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Original Article

Vitamin D Supplementation in Patients with Atopic Dermatitis, Chronic Urticaria and Contact Irritant and Allergic Dermatitis - Possible Improvement without Risk

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Abstract

Introduction: There has been a lot of talk lately about the importance of reduced serum vitamin D levels and their supplementation for patients with inflammatory skin diseases such as atopic dermatitis (AD) and other allergic diseases. Serum vitamin D values are associated with a number of factors such as limited sunlight exposure (modern lifestyle, extended indoor stay, enhanced sun protection, etc.) which can affect different diseases.

Aim: To evaluate serum vitamin D values in patients with inflammatory skin diseases, comparing them on the basis of other parameters (age, gender/sex, residential areas, total serum IgE), and establishing whether vitamin D supplementation would affect the improvement of the clinical picture of the disease.

Patients and methods: A total of 157 patients participated in this prospective study: 51 patients with AD, 55 with chronic urticaria (CU) and 51 with contact dermatitis (CD): 38 with irritant CD (ICD) and 13 with allergic CD (ACD). In all patients, the values of serum vitamin D were determined by chemiluminescence microparticle immunoassay (CMIA) and compared by diagnosis, age, sex, living environment, values of total IgE. In patients with reduced values of vitamin D, its supplementation for 3 months was recommended, after which the second evaluation of D vitamin values and disease status were determined and compared with an untreated/unsupplemented group with normal vitamin D values.

Results: Vitamin D deficiency was often observed in patients with AD, CU and CD, most frequently in the ICD group, and least frequently in the ACD group. No significant differences were found in terms of age, gender or living environment, nor was any correlation with total IgE found. In the subjects supplemented with vitamin D, their levels increased significantly and, after its supplementation, improvement of the clinical condition was more common than in the untreated group; however, the differences were not statistically significant (69.8 vs. 58.1, p=0.428).

Conclusions: Although serum vitamin D levels of the groups did not differ significantly, the supplementation of vitamin D in patients with prominent vitamin D deficiency may be useful and crucial for improving the prognosis of the disease.

Keywords

allergic diseases, cholecalciferol, eczema, vitamin D deficiency, skin inflammatory diseases

INTRODUCTION

In the past years, many studies and ample research have addressed the importance of vitamin D deficiency in certain diseases and their treatment, including inflammatory skin diseases such as atopic dermatitis (AD) and vulgar psoriasis.[1,2] As we know, people obtain vitamin D predominantly by its synthesis in the skin under the influence of sunlight and by means of food. The reduction of the serum vitamin D values is associated with a number of factors such as limited exposure to sunlight (modern lifestyle, increased indoor staying, enhanced sun protection, etc.).[1]

The impact of vitamin D status on health problems/outcomes is discussed in many branches of medicine and in many diseases, including allergic skin diseases.[3-6] The higher incidence of allergic diseases observed on higher latitudes (with more frequent vitamin D deficiency) suggested that there may be a connection between the development of allergic diseases and vitamin D deficiency ("the vitamin D hypothesis").[1] Other factors, such as the bone health/condition of the patient, are also important and potentially related to it, especially given the frequent use of corticosteroids (topical and systemic), the existence of chronic inflammation and the like.

Concerning AD, the occurrence of eczema within AD is often the first manifestation of allergic disease in early childhood, usually followed by allergic rhinitis and asthma.[1] An increased incidence of eczema has been observed in persons with lower serum vitamin D levels, especially in children, which is even more pronounced in adults. Various findings have been observed regarding the correlation between vitamin D levels and eczema severity. While some studies established that lower levels of vitamin D were associated with increased disease severity, others did not find any correlation with disease severity. A negative association between eczema severity and vitamin D levels (which was not observed in the patients without allergic sensitization) was also observed in the patients with proved allergic sensitization.[7,8] To understand this correlation, it is important to know that eczema phenotypes are also associated with multiple vitamin D gene pathways, which suggests that vitamin D deficiency predisposes to eczema. As an endogenously produced hormone, vitamin D has effect on the regulation of more than 200 genes in different cell types. Aside the skin as the source of vitamin D for the body, it is incapable of responding to active metabolite of vitamin D [1,25$(OH)_2$D] and also express receptor for D vitamin and metabolizes it to a hormonally active form. Vitamin D regulates epidermal differentiation and hair follicle cycling (thus promoting barrier function, wound healing, hair growth, etc.). In addition, vitamin D participates in cellular and humoral immunity and in the formation and maintenance of the epithelial and endothelial barriers; it also participates in the metabolic pathways. In this respect, another important matter is the correlation between the beneficial effects of vitamin D and several biological pathways of the disease. In eczema, for example, the regulation of the immune system and the skin barrier are disturbed under the influence of vitamin D.[1] Also, a lower vitamin D value can, for example, increase the skin's sensitivity to bacterial and viral infections (inadequate antimicrobial defense), and it changes and modulates the outcomes of allergic conditions by its multiple effects on altered epidermal barrier function, impaired immune regulation, and others.[1,9]

