SZYDZIAK, Joanna Maria, HRAPKOWICZ, Aleksandra, JANOWSKA, Kinga, DĄBKOWSKA, Daria, SZEIDL, Olga, REHAN, Dominika, WOŁOSZCZAK, Julia and MIOSKOWSKA , Agnieszka. The Role of Vitamin D in Allergic Diseases. Quality in Sport. 2024;31:55762 eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.31.55762
https://apcz.umk.pl/QS/article/view/55762

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assig589 ned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 28.10.2024. Revised: 07.11.2024. Accepted: 08.11.2024. Published: 12.11.2024.

The Role of Vitamin D in Allergic Diseases

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1. ABSTRACT

Introductions: Vitamin D has gained recognition in recent decades not only as a key regulator of calcium and phosphorus metabolism and bone health but also as an important factor modulating the immune system. Research indicates that vitamin D influences both innate and adaptive immune responses, which is significant in the treatment of allergic and inflammatory diseases. Vitamin D has a beneficial effect on asthma exacerbations and may help reduce respiratory inflammation, as well as alleviate symptoms of allergic rhinitis. Vitamin D deficiency may increase the risk of food allergies, worsen symptoms of atopic dermatitis, and contribute to the transition from acute to chronic urticaria. Conversely, supplementation may help prevent allergies, reduce the severity of atopic dermatitis by supporting skin barrier function and antimicrobial peptide production, and relieve symptoms in patients with chronic urticaria.

Purpose of the study: The review article aims to present the current state of knowledge on the role of vitamin D in the treatment of asthma, allergic rhinitis, food allergies, atopic dermatitis, chronic urticaria, and eczema

Material and methods: To summarize the current knowledge on the topic, a literature review of English language papers with a focus on the most current literature was performed. The review was conducted with the PubMed database with 64 works used, accessed before October 2024.

Conclusions: Although the impact of blood vitamin D levels on the development and progression of allergic diseases has not yet been fully clarified, scientific studies suggest its significant role in modulating immune responses. Due to its immunoregulatory properties, vitamin D offers new hope for more effective treatment and prevention of allergic diseases.
Keywords: vitamin D, asthma, Allergic rhinitis, Food allergies, Atopic dermatitis, Chronic urticaria, Contact dermatitis

2. INTRODUCTION

Over the past two decades, vitamin D has gained recognition not only for its classic role in calcium-phosphate metabolism and skeletal health but also for its broader effects on immune regulation and modulation. Emerging research indicates that vitamin D is more than just a regulator of bone mineralization; it functions as a critical modulator of the immune system, influencing both innate and adaptive immune responses. The discovery that nearly all human tissues, including immune cells, express vitamin D receptors (VDRs) has further propelled interest in its potential involvement in various immune-mediated conditions, including asthma, allergic rhinitis, chronic urticaria, contact dermatitis, and atopic dermatitis [1].

Vitamin D, particularly in its active form (1,25-dihydroxyvitamin D or calcitriol), exerts potent effects on the immune system by modulating the activity of immune cells such as dendritic cells, macrophages, T and B lymphocytes [2]. It influences the maturation of dendritic cells, promoting a tolerogenic phenotype, and suppresses the proliferation of T-helper 1 (Th1) and T-helper 17 (Th17) cells, which are typically associated with inflammatory and autoimmune conditions. On the other hand, vitamin D stimulates T-helper 2 (Th2) and regulatory T cells (Tregs), which promote anti-inflammatory responses and maintain immune tolerance [3]. These immunoregulatory properties have sparked significant interest in the potential therapeutic applications of vitamin D for managing chronic inflammatory and allergic diseases.

A growing body of epidemiological evidence has linked low serum levels of vitamin D with an increased susceptibility to various allergic disorders, such as asthma and atopic dermatitis. A notable study by Camargo et al. (2007) found that children born to mothers with low vitamin D levels during pregnancy were at a higher risk of developing asthma and other allergic diseases later in life [4]. This association has prompted investigations into whether vitamin D supplementation could serve as an effective intervention for preventing or mitigating allergic conditions. In asthmatic patients, for instance, vitamin D has been shown to enhance the efficacy of corticosteroids and reduce exacerbations, particularly in individuals with baseline vitamin D deficiency [5]. However, clinical trials assessing the role of vitamin D supplementation in treating allergic diseases have produced mixed results.

