, which normally initiate a psoriasis inflammatory cascade, lead to expression of transcriptionally active vitamin D receptor (VDR) and metabolizing enzymes CYP27B1 and CYP24A1, which metabolize vitamin D. Vitamin D treatment diminishes pDCs competence to induce T cell proliferation and IFN-γ secretion, which has been shown to be beneficial in patients with psoriasis.

The role of vitamin D in chronic urticaria

Chronic urticaria (CU) is usually defined by frequent outbreaks of hives lasting for 6 or more weeks and is often therapy resistant (Fig. 2)[35,36]. According to different studies, serum 25(OH)D levels were significantly lower in CU patients, and especially chronic spontaneous urticaria (CSU) patients, than in the control groups[25]. Other studies, including Thorp *et al.*, did not find any connection between vitamin D levels and duration/severity of CU, and Woo *et al.* and Chandrashekar *et al.* report negative correlation between urticaria severity and serum 25(OH)D levels[36-38].

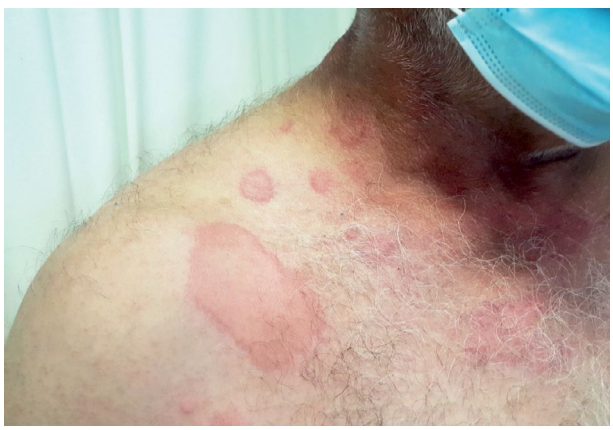

Fig. 2. Urticaria.

According to study results by Woo *et al.*, significantly lower serum 25(OH)D values were recorded in CU patients than in patients with acute urticaria, AD or healthy controls. Furthermore, the majority of CU patients had very low levels (<10 ng/mL)[38]. It has also been reported that vitamin D deficiency can increase the probability of acute urticaria turning into CU[7]. A possible correlation between vitamin D values and the autologous serum skin test (ASST) has also been noticed in CU. While Chandrashekar *et al.* and Woo *et al.* report significantly lower serum 25(OH) D levels in patients with positive ASST compared to patients with negative ASST, Thorp *et al.* and Grzanka *et al.* state that a positive ASST did not correlate with serum 25(OH)D levels in CSU patients[36-39]. Studies on the relationship between total IgE and vitamin D levels have shown that vitamin D influences IgE production by significantly decreasing stimulated B cell IgE production after vitamin D administration (*in vitro*), so it is most likely that vitamin D affects urticaria through immunomodulation of IgE-mediated pathways. However, since both immune and non-immune mechanisms can stimulate mast cell activation in urticaria, the precise role of vitamin D in the pathogenesis of CU is still unknown[7].

The role of vitamin D in contact dermatitis

Contact dermatitis (Fig. 3) is skin inflammation caused by an irritant (irritant contact dermatitis, ICD) or allergen (allergic contact dermatitis, ACD) exposure[7,40]. In contrast to AD and CU, ACD encompasses cell mediated type IV hypersensitivity (delayed hypersensitivity). Th1 cells, which stimulate keratinocytes to release proinflammatory cytokines, play an important role here. Research results from one study on ACD with animal (mice) models, with analysis of vitamin D role in ACD, produced useful data[7]. Male mice with normal vitamin D levels responded better to treatment compared to those with vitamin D deficiency (this effect was not reported in female mice), which indicates that vitamin D supplementation could be beneficial