As for chronic urticaria (CU), it is characterized by hives that can persist for more than 6 weeks, often associated with angioedema; according to etiology, the urticaria can be either induced or spontaneous (chronic spontaneous urticaria, CSU).[10,11] As for the vitamin D levels in patients with urticaria, numerous studies in CSU patients have shown significantly lower serum levels of 25-(OH)-D than in the control group.[12] However, there are differences between studies concerning the importance of vitamin D for CU. Some authors showed a negative association between the severity of CU and the serum 25-(OH)-D levels.[13,14] Other authors did not report a significant correlation between CU duration/severity and correlation between CU duration/severity and vitamin D levels.[15,16]

Contact dermatitis (CD) is an inflammation of the skin that occurs after skin contact with specific substances and has two main subtypes – allergic CD (ACD) and irritant CD (ICD).[10] Studies on animals with ACD (mice) that examined the importance of vitamin D showed that the male mice with normal vitamin D levels had a better response in repairing ACD than the mice that lacked such levels, which was not observed in female mice (the mechanisms of different responses remain unknown).[10] Although studies on the levels of vitamin D and the effects of its supplementation in CD patients are scarce, this animal study suggests that vitamin D supplementation may be beneficial to patients with ACD.

AIM

Due to insufficient scientific and clinical knowledge about this topic, we decided to examine the values of serum vitamin D in patients with AD, CU and CD (ICD, ACD) and the effects of its supplementation in the patients with low vitamin D levels.

PATIENTS AND METHODS

In this study, we determined the values of serum vitamin D in patients with AD, CU and CD (ICD, ACD) and compared them within each disease; we also compared the vitamin D values among different patients grouped by such variables as age, gender, living environment, and total serum IgE levels (normal/elevated). In patients with established low vitamin D plasma concentration, its supplementation was recommended and, after compensation, a second evaluation of D vitamin blood concentration was done in the patients who were able to undergo such evalua-

tion. In the patients who received supplementation, the disease status was also determined on the basis of the clinical disease condition established during visits after the vitamin D therapy (improvement, worsening, stable/unchanged manifestations). Finally, we aimed to determine whether vitamin D supplementation affected the improvement of clinical picture of the disease in comparison with patients with normal vitamin D levels who were not supplemented.

Patients

This prospective study was conducted in the Unit for Allergology and Clinical Immunology in Dermatology at the Clinical Department of Dermatovenereology of Sestre milosrdnice University Hospital Center, which included adult patients with diagnoses of AD, CU, and CD (over 18 years of age) who were examined and treated during an 18-month period (January 1, 2019 to June 30, 2020). The research was conducted according to the rules of the Ethics Committee of Sestre milosrdnice University Hospital Center and in accordance with the Declaration of Helsinki, and the study was registered under the code of 003-06/20-03/019. Initially, the patients were informed in detail about the study and were also asked to sign their informed consents.

The inclusion criteria were: adult patients (over 18 years) with AD, CU, and CD (ICD, ACD), treated under dermatologically and clinically verified diagnoses. All patients received appropriate treatments according to their diagnoses. The diagnosis of AD was made according to the Hanifin and Rajka criteria.[17] In CU, only patients with CSU were considered, while inducible urticaria and drug-induced urticaria were excluded. In patients with CD, a patch test was performed with a standard series of allergens (and if necessary with an additional series of allergens as well) to differentiate ACD and ICD. ACD was verified by clinical monitoring of the effect of allergens on the disease. All patients received a standard background treatment according to the specific disease.

Ultimately, a total of 157 patients participated in the study: 51 patients with AD, 55 with CU, and 51 with CD (ICD 38, ACD 13), aged between 18 and 78 years; there were 118 women and 39 men.

Methods

Initial parameters (T1)

At baseline, patients' serum values of vitamin D were determined and their additional parameters were also taken. The following instruments were used: examination by a dermatovenereologist, medical documentation that provided basic data about the subject (age, sex, and living environment) and the findings of total serum IgE and skin tests for allergens (inhalant, food, contact).

The serum vitamin D values were determined in each patient by chemiluminescence microparticle immunoassay (CMIA). Based on the division of values into several levels of vitamin D, the values thus obtained were verified as three categories (increased, decreased, normal), as well as the division into additional 4 categories and 5 categories. So, the vitamin D values above 75 nmol/L were considered as normal; borderline values 50-75 nmol/L; mild deficiency 25-50 nmol/l; moderate deficiency 12.5-25 nmol/L, and severe deficiency <12.5 nmol/L. These 5 categories comprised normal values, borderline values, mild deficiency, moderate deficiency, and severe deficiency. In addition, for statistical analysis, their values were also analysed as 4 categories*:* normal values, borderline values, mild deficiency, and moderate/severe deficiency.

Total serum IgE was determined by the fluorimetric enzyme-linked immunoassay method (FEIA). The IgE values below 114 kIU/L were considered normal.