While some studies have reported improvements in symptom control and disease severity, particularly in conditions like atopic dermatitis and chronic urticaria, others have found no significant therapeutic effect [6]. These inconsistencies may be attributed to differences in study design, dosing regimens, population heterogeneity, and baseline vitamin D status. Moreover, genetic variations in vitamin D metabolism, including polymorphisms in genes encoding the VDR, may influence individual responses to supplementation, further complicating the interpretation of results.

In addition to its effects on immune modulation, vitamin D plays a crucial role in epithelial barrier function. Studies have shown that vitamin D enhances the production of antimicrobial peptides, such as cathelicidins, which are important in maintaining skin integrity and preventing infections. This is particularly relevant in conditions like atopic dermatitis, where skin barrier dysfunction is a hallmark feature [7]. As such, vitamin D may exert protective effects by not only modulating immune responses but also by reinforcing physical barriers that are compromised in allergic diseases.

Given the widespread prevalence of vitamin D deficiency globally, particularly in higher latitudes, the potential public health implications of correcting deficiency through supplementation are vast. Despite promising early findings, the inconsistent outcomes of clinical trials suggest that more rigorous studies are needed to establish optimal dosing strategies, clarify the patient populations that would benefit most, and further elucidate the molecular mechanisms underlying vitamin D's immunomodulatory effects. This paper aims to critically review and assess the current state of research on the role of vitamin D in the immune system, with a specific focus on its application in asthma, allergic rhinitis, chronic urticaria, contact dermatitis, and atopic dermatitis. By synthesizing evidence from clinical trials, observational studies, and mechanistic research, we hope to provide a comprehensive overview of vitamin D’s potential as a therapeutic agent in managing these allergic conditions and to identify key areas where future research is necessary.

3. STATE OF KNOWLEDGE

1. ASTHMA

Asthma is a common chronic respiratory disease caused by complex gene-environment interactions. It is characterized by variable respiratory symptoms, varying intensity of inflammation, and airway remodeling, and affects children and adults worldwide, leading to significant morbidity, mortality, and economic burden [8,9,10].

There are regions on chromosome 17 associated with various immune diseases, including asthma. Additionally, there are sites on this chromosome where the vitamin D receptor (VDR) can bind. These sites overlap with genetic variants associated with diseases caused by Th2 cells, which respond actively to pathogens by producing inflammatory mediators and modulating the activity of other cells in the immune system. They are also activated by mites and pollen, causing allergic inflammation and diseases such as asthma [11]. Single nucleotide polymorphisms located in the vitamin D receptor gene can modify its expression, ultimately leading to a change in the biological function of vitamin D and the appearance of asthmatic disease.

There is a significant association between the presence of the A allele in the VDR Cdx2 polymorphism (rs11568820), located in the promoter region of the 5' end of the VDR gene, which can affect the correct binding of the primer, and consequently change transcription, and the risk of asthma [12]. The rs11168293 G allele in the VDR gene is associated with a lower level of 25(OH)D and a higher number of eosinophils in the blood, while the rs7041 A allele in the VDBP gene coexists with a higher level of IgE in asthma [13].

A meta-analysis conducted by Marharyta Sobczak et al. included 15 studies and shows that vitamin D supplementation can prevent asthma and wheezing and support the treatment of asthma depending on the patient's age. Vitamin D supplementation during pregnancy can reduce the occurrence of wheezing in children, but in infancy, it does not affect asthma parameters. A positive effect of vitamin D is also seen in the ACT result in adults, but it hurts the change in FEV1 before and after treatment in children [14].

In a review of 71 studies on the association between serum vitamin D (25(OH)D) levels and inflammatory biomarkers in patients with asthma, vitamin D was shown to reduce levels of proinflammatory cytokines such as IL-1, IL-6, and TNF-α, to affect B lymphocytes by inhibiting their differentiation, limiting their proliferation, and reducing the production of immunoglobulins such as IgE, and to increase the production of IL-10, thereby exerting additional regulatory effects. The role of vitamin D in the immune response is very complex, but the findings underscore its potential as a key regulator of both innate and adaptive immunity. The lack of high-quality in vivo data makes it impossible to draw firm conclusions on the validity of these putative mechanisms of action in patients with asthma [15].

A meta-analysis by Asmae El Abd et al. showed that vitamin D supplementation in asthmatics has no significant effect on inflammatory biomarkers such as serum IgE, blood and sputum eosinophils, and FeNO. However, it increases IL-10, which may be responsible for the anti-inflammatory effect in asthma [16].

In a study of humans with asthma and mice with two common asthma endotypes, vitamin D deficiency was found to be associated with the expression of inflammatory cytokines, which can cause airway inflammation, small airway dysfunction, and increased airway resistance [17].