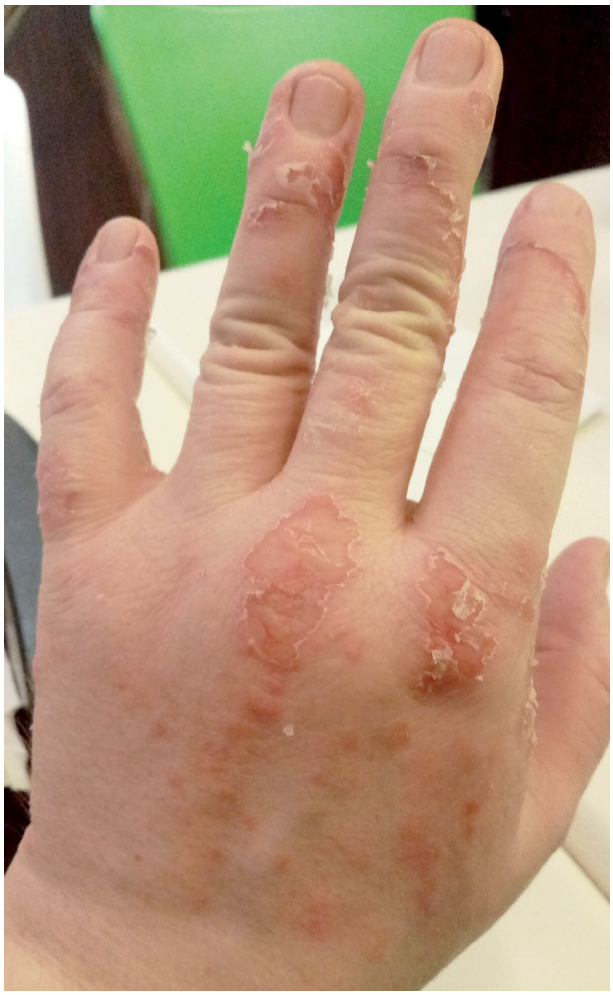

Fig. 3. Contact dermatitis.

in humans with ACD. According to a recent study on irritant CD and ACD treated with vitamin D supplementation, slightly more improvement in clinical conditions was recorded in the group given supplements than in the group not receiving supplements (although the difference was not statistically significant) with no adverse effects of treatment observed[8].

Vitamin D Supplementation Effect and Perspective of Vitamin D Use in Practice

In the absence of well-designed randomized controlled studies on the effect of vitamin D (from food, nutrition supplements and/or sunlight exposure) on eczema development, only limited and contradictory evidence is available. However, we do know that, among other factors, determining the role of certain genetic polymorphisms and its effect on vitamin D status in early life and eczema development, are important, as well as the impact of dietary and other lifestyle factors as potential preventive strategies for allergies[6,41].

Concerning the role of vitamin D in eczema development in infancy, it is important to consider that the levels of vitamin D (25[OH]D) in breast milk are mostly low (approximately 25 IU/L). Yet, nursing women themselves have sufficient levels of 25(OH)D, which can be increased to the benefit of the infant by greater sunlight exposure and vitamin D supplementation[6]. According to the literature, mothers of neonates minimally exposed to sun should receive 6000 IU *per* day to achieve the neonate daily intake needs of 400 to 500 IU (either through UV exposure or oral intake). According to research, diminished hypersensitivity (allergy) to allergens in childhood was observed in those neonates whose vitamin D levels were greater and whose mothers' vitamin D intake during pregnancy was greater. On the other hand, Weisse *et al*. observed a correlation between pregnant women's greater 25 (OH) D levels (approximately 55 nmol/Ln during the third trimester) and an increased risk of allergy to food allergens[41]. A recent meta-analysis including trials pulled from multiple databases found that a daily vitamin D dose of 400 IU was enough to prevent rickets[42]. However, taking the use of topical vitamin D treatments/products in patients with eczema and AD into consideration, a significant negative impact from calcipotriene (a vitamin D analog used for psoriasis) on eczema was recorded. According to research on mouse models with AD, lasting eczematous dermatitis appeared at the sites where calcipotriene was applied; thus, topical vitamin D analogs are not recommended for the treatment of eczema[6,43].