In patients with established low vitamin D values, supplementation with vitamin D (D3 vitamin, cholecalciferol) in the forms of 5 oral drops (i.e. 1.000 IU daily for mild) or 7 oral drops for a more severe deficiency (i.e. 1.400 IU daily) was administered during a period of three months.[18]

Second evaluation of vitamin D values (T2)

After supplementation with vitamin D, the effect of this therapy on the condition of each disease was determined both in the patient group receiving vitamin D and in the untreated group. The second examination of the condition of patients' disease compared to the initial condition was also clinically recorded/determined by dermatovenereologist's assessment during the second examination of the patient, based on clinical manifestations (disease condition: stable, improved, worsened).

Since some of supplemented patients were not able to come for the second evaluation of their vitamin D values, we took into account only the reliable data/values of the patients for whom these data/values had been determined.

In patients with initially established normal values of vitamin D, only a dermatologist's examination was performed and the condition of the disease was recorded. They were considered as an non-treated group.

Statistical analysis

Non-parametric statistical methods (Kruskal-Wallis, Mann-Whitney, and Spearman correlation tests) were used to compare the vitamin D and IgE levels between the categories of the subjects. The χ^2 test was used to compare the frequencies. The vitamin D levels before and after vitamin D therapy were compared using the Wilcoxon test. Since for some analysis of parameters we did not have a healthy group for comparison of their vitamin D values with our patient values, they were only done according to the potentially expected ratio 50:50. All analyses were performed using SPSS 22 (IBM Corp., Armonk, USA).

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RESULTS

Results of the initial parameter analysis (T1)

The sample consisted of 157 patients aged 18–78 (median: 48; interquartile range: 29–59 years). Of these, there were 118 (75%) females and 39 (25%) males. Concerning the proven allergy (in medical documentation), an analysis of all patients showed that those without proven allergies dominated (73.2% of the patients) over those with allergies (26.8%). Among the accompanying allergies, 13.4% of the patients had allergic rhinitis, 9.6% had food allergy and 6.4% had asthma. The initially measured values of D vitamin and total IgE in whole sample are shown in **Table 1**. There was a mild deficiency of vitamin D in 41.4% of the patients, borderline deficiency in 27.4%, normal status in 15.9%, moderate deficiency in 12.7%, and severe vitamin D deficiency in 2.5% of the subjects (at time T1).

The statistical analysis showed that if vitamin D categories were dichotomized into two categories (0=normal or borderline and 1=mild, moderate or severe) **(Table 2)**, vitamin deficiency was the most common in ICD and the least common in ACD. However, no statistically significant differences were observed between the categories (p=0.539). Also, if a 50:50 ratio is expected for each of the diagnoses, then the differences are not significant for any of the diagnoses.

An additional statistical analysis with a different dichotomization (0=normal, borderline or mild and 1=moderate or severe) also did not show any statistically significant differences between the groups (p=0.717) **(Table 2)**. However, if a 50:50 ratio is expected, then moderate or severe deficiencies are significantly more common in all diagnoses than the normal, borderline or mild ones (p<0.05) **(Figs 1, 2)**.

Comparison of the initially measured vitamin D in the whole sample (T1) and patient group before (T1) and after vitamin D supplementation (T2)

Vitamin D supplementation (due to low vitamin D values) was received by 80.3% of the subjects, and improvement in the disease manifestations was observed in 69.8% of them, stable manifestations in 28.6%, and worsening of the disease in 1.6% of the subjects.

In the untreated/non-supplemented patients (those with normal vitamin D values), improvement was observed in 58.1%, stable manifestations in 38.7%, and worsening in 3.2% of them. Differences between the treated and untreated/unsupplemented patients were not significant. Measurement of vitamin D was also performed in the patient group after supplementation (T2 time). After vitamin D treatment, there were no cases of severe vitamin D deficiency; moderate deficiency was found in 7.5%, mild deficiency in 22.5%, borderline deficiency in 37.5%, and normal findings were found in 32.5% of the subjects. A total of 51% of subjects had elevated total IgE (i.e., atopic tendency). Of the total number of the subjects (treated and untreated), improvement of the disease was found in 67.5% of them; manifestations were stable in 30.6%, and worsened in 1.9% of the cases.

Table 1. Description of the age, vitamin D level and total IgE of the sample

	N	Mean±SD	95% CI	Median (IQR)	Min-max range
Age (years)	157	45.7±16.7	43.0–48.3	48 (29-59)	17–78
Initial vitamin D (T1) (nmol/L)	157	48.7±23.5	45.0–52.4	47 (32.5-60)	3–142
IgE (T1) (kIU/L)	157	454.0±951.5	304.0–604.0	100 (34-333)	4–5000
Vitamin D after 3-month supplementation (T2) (nmol/L)	39	61.5±22.8	54.1–68.9	58 (45-77)	14–116

* SD: standard deviation; CI: confidence interval; IQR: interquartile range

Table 2. Comparison of the distribution of vitamin D level categories, with two cut-offs (mild deficiency and moderate deficiency), by individual diagnoses