The potential mediators and modifiers of asthma exacerbations influenced by vitamin D status are miRNAs. Eleven miRNAs were identified during the study, which was mainly related to functional modules in the immune system such as leukocyte development, leukocyte migration, and immune response, through in vitro microarray experiments. Both historical and future hospitalization could be predicted by hsa-miR-143-3p and hsa-miR-451a [18].

Vitamin D has a beneficial effect on the respiratory tract, reducing inflammation and regulating collagen synthesis, inhibiting the contraction and remodeling of airway smooth muscle cells, and may also modulate the function of bronchial fibroblasts [19]. It does not affect the occurrence of upper respiratory tract infections or the duration of asthma exacerbations in adults with vitamin D deficiency [20]. A study in asthmatic mice shows that vitamin D alleviates airway inflammation by reducing mucus secretion without affecting the loss of alveolar structure, reduces inflammatory cell infiltration, and attenuates alveolar wall thickening [21]. Increased concentrations of 25(OH)D in overweight and obese people reduce the incidence of asthma [22].

2. ALLERGIC RHINITIS

Allergic rhinitis (AR) is inflammation of the inside of the nose caused by inhaled allergens. It is commonly recognized as it affects one in six individuals. AR is associated with significant morbidity, loss of productivity, and healthcare costs [23]. It is mediated by immunoglobulin E, and it clinically manifests as sneezing, nasal congestion, and itching of the nose.

According to research, vitamin D plays a crucial role in allergic rhinitis as it influences the immune system by modulating dendritic cells, and T and B cells. It participates in the pathogenesis of AR by shifting the balance of CD4+ T cells from Th1 to Th2, which might enhance Th-2-mediated allergic inflammation. Vitamin D also promotes the induction of Foxp3+ Treg cells, which can have anti-inflammatory effects, and suppresses Th17 cells, potentially reducing inflammation [24].

Clinical studies provide mixed results regarding vitamin D's influence on AR. Some research shows a positive relationship between early vitamin D supplementation (especially in infancy) and the increased risk of AR in adulthood. For instance, Hyppönen et al. found a higher prevalence of AR in individuals who received infant vitamin D supplementation [25]. Conversely, other studies, like those by Bunyavanich et al., suggest that food-based maternal vitamin D intake during pregnancy may lower the risk of AR in children [26]. Observational studies have found either positive, negative, or no associations between serum vitamin D levels and AR across different populations. Most of them claim that individuals with AR often have vitamin D deficiencies [27]. The severity of symptoms also increases with lower vitamin D levels and deficiency of vitamin D is considered as a potential etiologic and disease-modifying factor [28]. Jung et al. [29] conducted a large-scale national survey involving 8,012 Korean adults aged 18 and above, showing that lower levels of 25(OH)D were associated with a higher incidence of allergic rhinitis. Other observational studies confirm a higher prevalence of vitamin D deficiency in AR patients, rating between 30% and 90% [28]. Agarwal et al. found that supplementation of vitamin D at a dose of 1000 IU daily over 30 days significantly reduced the Total Nasal Symptom Score (TNSS) in AR patients when compared to a placebo group [30]. This finding highlights the potential role of vitamin D supplementation in alleviating AR symptoms.

However, some research does not confirm the correlation between vitamin D and allergic rhinitis. Cheng et al. conducted a large cross-sectional study in Korea with 15,212 adults aged 19 or above which used multivariate linear regression analysis. It showed that vitamin D deficiency was not associated with an increased likelihood of asthma, allergic rhinitis, or IgE sensitization in adults [31]. Mendelian randomization study also found no evidence of a relationship between serum vitamin D levels and AR risk within people of European origin [32]. Therefore, more research is needed to confirm the role of vitamin D in allergic rhinitis.

3. FOOD ALLERGIES

Food allergies (FA) occur when the immune system is triggered by a food protein mistakenly identified as a harmful antigen. They can be classified as IgE-mediated, IgE-

dependent, non-IgE-mediated, and IgE-non-dependent [34], with IgE-mediated being the most common form of food allergy [34].

In recent years, the prevalence of FAs has been increasing, as has the number of hospitalizations due to food-induced anaphylaxis [35]. The greatest increase has been noticed in infants and children [36]. FAs can manifest as esophagitis, enterocolitis and rectal colitis, and are considered a health burden that can negatively affect the quality of life [38]. While the pathogenesis of food allergies is complex, various studies have suggested the role of vitamin D in their development [38].

