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ORIGINAL ARTICLE

Relation between Serum 25 Hydroxy Vitamin D Levels and Severity of Atopic Dermatitis

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Abstract

Background & Aim: Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disorder. The ethiopathogenesis of AD is complicated, but is mainly due to a multifactorial interplay between the presence of a defective skin barrier, immunological dysregulation and environmental factors. Vitamin D is a fat-soluble vitamin synthesized in the skin. Recently, there have been several reports that low vitamin D plays a role in the pathogenesis of many conditions including AD. Adaptive and innate immune systems are both regulated by Vitamin D. Consequently, an obvious link between Vitamin D and allergic diseases was constantly a matter of investigation and research. Therefore, the aim of this study was to determine if there was a relationship between Vitamin D deficiency and the severity of Atopic Dermatitis.

Methods: The study included 36 patients suffering from mild, moderate, and severe atopic dermatitis assessed according to SCORAD index and 36 apparently healthy subjects as a control group. The study was conducted in the Dermatology, Venereology and Andrology outpatients' clinic at Zagazig University hospitals from November 2018 to April 2019 to avoid seasonal variations in Vitamin D levels.

Results: Our study showed that 81.8% of the severe AD cases had deficient vitamin D levels compared to 23.1% and 50% among mild and moderate AD cases respectively, with a statistically significant difference among cases.

Conclusion: Vitamin D deficiency is a contributing factor for the worsening of AD in the form of a high SCORAD index.

Keywords
Atopic dermatitis, Vitamin D deficiency, SCORAD

Introduction:

Atopic dermatitis (AD) is a long standing, deteriorating inflammatory cutaneous condition. Itching and a red colored rash that usually takes place anywhere characterize it. AD patients are susceptible to encounter allergic rhinitis, asthma as well as food allergy, which are also atopic conditions **[1].** Atopy can be described as the tendency for allergic diseases to occur in a certain individual. It is characterized by an elevated serum immunoglobulin E level. Some examples of allergic or atopic conditions are allergic rhinitis, asthma and atopic eczema **[2].** One out of five children in high income countries suffer from atopic dermatitis, and its popularity keeps increasing in developing countries as well **[3].**

The presence of a defective epidermis has been reported as one of the most important factors behind AD. An undamaged, healthy skin barrier is the initial most important factor for protection against many microorganisms, allergens, and irritants. AD patients have a high tendency for developing allergies and skin infections as a result of the significant epidermal barrier defect. Recent studies have revealed the role

of immunity, inflammatory disorders and environment in the ethiopathogenesis of atopic dermatitis **[4].**

For an extended period of time, Atopic dermatitis was considered a disorder of keratinocytes. However, over the past 20 years, with the breakthrough of science in trying to explain the mechanism by which AD occurs, AD is now considered a multifactorial disease. Recent postulations have come to light, illustrating inflammatory, immunological and environmental factors to be the main aspects behind the pathogenesis of AD **[5].**

The clinical presentation of AD varies according to age. In infants, the main sites affected are usually the scalp, face, neck, chest and extensor aspect of the limbs. The diaper area however is usually not affected. In children, the typical sites involved are the flexural surfaces of the limbs (the antecubital and popliteal fossae), neck, wrists, and ankles. In puberty and adulthood, the sites usually affected are the flexural surfaces of limbs, hands, and feet. The pruritis that accompanies AD mainly persists throughout the day and exacerbates at night, regardless of the age of patients, causing sleep loss and considerable affection of quality of life **[6].**

Vitamin D is a lipid soluble micronutrient that is to a large extent produced in the skin. When we get exposed to ultraviolet B rays, 7-dehydrocholesterol gets transformed into cholecalciferol, also known as vitamin D3. Outer supplements and food are an example of external sources of vitamin D [5]. The prevalence of Vitamin D deficiency is becoming a popular problem. Despite the fact that the optimal amount of vitamin D remains controversial, any individual with 25 hydroxy vitamin D levels below 20 ng/ml is considered vitamin D deficient **[7].** Insufficient vitamin D levels have recently been incriminated as the cause behind several disorders such as malignancies, heart disease, contagious diseases, autoimmune conditions and allergic conditions such as AD **[8].**

Apart from bone metabolism and calcium homeostasis, vitamin D proved to be a major factor behind the human well being specially in the immunology field. Vitamin D has been indicated to having an important effect in maintaining the innate as well as adaptive immune systems, thus making the connection between allergic conditions and vitamin D quiet an interesting field. The presence of Vitamin D is very essential when it comes to the physiology of healthy skin. Vitamin D is highly involved in the synthesis of fillagrin, which is the main structural protein essential for the formation of the outermost layer of the epidermis. Enhanced wound healing and reduced inflammation include some of the impacts that vitamin D has on the skin **[9].**