Group	Vitamin D T1 Categorisation I		Vitamin D T1 Categorisation II		Total
	Normal or borderline	Mild, moderate or severe	Normal, borderline or mild	Moderate or severe	
Irritant CD, n (%)	13 (34.2%)	25 (65.8%)	30 (78.9%)	8 (21.1%)	38 (100%)
Allergic CD, n (%)	7 (53.8%)	6 (46.2%)	11 (84.6%)	2 (15.4%)	13 (100%)
Atopic dermatitis, n (%)	24 (47.1%)	27 (52.9%)	44 (86.3%)	7 (13.7%)	51 (100%)
Chronic urticaria, n (%)	24 (43.6%)	31 (56.4%)	48 (87.3%)	7 (12.7%)	55 (100%)
Total, n (%)	n (%)	89 (56.7%)	133 (84.7%)	24 (15.3%)	157 (100%)

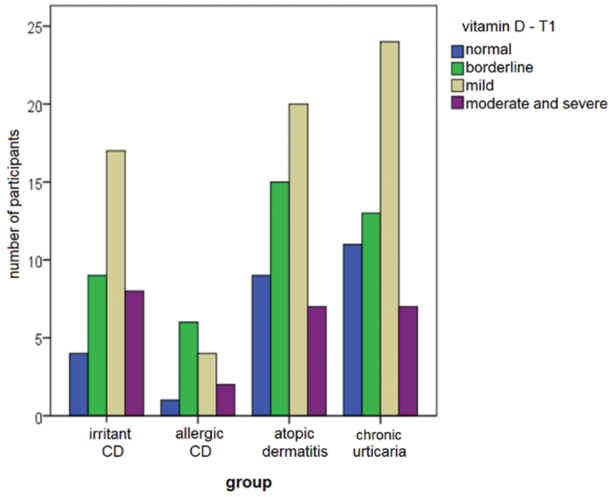

Figure 1. Four categories of the initially measured vitamin D deficiencies in the total sample by individual diagnoses (T1).

Initial vitamin D values and their values after vitamin D treatment (at time T1 and T2) in different diagnoses

Concerning each individual diagnosis, the vitamin D levels did not significantly differ between diagnoses, either in the whole sample of untreated patients (T1), or in the patient groups before or after vitamin D treatment (T2) **(Table 3)**. The categories of vitamin D deficiency levels did not reveal any significant statistical difference in the mean serum values of vitamin D among different allergic conditions, neither when the moderate and severe categories were combined, nor when they were separated at time T1 (p=0.753 and 0.856) **(Figs 1, 2)**. Also, the measured values of vitamin D did not differ significantly in the patient group after the vitamin D treatment (T2) (p=0.597) **(Fig. 3)**.

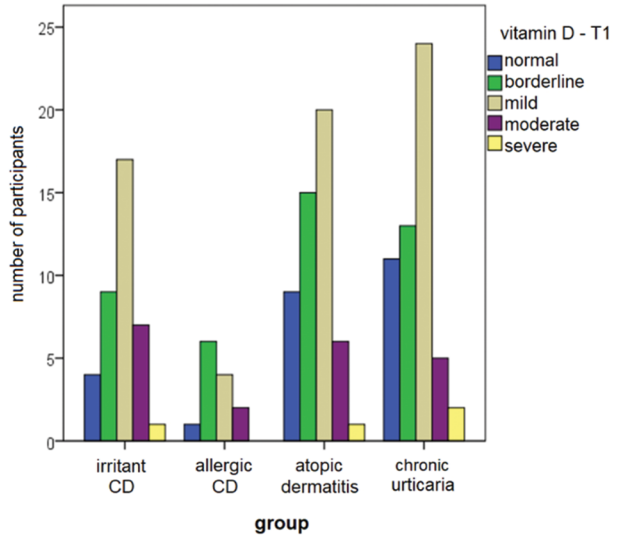

Figure 2. Five categories of the initially measured vitamin D deficiencies in the total sample by individual diagnoses (T1).

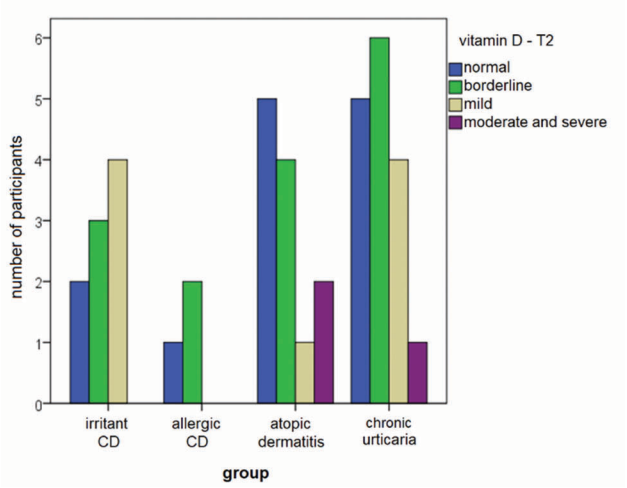

Figure 3. Categories of the values of vitamin D deficiency after 3 months supplementation by individual diagnoses (at time T2).

