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Original Article

The relationship between serum vitamin D levels and childhood atopic dermatitis

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Abstract

Aim: We aimed to evaluate serum vitamin D levels among children who have atopic dermatitis (AD) and to determine relationship with its clinical features and laboratory.

Material and Methods: One hundred twenty children (66 B, 54 G) with AD, aged between 1-16 years, followed up from Pediatric Allergy Outpatient Clinic were enrolled. Family history of atopy, comorbid allergic diseases, allergy skin prick tests, serum total peripheral blood eosinophil counts, IgG, IgA, IgM, IgE levels, were recorded. AD severity was determined by using Scoring Atopic Dermatitis (SCORAD) index. The serum 25(OH)D vitamin levels were studied with HPLC method.

Results: The mean serum total IgE level was 557 ± 425.3kU/L and mean blood eosinophil count was 557 ± 425.3 mm3. The mean serum 25(OH) vitamin D level was 28.42 ± 10.56 ng/ml. One of the patients (0.83%) had severe vitamin D deficiency, 16 (13.3%) had deficiency and 55 (45.8%) had insufficiency. Serum vitamin D level was normal in 48 (40 %) patients. According to SCORAD index, mean serum vitamin D level was higher in patients with mild AD (32.18 ± 7.91 ng/ml) than in patients with moderate disease(28.79 ± 11.02 ng/ml) or in patients with severe AD (23.78 ± 8.92 ng/ml)(p<0,05).Serum 25(OH)D levels were inversely correlated with SCORAD index values (r =-0.273, p= 0.003).

Conclusions: In this study, we showed a reverse correlation between serum 25(OH)D vitamin level and atopic dermatitis severity. Vitamin D deficiency should be thought in unresponsive AD cases.

Keywords: Atopic dermatitis; childhood; IgE; SCORAD; vitamin D

INTRODUCTION

Atopic dermatitis is a chronic relapsing inflammatory skin disease usually rises in infancy and early childhood (1,2). Patients generally have elevated serum immunoglobulin E levels, family or personal asthma and / or allergic rhinitis history (3).

Atopic dermatitis is a common and major health problem in the world in general that is increasing because of the influence of various factors in the developing countries in the last decade (4). At last 40-50 years, 2-fold increase in every 10 years, has been detected in AD (5-7).

Due to natural history of the disease,AD is frequently seen in childhood, frequency and severity of AD decrease with age (8). Life style and environmental factors likely make contributions to clinical expression of AD (9). The prevalence of AD in children is ranged from 1.7% - 23%. Although AD may begin in every period of life, 45% of AD starts in first 6-months of life, 60% of in the first one year and 85% occur within the first 5 years. Symptoms begin before the age of two has made resistant tables. Intermittent symptoms up to 7 years can only be seen in 17% of patients,and 16,8% of AD starts in adulthood (10).

Although the etiology of the disease isn't known exactly; infectious, environmental and genetic factors are thought to play role in the multifactorial etiology(1-2).

Vitamin D which has affects on calcium homeostasis shows major effects on both innate and adaptive immunity. These effects constitute a field of question about the association between allergic diseases and vitamin D (11).

For normal development and function of keratinocyte, vitamin D3 should present in skin. The function and inflammation of normal cutaneous barrier are likely affected by the concentrations and/ or activation of vitamin D3. Antimicrobial peptides (AMPs) are responsible for protection of skin against infections and their production can be stimulated by vitamin D3 (12). One of the primarily discovered families of AMPs were cathelicidins on the skin. The regulation and production

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of AMPs such as cathelicidins, are also stimulated by Vitamin D (13). The biological effects of vitamin D go beyond the bone metabolism and calcium homeostasis. The immunomodulatory features of vitamin D affects both the innate and adaptive immune system (14).

According to the hypothesized mechanisms of vitamin D, it seems to act on Toll-like receptor 2. AMPs shows both induced host cellular response and direct antimicrobial activity which result with inflammation, cytokine release and angiogenesis. Therefore, lack of vitamin D might induce predisposition of AD patients to skin superinfection caused by Staphylococcus aureus and related superantigens (15).

The significance of vitamin D as a potential parameter in the development and progress of atopic diseases has become remarkable as a result of its effect on the same part and function of the skin. According to the literature,

decreased serum vitamin D levels are shown to associated with allergic skin diseases, particularly with AD (17). On the other hand, more randomized studies with large-scale prospective are needed. As a consequence of all available data, the relationship between vitamin D and AD severity should be further analyzed.

This study was conducted to investigate the relationship, between vitamin D status and AD severity.