There is an increased concern whether a decreased vitamin D serum level is involved in the progression of AD. It has been documented that atopic dermatitis worsens in the winter, especially in countries lying far from the equator, where vitamin d serum levels tend to be predominantly low in this season **[10].** In addition, the occurrence of AD has been contributed to genetic mutations in the vitamin D receptor **[11].** A relationship has been recorded between vitamin D and allergic conditions including conjunctivitis, allergic rhinitis, recurrent wheeze, bronchial asthma, food allergies, chronic spontaneous urticaria and of course atopic dermatitis **[12].**

Methods:

Ethical consideration

The study was accepted by the Dermatology, Venereology and Andrology department and the institutional review board (IRB) at Zagazig University. IRB number ZU4436. An informed consent was obtained from each participant before taking blood samples. In case of children, an informed consent was taken from their parents. The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans was followed in this work.

Study design

This study included 36 patients suffering from mild to severe atopic dermatitis **(Figure 1A)** and 36 apparently healthy age and sex matched subjects as a control group**.** This was done after excluding any patients suffering from chronic dermatosis apart from AD, any current or previous consumption of Vitamin D (in the past 6 months), patients suffering from any systemic diseases, patients receiving any

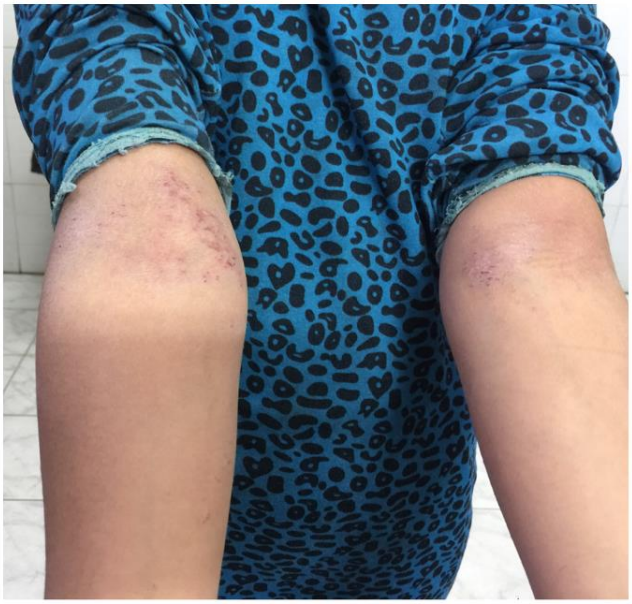
systemic treatments such as systemic steroids and patients suffering from bowel diseases.

The study took place in the Dermatology, Venereology and Andrology outpatients' clinic in the hospitals of Zagazig University during the period from November 2018 to April 2019 in order to prevent changes in the levels of vitamin D related to season.

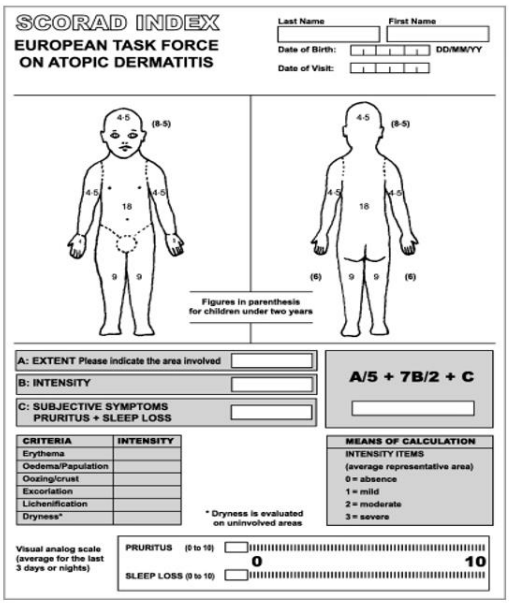
Full history was taken from patients regarding age, sex and occupation, history of the dermatological condition including onset, course, duration, site, drug intake and any previous treatments and associated itching and family history of AD or any other allergies like bronchial asthma, food allergy or allergic rhinitis. A full clinical examination was done for each patient in order to assess the objective signs and the subjective symptoms. Objective signs include the intensity and extent of the lesions. While the subjective symptoms refer to itching and disturbances in sleep as described by the patient. This is done to evaluate the scoring of Atopic Dermatitis (SCORAD) index.