Table 3. Vitamin D values in different diagnoses in the total sample and in patient groups before and after treatment/supplementation

Time	Diagnosis	n	Median in nmol/L (interquartile range)	*P*
T1 Total sample	Irritant CD	38	37 (27.8–57)	0.244
	Allergic CD	13	50 (26.5–56)	
	Atopic dermatitis	51	48 (35–63)	
	Chronic urticaria	55	49 (35–60)	
T1 Patient group before	Irritant CD	9	35 (21–53.5)	0.749
	Allergic CD	3	40 (27–40)	
	Atopic dermatitis	11	45 (39–56)	
	Chronic urticaria	16	34 (26.5–53.5)	
T2 Patient group after	Irritant CD	9	50 (38–71)	0.543
	Allergic CD	3	53 (53–70.5)	
	Atopic dermatitis	11	69 (54–77)	
	Chronic urticaria	16	59 (45.3–89.3)	

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Correlation of the initial vitamin D values and their values after 3 months supplementation by age

Vitamin D values at T1 and T2 were not linearly correlated with age (Spearman correlations r=−0.154 and 0.066; p>0.05).

Comparison between the initial vitamin D values and their values after 3 months supplementation by sex

The vitamin D level did not significantly differ between men and women, either in the whole sample at T1 (median 50 nmol/L (IQR 35-66) vs. 46.5 (IQR 32-58.3)) or in the treated patient groups at T1 (52 nmol/L (IQR 40.5-63.5) vs. 39 (IQR 27-54)) or T2 (78.5 (IQR 71.8-86) vs. 56 (IQR 43-75)).

Comparison of vitamin D values by living environments

Vitamin D levels did not differ significantly by the patients' living environments, either in the total sample (T1) or in the patient groups before (T1) and after the treatment (T2) **(Table 4)**.

Vitamin D values depending on allergies and allergic diseases

Vitamin D levels did not differ significantly depending on the presence and type of allergy either in the total sample (T1) or in the patient groups before the treatment (T1) or after the treatment/supplementation (T2) **(Table 5)**.

Table 4. Comparison of vitamin D values by living environments

Time	Living environment	n	Median nmol/L (interquartile range)	*P*
T1 Whole sample	Zagreb	97	45 (32–61)	0.783
	Hinterland	51	49 (35–60)	
	Mediterranean region	9	40 (16.5–68)	
T1 Patient group before treatment	Zagreb	25	39 (26–51)	0.276
	Hinterland	14	47 (30–59.3)	
T2 Patient group after treatment	Zagreb	25	56 (42.5–76.5)	0.392
	Hinterland	14	63 (52.3–81)	

Table 5. Vitamin D values depending on presence and type of allergy

Time	Allergy	n	Median nmol/L (interquartile range)	*P*
T1 Whole sample	Present allergy	42	47 (32.8–56.8)	0.506
	No allergy	115	46 (32–61)	
	No asthma	147	45 (32–60)	0.281
	Present asthma	10	50.5 (45–62.5)	
	No food allergy	142	45 (32–60.3)	0.707
	Present food allergy	15	49 (41–56)	
	No allergic rhinitis	136	48.5 (35–60)	0.05
	Present allergic rhinitis	21	36 (25.5–51.5)	
T1 Patient group before treatment	Present allergy	8	37 (23.3–52)	0.542
	No allergy	31	40 (31–55)	
	No asthma	37	40 (29–54.5)	0.293
	Present asthma	2	30.5 (22)	
	No food allergy	36	39.5 (27–54)	0.329
	Present food allergy	3	49 (35)	
	No allergic rhinitis	35	40 (32–55)	0.110
	Present allergic rhinitis	4	24.5 (16.8–46.5)	
T2 Patient group after treatment	Present allergy	8	64 (45.5–75)	0.781
	No allergy	31	56 (45–80)	
	No asthma	37	56 (44–78)	0.324
	Present asthma	2	73 (69)	
	No food allergy	36	56 (43.5–76.8)	0.178
	Present food allergy	3	69 (59)	
	No allergic rhinitis	35	59 (46–80)	0.211
	Present allergic rhinitis	4	48 (32.5–65)	

Correlation between the initial values of vitamin D and the IgE values

The vitamin D levels in the total sample in the initial group (T1) and in the patient group after treatment (T2) were not linearly correlated with the IgE values (Spearman correlations r=−0.088 and −0.014; p>0.05). The vitamin D values did not differ significantly between the subjects with normal and elevated total IgE (median 49 nmol/L (IQR 35–63) vs. 42.5 (32–60); p=0.293).

Comparison of vitamin D between the skin conditions in the patient group after the treatment

The comparison of vitamin D levels in the patient group after supplementation/treatment (time T2) between the examined diagnoses is shown in **Table 5**.

Comparison of disease status between patients supplemented with vitamin D and non-supplemented patients

In the group treated with vitamin D, improvement in the clinical condition was somewhat more frequent than in the untreated group with normal vitamin D values, but the differences were not statistically significant (69.8% vs. 58.1%; p=0.428) **(Fig. 4)**.