Currently, the most probable mechanism of vitamin D influencing the development of FA is its deficiency. Vitamin D acts directly on immune cells and promotes the anti-inflammatory state [39] by reducing the production of inflammatory cytokines and promoting tolerance [40]. It also seems to be an important regulator for maintaining the integrity of the wall of the intestine. Vitamin D deficiency (VDD) can affect intestinal barrier defenses and affect its permeability, potentially increasing the risk of colonization by abnormal bacteria and alternating microbiota [38]. The defective barrier is prone to penetration by food allergens, which stimulates B cells to produce more immunoglobulin E (IgE) [38]. Increased immunoglobulin level leads to stronger Th-2 type immune response, causing stimulation of mast cells to release its mediators, such as histamine, which is responsible for allergic manifestations, including gastrointestinal ones [41].

Production of vitamin D is related to sun exposure, and it is often insufficient among inhabitants of cold and dark areas. Various studies confirmed the increased risk of developing allergies in individuals living farther from the equator, sunless places or even born in winter [41]. Furthermore, in a study performed by K. J. Allen et al. on 5276 children, it was proven that among infants who were food-sensitized, those with insufficient vitamin D levels were six times more prone to develop food allergies compared to other infants. Moreover, they were three times more likely to develop egg allergy and 11 times peanut allergy. Infants with VDD were also found to have a higher likelihood of having multiple food allergies rather than just a single food allergy [42]. Sharief S. et al. studied 3135 children and proved that 11 of 17 food proteins were more common to induce allergy among children with VDD compared to those with adequate vitamin D levels. Those with deficiency were also more prone to developing peanut, ragweed, and oak allergy [43].

Introducing complementary foods early is considered one of the best ways to prevent allergy development, in contrast to the previous approach of food avoidance [36]. Furthermore, providing sufficient vitamin D supplementation during the first year of life can help sensitize children against allergies and reduce their risk of developing them [39].

Despite numerous studies proving the relationship between vitamin D deficiency and the development of food allergies, there have been theories that suggest that high levels of vitamin D can also influence allergy development by affecting dendritic cell maturation and Th1 responses [36]. C. Cairncross et al. studied 1329 participants aged between 2 and 5 years and concluded that children with 25(OH)D concentrations ≥75 nmol/L had two times increased risk of food allergy [44].

Differences in research results and the fact that both allergies and VDD are of high prevalence make further investigation into the relationship between vitamin D and the development of food allergies still necessary.

4. ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by periodic flare-ups that can significantly impact a patient's quality of life [45]. It is a common skin condition in children characterized by defects in skin structure, immune system dysregulation, and alterations in the skin microbiome [48]. Also, it's the most prevalent skin disorder in children, affecting around 15% to 20% of the global population. Clinically, AD is marked by intense itching, eczematous lesions, and a compromised epidermal barrier. The exact mechanisms behind AD remain unclear, involving a complex interaction of immune system dysfunction, genetic predispositions, and environmental influences. In patients with atopic dermatitis (AD), defects in the skin barrier, alongside reduced functional integrity and impaired regeneration, contribute to triggering immune responses and specific inflammatory reactions [45]. In acute AD lesions, these skin barrier issues lead to reduced production of antimicrobial peptides (AMPs), increased colonization by Staphylococcus aureus, and worsened disease severity, as well as heightened infection risk [48]. Current standard treatments for AD typically include immune modulators, such as topical and oral corticosteroids, as well as topical calcineurin inhibitors. However, achieving control of the condition can be challenging for some patients, indicating the potential involvement of additional factors [45].

While several new treatments have been developed that effectively reduce the severity of AD, the use of vitamin D as a therapy remains a topic of ongoing debate. Vitamin D plays a significant role in improving skin barrier function, boosting AMP production, and enhancing the activity of monocytes and macrophages. Its effects extend to both the innate and adaptive immune systems, with several mechanisms influencing the progression of AD lesions [48]. Vitamin D3 has been found to correlate strongly with the production of proteins essential for maintaining skin barrier function. By supporting the synthesis of these protective proteins, adequate levels of vitamin D could help improve skin integrity and reduce the severity of symptoms associated with AD [45]. These include promoting epidermal differentiation, increasing cathelicidin production (an important AMP), reducing Th2 cytokine levels, decreasing IgE production, limiting B cell proliferation, and upregulating T cell responses. Together, these functions suggest that vitamin D may help modulate the immune system and skin integrity in AD patients [48]. Interest in vitamin D supplementation as a potential preventive measure arises from the association between low vitamin D levels and a higher incidence and severity of atopic dermatitis. Vitamin D is recognized for its regulatory effects on skin barrier function and the immune system—both critical factors in the development of AD [47]. A recent meta-analysis of interventional studies found that vitamin D supplementation was associated with a significant reduction in the severity of atopic dermatitis in both adults and children [45]. A study by Wang et al. involving 498 children with AD found that 47.8% had vitamin D deficiency, 41% had vitamin D insufficiency, and only 11.2% had normal serum vitamin D levels. Similarly, research by Farazjadeh et al. reported that pediatric AD patients