The objective signs and the subjective symptoms are evaluated by a dermatologist in order to reach the SCORAD index. Subjective symptoms are evaluated by illustrating them on an analogue scale also known as the VAS (visual analogue scale) ruler. Items used for the calculation of SCORAD index are illustrated in **Figure 1B.**

Figure 1



A) A patient with Atopic Dermatitis



B) The SCORAD index

SCORAD index was calculated for each patient. We calculated extent using the "rule of nine" by expressing the percentage of involved surface area. Intensity: was measured according to presence of the following items, while giving from 0 to 3 points for each item according to its presence/severity: edema/papulation, erythema, oozing/crusts, excoriations, dryness, and lichenification of the skin involved (from 0 to 3 points for each item). Pruritus and sleep disturbance were scored where 0 is no itch (no sleeplessness) and 10 is the most terrible itch to be imagined leading to sleeplessness, according to

VAS ruler (from 0 to 10 points for each item). This equation was used in order to calculate the final score for each patient: [A/5 + 7B/2 + C (A = extent; B = intensity; C = subjective symptoms)]. A maximum achievable score is 103**.** Patients were categorized according to their score into mild (scoring less than 25), moderate (scoring 25 to 50) or severe (scoring more than 50) **[13].**

The VAS is used by patients to describe the level of their itching intensity. This is achieved by placing a vertical mark on the VAS scale which is a 10 cm long horizontal line. On this scale, zero represents absence of itch, while 10 represents the most terrible itch. VAS was originally designed to evaluate pain. However it has also been employed for the description of itch and the severity of sleep disturbance.

Using disposable syringes, three ml of blood were withdrawn from every patient. The withdrawn blood was then put in a test tube and left at room temperature for a 30 minute duration for coagulation to take place. The tube is then centrifuged for 15 minutes at 1500 rpm. The final serum was then stored at at -20°C to be further tested. The levels of Serum 25-hydroxyvitamin D levels of all subjects were then measured using the MINIVIDAS® 25 OH Vitamin D Total kits provided by bioMérieux\France (REF 30 463). The results were automatically calculated using calibration curves which are stored by the instrument (4-parameter logistics model) and are expressed in ng/mL or nmol/L.

Statistical analysis:

The gathered information was outlined in the form of mean ± Standard Deviation (SD). Quantitative information were given a range and qualitative information were given a frequency and percentage. The differences in proportions between the groups in our study were all compared via the Chi- square test (χ^2). On the other hand, parametric information of the studied groups were compared using the student's T test (t), while the non parametric information were compared using the the Mann Whitney test (z). When wanting to compare more than 2 groups, we worked with The One-way Analysis of Variance (ANOVA; F) and the Kruskal Wallis (KWT) test. Pearson correlation coefficient (r) was also used.

The corresponding distribution tables were used in order to deliver the probability value (p value). This was done after all test statistics were calculated. A P value less than 0.05 was considered statistically significant. A p value less than 0.01 was regarded as highly significant. However, a p value that was higher than 0.05 was regarded as non significant. All statistical analyses were carried out in SPSS version 21 for Windows.

RESULTS:

The patients had an average age of 8.4 ± 9.3 years old. There were 16 males and 20 females among cases. However there was no statistically significant difference among both studied cases and their controls regarding sex and age (P-value > 0.05). Out of 36 patients diagnosed with AD, 27 (75%) had history of allergic rhinitis, bronchial asthma or food allergy.

Table 1 shows a statistically significant difference among both studied cases and controls regarding serum levels of vitamin D (with p value less than 0.001), which was higher among controls with a mean of 23.4 ± 9.16 ng\ml versus 12.9 ± 6.28 ng\ml among studied cases.

The difference among both cases and control group regarding frequency of reference level of vitamin is shown in **Table 2**. This table clearly shows that 50% of the studied cases presented with deficient levels of vitamin D and the other 50% had insufficient levels versus (11.1% and 52.8% respectively) among their controls, showing a highly statistically significant difference. None of the studied cases were vitamin D sufficient. This is also clearly illustrated in **Figure 2**.

By comparing the serum levels of vitamin D among the patients, it was shown that the more severe the disease, the lower was the level of vitamin D with a statistically significant difference among the patients (Mild AD; 16.7 ± 7.22 ng\mL, Moderate AD; 12.5 ± 5.18 ng\mL, Severe AD; 8.8± 3.1 ng\mL, P-Value = 0.007) (**Table 3).**

Eighty two percent of severe AD cases (81.8%) had deficient vitamin D level compared to 23.1% and 50.0% among mild and moderate AD cases

respectively, with a difference that was statistically significant (P-Value= 0.02) as shown in **Table 4**.