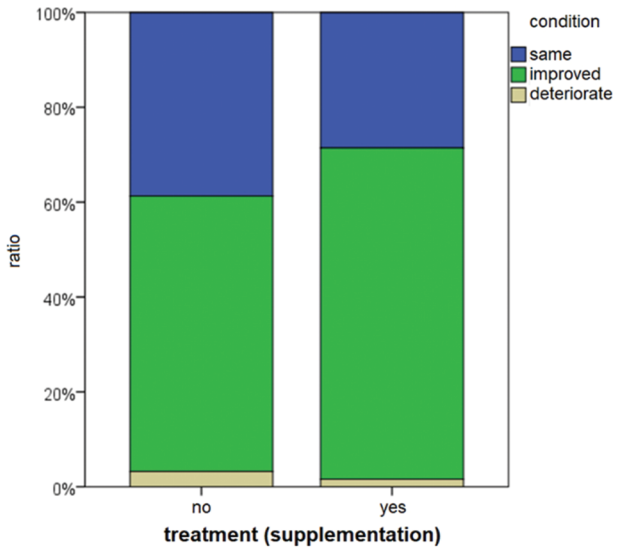

Figure 4. Comparison of conditions between the treated and untreated groups.

Comparison of vitamin D within the patient group after treatment/supplementation by disease outcome (improvement, exacerbation, same)

Control serum vitamin D levels did not differ statistically by disease outcome **(Table 6)**; improvement was recorded in most of the subjects after vitamin D therapy and worsening was recorded in none of them.

Comparison of vitamin levels before and after vitamin D therapy in the patients treated with vitamin D

The vitamin D levels increased significantly in the treated group with large effect size (from 40.4±16.2 to 62.0±22.89; p<0.001, r=0.780) **(Fig. 5)**.

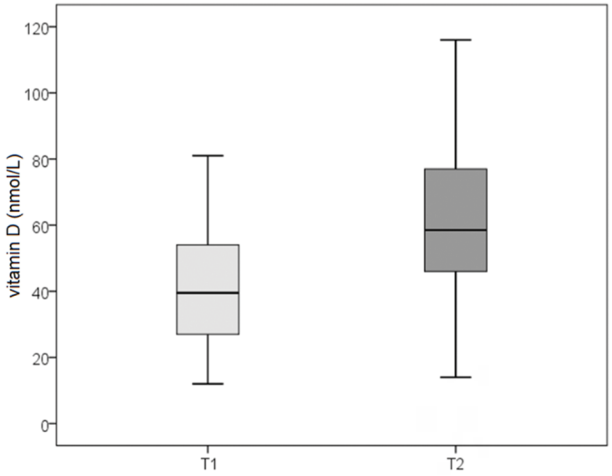

Figure 5. Comparison of vitamin D levels before and after the therapy.

DISCUSSION

According to the results for vitamin D values in our patients with AD, CU, and CD, their levels did not differ significantly by age, sex, or residential area. Also, vitamin D levels did not differ significantly between AD, CU and CD with regard to the presence and type of allergy either. According to additional statistical analysis of the sample, vitamin deficiency was most common in ICD patients and least common in ACD, although these differences between diagnoses were not statistically significant. So, although

Table 6. Comparison of vitamin D values within the patient group after treatment/supplementation by disease outcome

Therapy outcome	n	Median nmol/L (interquartile range)	*P*
Same condition	9	43 (29-93.5)	0.404
Improvement	30	58.5 (50-76.3)	

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our results did not confirm significance of vitamin D for examined diseases, the results by other authors could be taken into account. Thus, looking at the relationship between the occurrence and condition of AD/eczema and the values of vitamin D, the data from previous research (including in utero studies) provided inconsistent findings. While some observational studies support the protective effect of vitamin D (in utero) on the risk of developing eczema, according to other studies, its high level may even be a risk factor for eczema.[1] As for skin diseases, vitamin D has so far been primarily investigated in patients with AD. In adults with AD, different study results (several randomized, placebo-controlled, double-blind studies) were found that examined its values and the significance of vitamin D supplementation for AD patients. Regarding the status of vitamin D in relation to the proven hypersensitivity of patients to allergens and the possible effects of vitamin D on hypersensitivity, heterogeneous results have been observed across observational studies.[1] Based on the determination of vitamin D, it was observed in newborns that their mothers' higher intake of vitamin D through food during pregnancy or newborns' higher vitamin D levels are associated with reduced sensitivity to allergens in childhood. On the other hand, by monitoring pregnant women, Weisse et al. found that higher levels of 25(OH)D during the third trimester of pregnancy (with an average of 55 nmol/L) were associated with an increased risk of the child being allergic to food allergens.[1,19]