MATERIAL and METHODS

Study Group

One hundred and twenty children, aged between 1-16 years, followed up with AD between January 2013 and June 2013 from Istanbul University Istanbul Medical Faculty Pediatric Allergy Outpatient Clinic were enrolled in the study.The inclusion criteria for the study were not to be on regular vitamin supplements for at least 6-months, not being received topical steroids in the previous 3 months and not having any chronic diseases except allergic diseases. Serum concentrations of 25(OH) D3 in patients with AD were compared with a control group of 60 healthy children (36 B, 24 G), aged between 1-16 years.

Diagnosis Of AD And Severity Of AD

AD patients were diagnosed according to the criteria of Hanifin and Rajka (18). There are many tests showing the severity of AD. The best known of these tests are Severity Scoring of Atopic Dermatitis (SCORAD), Objective SCORAD and Three item score (TIS). Of these tests, SCORAD is a commonly used and well-adapted testthat includes objective and interest-related coexistence.

The SCORAD system is operated by the European Atopic Dermatitis Operating Arm (European Atopic Dermatitis Task Force,ETFAD). SCORAD proposed by acronym Arnold Orange. SCORAD index was used to grade AD severity.For measuring the AD's extent which is graded from 0 to 100, the rule nines is applied on a front or back drawing of the inflammatory lesions of patients. SCORAD index includes six items to evaluate intensity as follows: edema/ papulation, erythema, lichenification, excoriations, dryness and oozing/ crusts. The scale of each item ranged from 0 to 3. Sleeplessness and daily pruritus are the subjective items which can be graded on a 10-cm visual analogue scale. The maximum subjective score is 20. All evaluated items are filled out in the SCORAD form. The SCORAD index is calculated by A/5+ 7B/2 + C formula, in which A defines the extent (0-100), B defines intensity (0-18) and C defines the subjective symptoms (0-20). The maximum score of SCORAD index is 103. Thesubjective symptoms (objective SORAD) were excluded to modify SCORAD index predicate on training sessions by ETFAD. Thus, the objective SCORAD index included extent and intensity items which were calculated by A/5 + 7B/2 formula. The maximum objective SCORAD index score is 83 with a bonus ten points. Eczema was scored and < 25 defined as mild, 25 to 50 as moderate and > 50 severe by using SCORAD index (19).

Laboratory Tests

Two-four milliliters of blood sample was obtained from patients, taken to eppendorph tubes, allowed for clotting and then centrifuged at 3000rpm for 10-15 minutes and seperated for quantitative detection of 25—hydroxyvitamin D (25(OH)D). All samples were protected at -80 degree. When all samples were completed, we began to examine centrifuged samples.

Serum samples of 25 (OH) vitamin D level was measured in İstanbul Faculty of Medicine, Department of Clinical Biochemistry Endocrinology laboratory with High Pressure Liquid Chromatography (HPLC) method. For determining, Thermo Finnigan Spectra HPLC System® (U.S.A) tools and Recipe kit (German) were used. The Coefficient of variation (CV) value of Thermo Finnigan Spectra HPLC System® was 3.1 %.

Full blood count was measured with laser (validation with impedance method) method,and Cell-DYN machine. Eosinophil counts above 500/mm^3 were admitted eosinophilia.

Serum IgG, IgA, IgM levels were measured with Roche Cobas Integra 400/800 Plus Biochemistry Autoanalyserin pediatric biochemistry laboratory.Serum Total IgE levels were calculated with Immulite 2000 XPI machine and chemiluminescence immunoassay method and serum total Ig E level > 100 IU/L were considered as high level.

Vitamin D status definitions

Vitamin D (as 25 (OH)D) single measurement was obtained from all children by HPLC method. The various states of vitamin D status were defined as: high deficiency < 5ng/ml (12.5 nmol/L), deficient 5-20 ng/mL(12,5-50 nmol/L); insufficient 20-30 ng/mL(50-75 nmol/L; sufficient 30-100 ng/mL(75-250 nmol/L) and desirable >100 ng/mL (>75 nmol/L) (20).

Skin prick tests

Skin prick tests (SPTs) were applied to observe reactivity against some foods such as cow's milk, wheat, hen's

egg white, peanut, fish, soybean and against common aeroallergens such as animal dander, house dust mites, grass pollens and molds. After 15 minutes of performing SPTs on the volar aspect of the forearm, the reactions were read. SPTs were defined as positive when wheal diameter was at least 3-mm greater than the negative control (21).