Concerning vitamin D supplementation in AD patients, differing outcomes have been observed in adults in several randomized double-blinded placebo-controlled studies. During follow-up of the effect of oral vitamin D supplementation (1600 IU/day for a 60-day period), significant improvement of AD severity was observed (compared to the placebo group)[44,45]. According to research results, using a higher dose (4000 IU *per* day for 21 days) did not improve eczema

symptoms[6,44,45]. Thus, further research is needed to determine how vitamin D supplementation should be used as a complement treatment. The proper dose and duration of treatment, as well as the effects of different related factors (race, latitude, time *per* year spent outdoors, gender, skin type by Fitzpatrick's classification, alcohol intake, physical activity, body mass index, and one nucleotide polymorphism of vitamin D binding protein) should be explored in future research.

Studies on CU suggest there is a benefit of assessing vitamin D status in these patients. According to research, vitamin D deficiency can also be an additional indicator of autoimmune urticaria[7]. According to a case report of a patient with a ten-year history of CU and severe vitamin D deficiency (4.7 ng/mL), vitamin D supplementation led to complete recovery. Based on a retrospective case series study (28 patients with urticaria and angioedema and very low vitamin D levels of >32 ng/mL), supplementation induced positive response with complete symptom resolution in 61% of cases. According to a study by Boonpiyathad *et al.*, CSU patients with serum 25(OH)D levels <30 ng/mL experienced significant improvement after 6 weeks of vitamin D supplementation[46]. So, at the end of 6 weeks of vitamin D supplementation, the CSU patients had Urticaria Activity Score (UAS) and Dermatology Life Quality Index (DLQI) scores similar to those of healthy controls. Different prospective studies indicate that supplementation with high vitamin D3 doses is safe and beneficial for CSU patients[46]. Follow-up of vitamin D supplementation in CSU patients shows that patients on higher doses had a lower incidence of urticaria (fewer days with urticaria), and less of their body surface was affected. In CSU patients with low 25 (OH) D levels (<30 ng/mL) treated with vitamin D (300,000 IU/month), significant improvement was seen after 12 weeks in UAS and patient quality of life (hCU-Q2oL) scores[7]. Further clinical trials with greater numbers of CU patients could help determine what an optimal supplementation dose would be, and they could possibly uncover some of the etiologic mechanisms of vitamin D in CU patients.

In ACD, it has been established that low doses of UV light can be therapeutic. Since UV light contributes to vitamin D reserves, this could indicate a positive correlation between vitamin D levels and ACD improvement, but further research is needed to look at the precise factors involved[7]. One study on animal models demonstrated that mice with higher serum vitamin D values were more likely to experience ACD convalescence. According to our recent prospective study in 157 patients (51 AD patients, 51 CD patients and 55 CU patients), vitamin D supplementation made a significant difference in clinical pictures of these conditions, with improvement seen in most of the patients[8]. Of all the above-mentioned diagnoses, vitamin D deficiency was mostly found in those with ICD, and less often in those with ACD, but with no statistically significant differences. These results indicate that even though vitamin D values are not of critical importance in all patients with these inflammatory skin diseases, vitamin D supplementation can be beneficial in some of them without presenting a risk to others[8].

Key Data on Vitamin D in Other Skin Diseases

Among other skin diseases and conditions, a few of them stand out in relation to vitamin D. According to a meta-analysis of observational studies, there is an established correlation between vitiligo and low vitamin D levels. Even though it is unclear whether vitamin D is involved in the pathogenesis of vitiligo, UVA or UVB exposure treatment combined with topical vitamin D analogs has been shown to be beneficial[47]. In SLE, a strong correlation between low 25 (OH) D levels and SLE activity has been observed[48,49]. According to Mok *et al.*, vitamin D deficiency is a marker of SLE activity, and its specificity can be compared to that of an anti-double stranded DNA and anti-C1q[49].