Table 5 illustrates Pearson's correlation between vitamin D with SCORAD index and with age among studied cases. This table shows a negative relationship that is statistically significant, between vitamin D and SCORAD of atopic dermatitis, while there was a positive correlation with age, however it was not statistically significant.

Table 1: Difference in vitamin D level among both studied cases and their controls

	Cases (N=36)	Controls (N=36)	MW	P-value
Vitamin D (ng\ml)				
Mean ±SD **Range**	12.9 ± 6.28 7.3 - 28.6	23.4 ± 9.16 8.1 - 36	**4.85**	**<0.001 HS**

HS: Highly significant, MW: Mann-Whitney, P-value < 0.001 is high significant

Table 2: Difference among both cases and control group regarding frequency of reference level of vitamin D.

	Cases (n=36)		Controls (n=36)		X^2	p-value
	N	%	N	%		
Vitamin D (ng\ml)						
Deficient Insufficient Sufficient	18 18 0	50.0 50.0 0.0	4 19 13	11.1 52.8 36.1	**21.9**	**<0.001 (HS)**

HS: P-value<0.001 is high significant

Table 3: Comparison between severity of atopic dermatitis and vitamin D level among studied cases.

	Studied cases (n=36)			KW test	P-value
	Mild (N=13)	Moderate (N=12)	Severe (N=11)		
Vitamin D (ng\ml)					
Mean ±SD Median (range)	16.7 ± 7.22 13.7 (7.3 - 28.6)	12.5 ± 5.18 10.1 (6.8–19.1)	8.8 ± 3.1 7.5 (6.4-16.1)	9.88	0.007 S

S: P-value<0.05 is significant, KW: Kruskal-Wallis

Table 4: Relation between severity of AD and reference level of vitamin D among AD cases.

	Mild (n=13)		Moderate (n=12)		Severe (n=11)		X^2	p-value
	N	%	N	%	N	%		
Vitamin D (ng\ml)								
Deficient Insufficient	3 10	23.1 76.9	6 6	50.0 50.0	9 2	81.8 18.2	**8.22**	**0.02 (S)**

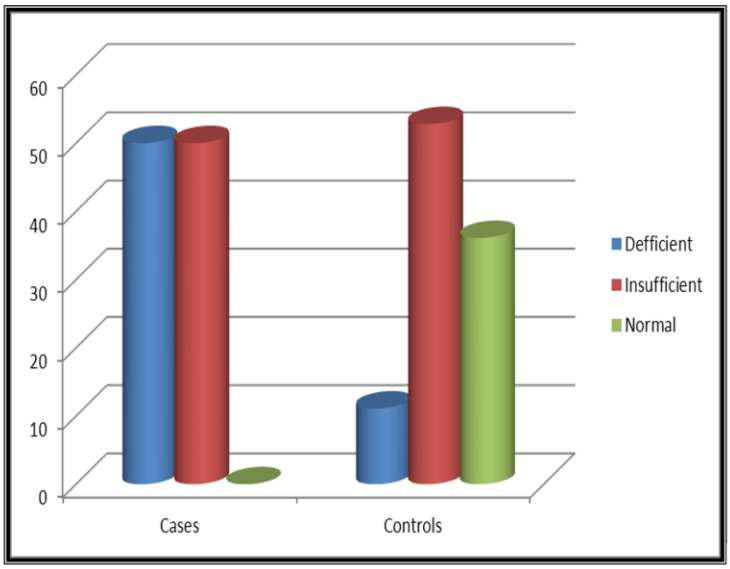
S: significant, P-value < 0.05

Table 5: Pearsons correlation between vitamin D with age, and SCORAD index among studied cases.

	Vitamin D	
	R	**P -value**
Age	0.068	0.394
Scorad	**-0.534**	**0.002**

R: Correlation coefficient

Figure 2: Reference level of vitamin D among both studied cases and controls



DISCUSSION:

Vitamin D and its correspondents appear to be an important factor in the control of disorders such as vitiligo, acne, psoriasis, rosacea and AD **[14].**

It has been reported that there is a connection when it comes to vitamin D and allergic diseases. Those conditions include asthma, rhino sinusitis, food allergy, chronic wheeze, chronic spontaneous urticaria (CSU) and AD. Some researches have revealed the fact that vitamin D plays a role in the etiopathogenesis of CSU. Furthermore, other studies have showed clinical improvement in CSU after vitamin D supplements **[12].**

Many studies have suggested a positive correlation between decreased serum levels of Vitamin D and the incidence of AD. Accordingly, we had designed this study in order to prove the fact that decreased vitamin D serum levels and atopic dermatitis are not only related through prevalence of the disease, but that they are also inversely related when it comes to AD severity and the levels of serum vitamin D.