Ethical Concerns

This study was approved by the local Hospital's Ethics Committee. The ethical procedures of the study protocol consisted of informed consent of all parents or caregivers for scientific reporting of research findings based on the study protocol.

Statistical Analysis

SPSS (15.0 version,LEAD Technologies Inc,2006) was used for statistical analysis of the study.We used descriptive statistical parameters (frequency tables, percentage,median,standart deviation vb) in statistical analysis of the sample group.For determining significance level of clinical score, non–parametric tests ANOVA and Kruskal-Wallis were used.Variables for descriptive statistics showed by number and percent.

Pearson correlation tests were used for parametric data (correlation coefficient).We used regression analyze for many variables and admitted Vitamin D as dependent variable; gender, age, peripheral blood eosinophils percentage, serum total IgE level, SCORAD index as independent variables . P value less than 0.05 was considered to statistically significant.

RESULTS

Demographic and Clinical Properties

There were one hundred twenty children diagnosed with AD and 56 of them(55%) were boys. The mean age of the study group was 5.6 ± 3.4 years, mean weight was 22.46 ± 12.67 kg (6.5/78) and the mean height was 110.4 ± 22.04 cm (63/185).The control group included 60 patients (36 boys and 24 s), aged 1–15 years (mean: 6.54).

In the study group; 53 (44.1%) out of patients had only AD, 26 (21.6%) had concomitant asthma, 17 (14.6%) patients had concomitant allergic rhinitis and asthma, 20 (16.62%) patients had concomitant allergic rhinitis and 4 (3.3 %) had concomitant food allergy.

In the study group, mean serum 25(OH) D vitamin concentration was 28.42 ± 10.56 ng/ml (min:4.8 max:101.8 ng/ml). 25(OH) D vitamin serum concentrations were found to be sufficient, insufficient, deficient and severe deficient, in 48 (40%), 55 (45.8%),16 (13.3%) and one patient (0.8%),respectively (Table 1). Mean 25 (OH) D vitamin serum concentration of the control group was 41.68 ± 10.56 ng/ml (min:10.3 - max:122.4 ng/ml).

Mean SCORAD level of study group was 39.46 ± 14.23 (min: 4- max: 86.1).Fifteen children (12.5%) had mild AD,86 (71.6%) had moderate AD and nineteen (15.9%)had severe AD.

Table 1. Clinical characteristics of patients

	n (%)
Family atopy	
No	47 (39.2)
Yes	73 (60.8)
Skin test positivity	
House dust mites	65 (54)
Weeds	45 (37,5)
Grass pollens	42 (35)
Animal dander	34 (28)
Fungus	24 (20)
Tree	37 (30.2)
Latex	16 (13.3)
Cow milk	9 (7.5)
Egg	24 (20)
Test positivity to any food	48 (40)
Skin test positivity to at least one allergen	102 (85)
No test	6 (5)
SCORAD groups	
Mild(0-25)	15 (12.5)
Moderate (25-50)	86 (71.6)
Severe(>50)	19 (15.9)
Vitamin 25 (OH) D group	
>30 ng/ml=Normal	48 (40)
20-30 ng/ml=Sufficiency	54 (45)
5-20 ng/ml=Deficiency	17 (14.16)
<5 ng/ml=High deficiency	1 (0.84)
	mean ± SD (min-max)
IgA(mg/dl)	95.21 ± 54.91 (12-380)
IgM(mg/dl)	109.7 ± 80.2 (29-834)
IgG(mg/dl)	898.1 ± 286.4 (308-1798)
Total IgE(IU/L)	448.9 ± 579.3 (1-2000)
Peripheric blood eosinophil counts (mm^3)	557 ± 425.3(39-3040)
Vitamin 25(OH)D 0(mg/dl)	28.42 ± 10.56 (4.8-101.8)
SCORAD index	39.46 ± 14.23

Vitamin D Relations

The mean vitamin D serum levels of patients with AD and control group were 28.42 ± 10.56 ng/ml and 41.68 ± 10.56ng/ml, respectively. The serum vitamin D levels showed statistical significanct difference between these groups ($p < 0.05$).

The relationship between vitamin D levels and severity of AD (SCORAD) are shown in Table 2. Patient with mild SCORAD had a mean ±SD serum 25 (OH) D vitamin level of 32.21 ± 7.9, those with moderate SCORAD had a level of 28.7 ± 11, while in the severe SCORAD group the level was 23.7 ± 8.9 ng/ml. In the severe SCORAD group,mean serum 25(OH)D vitamin level was significantly lower than the others (p=0.005).