Looking at the effect of vitamin D supplementation recorded among our patients with low vitamin D values, improvement in their clinical status was observed somewhat more often than in the untreated/non-supplemented group (although the differences were not statistically significant). Clinical improvement was observed in most patients and none of them experienced any deterioration (in those treated with vitamin D supplementation vitamin D levels increased significantly). When looking at other literature data, particularly significant are the results of monitoring the effect of vitamin D supplementation on the disease in patients with AD. Using oral supplementation with vitamin D (1600 IU daily for 60 days), Amestejani et al. and Javanbakht et al. found a significant reduction in AD severity (compared to the placebo group), while according to Hata et al., a shorter use of a higher dose (4000 IU daily for only 21 days) did not lower the severity of eczema.[1,20-22] According to a wide meta-analysis by Kim et al.[23], AD patients have lower serum 25(OH)D levels than the control group, with significantly lower levels in children. Generally, vitamin D supplementation decreased AD severity and improved AD condition, although specific mechanisms are unclear/unknown.[23] Due to the lack of appropriate/high-quality randomized controlled trials on the effects of vitamin D (from food, dietary supplements and/or exposure to sunlight) on eczema development, as well as conflicting evidence, further research is needed, for instance, on the effects of sunlight on eczema incidence and severity (at different points in early life).[1] Exposure to UV rays (UVB) is also important and it needs to be investigated, for example, by measuring UV radiation by UV dosimeters. Therefore, the use of oral vitamin D supplementation as an adjunct treatment for AD in children and adults requires further studies to determine the appropriate dose and duration of treatment, especially in different populations (e.g., different races, latitudes and seasons).

While existing analyses of the role of vitamin D in AD have yielded conflicting results, studies on CU clearly indicate the benefit of assessing vitamin D status in them, although far fewer studies have investigated vitamin D in CU than in AD.[10] Thus, vitamin D supplementation has been shown to be beneficial for some CU patients. There are also scientific observations that vitamin D deficiency may be an additional indicator of autoimmune urticaria. According to the retrospective study by Woo et al. comparing four different disease groups (72 patients with CU, 26 patients with acute urticaria, 26 patients with AD and 72 healthy controls), serum levels of 25(OH)D were significantly reduced in CU patients compared to other groups.[14] It has also been observed that vitamin D deficiency may increase the likelihood of acute urticaria transitioning to CU (based on monitoring of 10 patients with acute urticaria with extremely low vitamin D <10 ng/ml, where 5 of these patients became chronic).[10] Cases of perennial CU have also been reported in which severe vitamin D deficiency (serum level 25(OH)D 4.7 ng/ml) was identified, and these cases of perennial urticaria were cured after vitamin D supplementation (at a dose of 2000 IU daily). Similarly, in a retrospective study involving 28 patients with urticaria and angioedema (with vitamin D levels <32 ng/ml), a positive response and complete resolution of symptoms was observed in 61% of them after vitamin D supplementation.

Although the connection between vitamin D and total IgE is also mentioned in the literature, according to our results, vitamin D values did not correlate linearly with total IgE, nor did they differ significantly between patients with normal and elevated IgE, so they were not significant for follow-up. However, earlier research on the relationship between the values of total IgE and vitamin D gave useful data. One earlier study found that vitamin D has an effect on IgE production in patients with CU (total IgE values are usually increased in CU patients). Thus, after vitamin D supplementation (in vitro), IgE production (from stimulated B lymphocytes) was significantly reduced, so vitamin D could act by immunomodulation of IgE-mediated pathways in urticaria, although other immunological and non-immunological factors should be considered as well.[10] Various prospective studies have shown that high-dose vitamin D3 supplementation in CU patients is safe and beneficial. Particularly significant is the study randomizing 42 CU patients to those with high (4000 IU/d) or low (600 IU/d) vitamin D3 supplementation over 12 weeks, with triple-drug therapy (cetirizine, ranitidine, and montelukast), which reduced the total severity of urticaria. The triple therapy in the first week reduced the Urticaria Severity Score (USS) by 33%, and in subjects supplemented with high doses of vitamin

D3, a further reduction in USS by 40% was observed by 12 weeks. Patients on high doses of vitamin D3 had less frequent occurrence of urticaria (fewer days with it) and a smaller body surface area affected by it. In one prospective study (58 patients with CSU and 45 controls), significantly lower levels of vitamin D were found in CSU patients than in controls.[10] After CSU patients whose levels of 25(OH)D were less than 30 ng/ml received 300,000 IU of vitamin D per month, a significant improvement in urticaria activity (UAS4) and quality of life (CU-Q2oL) was observed after 12 weeks. Furthermore, more extensive clinical trials would be needed to determine the most favourable dose of vitamin D supplementation for CU and possible mechanisms of vitamin D action.