Vitamin D deficiency has also been observed in skin lymphoma, e.g., in mycosis fungoides (MF). According to research, the prevalence of vitamin D deficiency in patients with skin T cell lymphoma is similar to that of cancer patients (when compared to healthy controls), and it is important that aberrant T cell clones express vitamin D receptors[50]. Also, a significant correlation between MF and vitamin D receptor polymorphism (Fok1 polymorphism) has been observed. When there is vitamin D deficiency, antimicrobial peptides are decreased, and colonization with *S. aureus*, as well as sepsis, commonly recorded in T cell skin lymphoma, are more commonly seen. In addition, stimulation of

staphylococcal superantigen may induce and promote T cell activation and production of aberrant clones. According to the results reported by Rasheed *et al.*, vitamin D levels did not significantly correlate with MF manifestations or duration, so vitamin D probably only plays a role in inducing MF[51]. Vitamin D status has also been well researched in patients with cancer and certain precancerous lesions, including a meta-analysis by Autier and Gandini[52]. They did not find a significant correlation between most neoplastic diseases and vitamin D concentrations, except for a significant correlation between decreased colorectal cancer incidence and increased 25 (OH) D levels[52]. Concerning vitamin D and skin tumors, vitamin D receptors are important, i.e., hyperproliferative keratinocytes which lack vitamin D receptors exhibit reduced levels of apoptosis. Polymorphisms of vitamin D receptors are involved in actinic keratosis development. Vitamin D enhances DNA damage repair and decreases production of UVR-induced cyclobutane pyrimidine dimer (CPD) production *in vitro*. Concerning melanoma, several studies confirm that there is a correlation between vitamin D status and melanoma, i.e., vitamin D receptor expression and polymorphisms of vitamin D receptors correlate with melanoma, even though vitamin D inhibits tumor invasion, angiogenesis and metastasis[5].

Conclusion

Vitamin D status plays a very important role in many skin diseases, and its supplementation can be beneficial in patients suffering from these diseases. Oral vitamin D supplementation contributes to maintaining sufficient vitamin D concentration and benefits most patients. Future research on this topic will provide better insight into the use and effect of vitamin D supplementation in patients with skin disorders.

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Sažetak

VITAMIN D U BOLESNIKA S UPALNIM BOLESTIMA KOŽE

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U potrazi za odgovarajućim liječenjem i poboljšanjem stanja kože bolesnika s upalnim bolestima kože, nadoknada vitamina D pokazala se korisnom prvenstveno zbog njegovih učinaka na niz funkcija kože: proliferaciju keratinocita, diferencijaciju i apoptozu, održavanje epidermalne barijere, kao i regulaciju imunosnih procesa u koži. Vitamin D je neophodan za opće zdravlje i zdravu kožu, a do njegovog nedostatka može doći zbog različitih čimbenika koji su rezultat produženog boravaka u zatvorenom prostoru i ograničene izloženosti sunčevoj svjetlosti, kao što su geograski uvjeti (mjesto stanovanja) i genetski čimbenici. Iako rezultati nisu sasvim dosljedni, dosadašnja istraživanja pokazuju da nedostatak vitamina D može utjecati na mnoge upalne bolesti kože, naročito atopijski dermatitis, ali i druge upalne bolesti kože. Također postoje dokazi o povezanosti nedostatka vitamina D i rizika od pogoršanja kožnih bolesti kao što su psorijaza, kronična urtikarija, kontaktni dermatitis itd. Prema većini istraživanja je kod ovih i niza drugih upalnih kožnih bolesti u bolesnika uočen pozitivan učinak nadoknade vitamina D.

Ključne riječi: *Vitamin D; Nedostatak vitamina D; Atopijski dermatitis; Psorijaza; Kronična urtikarija; Kontaktni dermatitis*