This case–control study provides evidential proof to the presence of a relationship between AD and Vitamin D in the Egyptian population. The results showed lower vitamin D serum levels in patients with AD than in the control group. Furthermore, a negative relationship was also found between vitamin D serum levels and the severity of Ad as shown by SCORAD index. However, the control group contained a high percentage of people with vitamin D insufficiency (52.8%).

The study has shown a statistically highly significant difference among both studied cases and controls regarding vitamin D serum levels (p value less than 0.001), which was higher among controls with mean of 23.4 ± 9.16 versus 12.9 ± 6.28 among studied cases. It is to be noted that none of the AD patients (0%) were vitamin D sufficient.

As regard to the severity of AD, our study showed that most of the severe AD cases (81.8%) had deficient vitamin D levels compared to 23.1% and 50% among mild and moderate AD cases respectively, with a statistically significant difference among cases.

This was consistent with several other studies. A study carried out in 2011 suggested that there maybe a relationship between decreased vitamin D serum levels and an increased SCORAD index **[15].** Another study in 2014 concluded that there was an inverse correlation between vitamin D serum levels and the severity of AD, whether long term or short term **[16].** Furthermore, a study carried out in Korea stated that patients who suffered low vitamin D3 levels were found to be more prone to bronchial asthma, had high levels of immunoglobulin E and had a higher SCORAD index **[17].**

The results of our study showed a statistically significant difference between severity of AD and serum levels of vitamin D (p-value <0.05), which was higher among mild cases with median of 13.7 ng\ml, median of 10.1 ng/ml in moderate cases and 7.5 ng/ml in severe cases. Those results came in agreement with a study that was carried out in Egypt where vitamin D serum levels were remarkably higher in mild AD (14.6±3.5 ng/mL) when compared to moderate and severe AD, with levels of (5.5±3.1 ng/mL) and (0.3±0.1 ng/mL) respectively **[18].**

Supporting the results from our study, previous clinical trials suggested the fact that vitamin D supplementation has a therapeutic role in the treatment of AD **[14].** In a randomized double-blind study carried out by Sidbury et al, 2008, an improvement was seen in 80% of the children who were supplemented with vitamin D, while only 16% in the control group showed an improvement (p=0.04) **[19].**

However, the result of our studies was inconsistent with the results of Han et al, 2015 who found that children with AD had lower vitamin D levels compared to healthy children, however, they did not observe the same relation in adults. Also, vitamin D serum levels were not significantly correlated with the severity of AD **[9].** In addition, D'Auria et al, 2017 did find a relationship regarding vitamin D levels and the presence of AD, but not regarding vitamin D levels and the severity of AD **[20].**

In our study, 50% of the studied cases presented with deficient vitamin D levels and the other 50% had insufficient levels. In this study, none (0%) of the participating patients had normal vitamin D serum levels. However, in the control group, deficient levels and insufficient levels were 11.1% and 52.8% respectively. This difference was highly statically significant.

This came in agreement with Sharma et al, 2017 who stated a statistically significant negative correlation between vitamin D levels and the severity of AD (r-value= -0.458, p-value= 0.003). AD patients had remarkably low vitamin D serum levels compared to the control group which was much higher, noting that all patients with AD had vitamin D deficiency (< 20 ng/ml) [21].

The presence of insufficient and deficient subjects in the control group maybe due to the fact that the deficiency and insufficiency of vitamin D is commonly seen in children. It is usually assumed that vitamin D deficiency is not common in sunny countries like Egypt, since the physiology of Vitamin D depends mainly on the presence of sunlight. However, it is surprising that the prevalence of vitamin D deficiency is high even in tropical areas. This is most likely due to the decreased intake of vitamin D specially in children. Vitamin D food fortification policy should therefore be considered within the future to compensate for the limited amounts of natural sources of vitamin D in the diet. Meanwhile, vitamin D supplements should be encouraged in children to supply the needed amount of this necessary vitamin for optimal health **[22].**

The main target of this research was to figure out the truth behind the presence of a relationship between serum levels of vitamin D and the severity of AD. A negative correlation between vitamin D serum levels and the severity of AD was stated. The results of our study showed a statistically significant difference among severity of AD cases' serum levels of vit. D (p-value <0.05), which was higher among mild cases

with median of 13.7 ng\ml, median of 10.1 ng/ml in moderate cases and 7.5 ng/ml in severe cases.

Conclusion:

This study stated that decreased vitamin D serum levels is a contributing factor for the deterioration of AD in the form of a high SCORAD index.

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