As for other skin diseases, the importance of vitamin D is mentioned only in some of them, e.g. in patients with ACD, which would help clarify its role in allergic and other inflammatory skin diseases.[10] There have been only two studies assessing the serum values of vitamin D and evaluating the effects of its supplementation in ACD. A study conducted on mice found that mice with higher serum vitamin D levels may be more likely to experience improvement in ACD.[10] Another important study is the one by Xavier et al.[24] on patients with ACD following exposure to Parthenium. In this study, 72 patients were recruited and randomized to receive either cholecalciferol tablet (60,000 IU per week) or placebo (for 8 weeks) with standard background treatment. They measured IL-10 and serum 25-hydroxyvitamin D levels at baseline and at 8 weeks which showed a significant increase in both groups. So, cholecalciferol supplementation for 2 months did not reduce ACD severity. In addition, there are some other important observations concerning the role of vitamin D supplementation for skin barrier functions recorded by other studies.[23,25-28] According to one previous in vitro study, after vitamin D supplementation, antimicrobial peptides such as cathelicidin and β-defensin increased, i.e. the supplementation promotes cathelicidin production and induces cathelicidin LL-37 expression. Since vitamin D promotes antimicrobial activity, its lower level reduces antimicrobial activity and external tolerability to pathogens, important for AD and CD.[23] Also, 1,25$(OH)_2$D and its receptor regulate the processing of long-chain glycosylceramides, which are crucial for the skin barrier formation and skin defending, and they also induce Toll-like receptor 2 (TLR2) and its co-receptor CD14, which initiate the skin innate immune response.[25] Activation of these receptors leads to the induction of CYP27B1 (the only enzyme capable of transferring the inactive form into the active vitamin D form), which in turn induces cathelicidin resulting in the killing of invasive organisms. In addition, according to literature, mice lacking the receptor for vitamin D (VDR) or the enzyme CYP27B1 show decreased lipid content of the lamellar bodies, leading to a defective permeability barrier and a defective response of the innate immune system to invading infections.[25] However, as to date there have been no studies on the role of vitamin D in ICD in humans, our results on ICD could be useful for gaining more knowledge about vitamin D in these patients. However, for now, vitamin D supplementation has not been included in the recommendations for ACD either and requires clinical studies.[10] Since UV radiation contributes to vitamin D stores, the added benefit of UV rays for patients with inflammatory skin diseases such as CD and AD should always be borne in mind.

Since our results did not show significance of vitamin D for our patients, probably due to small number of patients and a limited number of variables/parameters, further studies could take into account more patients and their data: season variations, sun exposure and sun protection, type and quality of conducted therapy (including the use of corticosteroids), patients' lifestyle, their atopic condition (atopic or non-atopic), other diseases, the existence of chronic inflammation, disease duration, etc. Therefore, further research on vitamin D supplementation in patients with CD and related factors involved is needed.

CONCLUSIONS

Our results indicate that patients with AD, CU, CD treated with vitamin D supplementation are slightly more likely to experience an improvement in clinical condition than the untreated group, although the differences are not statistically significant. It is also significant that vitamin D supplementation led to improvement in most subjects and that none of them experienced any deterioration, indicating the possibility of a beneficial effect in some patients without adverse effects. There remains a lot of room to examine the role of possible nutrition and other lifestyle factors as potential approaches to the prevention of allergic and inflammatory skin diseases.

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Author contributions

L.L.M. contributed to conception and design of the article; L.L.M., N.M., M.D., N.P., I.P., and MK analysed the data; L.L.M., N.M., and M.K. wrote the manuscript; all authors contributed to manuscript revision, read and approved the submitted version.

Competing Interests

The authors have declared that no competing interests exist.

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Приём добавок витамина D при пациентах с атопическим дерматитом, хронической крапивницей и контактно-раздражающим и аллергическим дерматитом – возможное улучшение без риска

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Резюме

Введение: В последнее время много говорят о важности снижения уровня витамина D в сыворотке крови и его приёма при пациентах с воспалительными заболеваниями кожи, такими как атопический дерматит (АД) и другими аллергическими заболеваниями. Значения витамина D в сыворотке связаны с рядом факторов, таких как ограниченное воздействие солнечного света (современный образ жизни, длительное пребывание в помещении, повышенная защита от солнца и т. д.), которые могут влиять на различные заболевания.

Цель: Оценить уровень витамина D в сыворотке у пациентов с воспалительными заболеваниями кожи, сравнить их по другим параметрам (возраст, пол, район проживания, общий IgE в сыворотке) и установить, повлияет ли добавление витамина D на улучшение клинического состояния.

Пациенты и методы: Всего в этом проспективном исследовании приняли участие 157 пациентов: 51 пациент с АД, 55 с хронической крапивницей (ХК) и 51 с контактным дерматитом (КД): 38 с раздражающим КД (РКД) и 13 с аллергическим КД (АКД). У всех больных значения сывороточного витамина D определяли методом хемилюминесцентного иммуноанализа микрочастиц (CMIA) и сравнивали по диагнозу, возрасту, полу, среде обитания, значениям общего IgE. Пациентам со сниженным уровнем витамина D было рекомендовано его добавление в течение 3 месяцев, после чего была проведена вторая оценка значений витамина D и статуса заболевания, которые сравнивались с группой, не получавшей лечения/не получавшей добавки, с нормальными значениями витамина D.

Результаты: Дефицит витамина D чаще наблюдался у пациентов с АД, ХК и КД, наиболее часто в группе РКД и реже всего в группе АКД. Значимых различий по возрасту, полу или условиям проживания не обнаружено, а также не обнаружено корреляции с общим IgE. У испытуемых, получавших витамин D, их уровни значительно повышались, и после его приёма улучшение клинического состояния наблюдалось чаще, чем в нелеченой группе; однако различия не были статистически значимыми (69.8 против 58.1, p=0.428).

Заключение: Хотя уровни витамина D в сыворотке в группах существенно не различались, добавление витамина D пациентам с выраженным дефицитом витамина D может быть полезным и иметь решающее значение для улучшения прогноза заболевания.

Ключевые слова

аллергические заболевания, холекальциферол, экзема, дефицит витамина D, воспалительные заболевания кожи