had lower average serum vitamin D levels compared to healthy controls, although the specific prevalence of deficiency or insufficiency was not detailed. A previous systematic review and meta-analysis conducted in 2019 found a highly significant reduction in the SCORAD (Scoring of Atopic Dermatitis) score following vitamin D intervention in both pediatric and adult populations.

In contrast, a systematic review published by Huang in 2018, focusing specifically on pediatric patients with atopic dermatitis, reported that 67% of the included studies observed a significant improvement in AD severity with vitamin D supplementation; however, this review did not perform a meta-analysis [48]. This evidence suggests that increasing vitamin D levels may provide clinically meaningful improvements for individuals suffering from this condition [45]. The last meta-analysis of four prospective cohort studies revealed that lower maternal vitamin D serum levels during pregnancy are linked to a higher risk of atopic dermatitis in offspring. Interestingly, this correlation between prenatal vitamin D levels and the risk of developing AD was more pronounced at higher latitudes, underscoring the influence of regional and geographical factors on this relationship. Conducted research and observation studies suggest that vitamin D deficiency may play an important role in the pathophysiology of atopic dermatitis [46]. However, a more recent and well-conducted randomized controlled trial found no significant benefit of vitamin D supplementation in infants for the primary prevention of atopic dermatitis [47].

In recent years, the connection between vitamin D serum levels and the prevalence and severity of atopic dermatitis has been extensively investigated. While there are promising findings regarding the potential role and therapeutic application of vitamin D in managing AD, the existing data remain inconsistent [46]. This highlights the need for further research to better understand the role of vitamin D in AD prevention [47]. To clarify these uncertainties, randomized controlled trials (RCTs) are necessary to determine the optimal dosage, target serum levels, treatment duration, and the effects of vitamin D supplementation for both the prevention and treatment of atopic dermatitis [46]. Recent advances in AD treatment have shifted toward targeting immune regulation and strengthening the skin barrier, alongside reducing inflammation. Poor adherence to topical treatments has prompted the exploration of alternative therapies that are safe, affordable, and easy to use. Vitamin D supplementation has emerged as a potential option in this context, although the results of intervention studies remain mixed and inconclusive [48].

5. CHRONIC URTICARIA

Chronic urticaria is recognizable through the appearance of characteristic itchy wheals on reddened skin. [49]. We talk about chronic urticaria when urticarial episodes occur daily or almost daily for at least 6 weeks [50]. Urticaria can be idiopathic or can present as a type I hypersensitivity reaction. Urticaria is commonly called "hives" [49]. Numerous cells are responsible for the clinical manifestation of urticaria. These are mast cells, dendritic cells, basophils, and monocytes [49]. Up to 30% of patients with chronic urticaria produce IgG autoantibodies against the FcεRIα or IgE receptor. These antibodies release histamine from mast cells [51]. Elevated levels of proinflammatory cytokines were also observed in patients [52]. In urticaria, cytokines such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, and IL-12

are released [53]. It seems that IL-6 plays one of the most crucial roles in the mechanism of urticaria because its amount is related to the clinical severity of chronic urticaria [54].

Numerous studies have compared vitamin D (25[OH]D) levels of patients without chronic urticaria with those suffering from chronic urticaria. Nevertheless, different results were achieved.

In the research study conducted by Thorp et al. [55], there was no correlation between vitamin D levels and chronic urticaria. In studies conducted by Woo et al. [49] and Chandrashekar et al. [56] a negative correlation has been shown. Other studies examining the correlation between ASST and 25[OH]D conducted by Thorp et al. [55] and Grzanka et al. [57] found no correlation between them, while Chandrashekar et al. [56] and Woo et al. [49] noted that in ASST-positive patients the serum 25[OH]D was lower than in ASST-negative patients. Even though Chandrashekar et al. [56] and Woo et al. [49] suggested that vitamin D deficiency may play a role in chronic urticaria, the differences in the findings of the aforementioned studies show that the correlation between vitamin D levels and chronic urticaria requires further investigation. Moreover, Woo et al. [49] suggested that vitamin D deficiency may play a role in the progression of acute urticaria into chronic urticaria.