Table 2. Relationship between serum 25(OH)D level and severity of AD(SCORAD)				
	Mild (SCORAD<25) n:15	Moderate (25<SCORAD<50) n:86	Severe (SCORAD>50) n:19	p
Serum 25 (OH) D level (ng/ml)	32.1 ± 7.9	28.7 ± 11	23.7±8.9	
Normal (n:48)	11 (73.3)	33 (38.4)	4 (21)	
Insufficient (n:54)	3 (20)	41 (47.7)	10 (52.6)	0.005
Deficient (n:17)	1 (6.7)	12 (13.9)	4(21)	
High deficient (n:1)	0	0	1 (5.3)	

In correlation analysis, between 25(OH)D vitamin level group and SCORAD group; significant reverse correlation was found (r =-0.273, p= 0.003) (Table 3).

Table 3. Correlation analysis between 25(OH)DVitamin level group and SCORAD group		
All group (n:120)	Vitamin 25 (OH) D (ng/ml)	
	r	p
SCORAD İndex	-0.273	0.003

DISCUSSION

Vitamin D is located in the center of the current debate recent years because of its role on both innate and acquired immune response. Receptor called VDR (vitamin d receptor) is included in most of our tissue and organs.

Due to this, vitamin D is believed to be an important material affecting directly more parts of our body.Vitamin D is synthesized in the skin. Skin is also one of the important parts of our body that include VDR and directly or indirectly has impact on the skin.

AD and effect of vitamin D deficiency on the skin have some similar stages on pathogenesis like immune response disorder and epidermal barrier dysfunction.

Although there are lots of studies showed direct correlation between severity of AD and vitamin D deficiency,a few studies also show no relation.

Peroni et al. (22) showed that there was a reverse correlation between 25(OH)D serum levels and AD severity.

In a systematic-review and meta-analysis (23)significant relation between severity of AD and supplementation of vitamin D was found. El Taieb et al.(24) reported that serum level of mild AD patients was 14.6 ±3.5 ng/ml, moderate 5.5 ± 3.3 ng/ml and severe was 0.3 ± 0.1 ng/ml. They found statistically important difference between the groups (p<0.001). Also Wang et al.(25) showed inverse relation between severity of AD and serum 25(OH) D levels. In a systematic review (26) examining the effects of 25 (OH) D levels on atopic dermatitis, a significant reverse correlation was found between the AD severity and 25 (OH) D serum levels in 10 of 16 studies.

In contrast to this study,there is also studies showing no relation between AD severity and 25(OH) D serum levels (27-29). Chiu et al.(27) found that mild AD had low 25(OH) D serum level and also found no correlation between Vitamin D level and the severity of the disease.

In contrast to this study,there is also studies show no relation between AD severity and 25(OH) D serum levels (27-29). Chiu et al.(27) found that mild AD had low 25(OH)D serum level and also no correlation.

Lara-Corrales et al. (28) showed that although Vitamin D levels correlated with AD severity, vitamin D supplementation did not significantly improve disease severity. Previous studies (29,30) also found no relation between SCORAD and 25(OH)D serum levels.

In our study,we found that in severe AD group, vitamin D levels were much lower than moderate end mild AD groups. Besides, there was a significant difference for 25(OH) D level between mild and moderate SCORAD group (p=0.03). Additionally, between mild and severe group the relation was strongly statistically important (p=0.005). There was also statistically important difference between moderate and severe group (p=0.02). The lowest 25(OH) D vitamin level seen in severe AD group may be due to fact that the majority of our patients(90%) had IgE-related type of AD

(extrinsic,atopic). Many studies (31-33) showed that skin barrier impairment was an important factor for extrinsic AD as well as vitamin D deficiencies. We studied especially in low sunlight season (September-January), this might be one of the reason of low vitamin D levels. However especially atopic-based diseases like asthma and allergic rhinitis aggravated in these season may be provoked by lower vitamin D level.

In our study subjective complaints scores in the total SCORAD index score was high. Especially subjective evaluations may be reason of high SCORAD index level. Also co-existing asthma and allergic rhinitis may aggravate the severity of atopic dermatitis.

CONCLUSION

In conclusion, our data showed a reverse correlation between 25(OH) D serum vitamin level and severity of AD. Vitamin D deficiency should be checked in unresponsive AD cases. Finally, further studies with large numbers of

patients including and other variables like age, sex, other types ADs can better reveal the interactions between AD and vitamin D more precisely.

LIMITATIONS

The current study encountered the following limitations: small number of participants.

Competing interests: The authors declare that they have no competing interest.

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