The authors of this study base their suggestion on the results of studies in which, among patients suffering from acute urticaria and vitamin D deficiency (<10 ng/ml), as many as 50% experienced the transformation of acute urticaria into chronic urticaria. Vitamin D deficiency may play a significant role here. It is worth adding that typically in patients with chronic urticaria, the level of IgE increases. Noteworthy are the studies comparing IgE levels with vitamin D levels. One of the clinical studies shows that after the administration of vitamin D, the level of IgE released by B lymphocytes is lower than without its administration. This information does not allow us to confirm the mechanism of action of vitamin D in chronic urticaria, but it can be supposed that vitamin D affects the immunomodulation of IgE-related pathways. This study was conducted to check how vitamin D supplementation affects chronic urticaria.

Promising results were achieved. Among the group of 28 patients suffering from chronic urticaria and deficiency in vitamin D, the symptoms of chronic urticaria disappeared in 61% of patients when vitamin D was supplemented [59]. Boonpiyathad et al. [60] revealed similar results in the case of a group in which 58 people took part [61]. People suffering from chronic urticaria and vitamin D deficiency (<30 μg/l) got an extra 300 000 IU/month of vitamin D in addition to standard therapy.

Clinical improvement was indicated after 3 months. The study concluded that the patients with chronic urticaria, in opposition to the control group, had significantly lower levels of vitamin D. Patients with modifications therapy for therapy with additional supplementation of vitamin D had better DLQI and UAS. The study outlines that vitamin D supplementation in patients with chronic urticaria may have a positive effect on reducing symptoms of chronic urticaria and positively improving the quality of life.

6. CONTACT DERMATITIS

Contact dermatitis is an inflammation caused by contact with contact allergens and irritants. There are two main subtypes of contact dermatitis: allergic contact dermatitis (ACD)

and irritant contact dermatitis (ICD) [62]. This paper focuses on ACD. Allergic contact dermatitis is associated with a type IV hypersensitivity reaction. This reaction is known as “the delayed type”. It consists of a phase of sensitization to the allergen and a phase of induction after the accompanying allergen [63]. A study was conducted to examine the correlation between allergic contact dermatitis and the levels of vitamin D. There was a study on animals - mice. The conducted research has shown differences between males and females.

The treatment of ACD was found to be more effective in the case of males with correct levels of vitamin D. Nonetheless such a correlation does not occur in the case of females [64]. These studies may lead to a correlation between vitamin D levels and ACD in humans, but this topic requires further investigation.

7. CONCLUSION

Due to its wide-ranging regulatory effects on the immune system, vitamin D has been recognized in recent years as an important factor in the development of allergic diseases. By modulating several immune mechanisms related to both cellular and humoral immunity as well as enhancing skin and intestinal barriers, it has the potential not only to reduce the risk of disease exacerbations but also the risk of disease development. In the discussion of the relationship between serum vitamin D levels and susceptibility to the described group of diseases, there are still many unknowns, but emerging scientific reports give hope for a new approach to the treatment and, more importantly, prevention of allergic disorders.

DISCLOSURE

Conceptualization: JK, AH, KJ, OS, JW, DD, DR, AM, Software: JK, AH, KJ, OS, JW, DD, DR, AM, Check: JK, AH, KJ, OS, JW, DD, DR, AM, Formal analysis:JK, AH, KJ, OS, JW, DD, DR, AM, Investigation: JK, AH, KJ, OS, JW, DD, DR, AM, Resources: JK, AH, KJ, OS, JW, DD, DR, AM, Data curation: JK, AH, KJ, OS, JW, DD, DR, AM, Writing rough preparation: JK, AH, KJ, OS, JW, DD, DR, AM, Writing review and editing: JK, AH, KJ, OS, JW, DD, DR, AM, Visualization: JK, AH, KJ, OS, JW, DD, DR, AM, Supervision: JK, AH, KJ, OS, JW, DD, DR, AM, Project administration: JK, AH, KJ, OS, JW, DD, DR, AM

Supplementary Materials:
They have not been provided.

Funding Statement:
This research received no external funding.

Institutional Review Board Statement:
Not applicable.

Informed Consent Statement:
Not applicable.

Data Availability Statement:

Not applicable.

Conflict of Interest:
The authors declare no conflict of interest.

All authors have read and agreed to the published version of the manuscript

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