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Estimation of Calcidiol Level in Serum of Atopic Dermatitis Patients before and after NB-UVB Phototherapy in Comparison to Oral Vitamin D Therapy

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Abstract

Background: Treatment of Atopic Dermatitis (AD) is still a challenge, with Narrow band (NB-UVB) considered to be a corner stone. Calcidiol deficiency is one of the factors in the pathogenesis of AD, thus supplementation with oral calcidiol is assumed to offer additional therapeutic option for such patients.

Aim of study: Was to assess the possible role of calcidiol in the treatment of AD whether it is induced by phototherapy or given as an oral supplementation.

Patients and methods: 30 pediatric patients with AD were enrolled in this study and divided into 2 equal groups. Group I patients received 24 sessions of NB- UVB and group II patients received oral calcidiol (600 IU/day orally) for 2 months. A blood sample was taken and SCORAD index was assessed before and after treatment for all patients. 20 controls were also included.

Results: At baseline, the mean level of calcidiol was significantly lower in AD patients (92.53 ± 22.42 ng/ml) in comparison to controls (132.18 ± 48.27 ng/ml) (P=0.005). Two months after therapy, both groups showed elevation of calcidiol level with no statistical difference between them (P=0.66), and also improvement of SCORAD index with no statistical difference between both groups (P=0.172).

Conclusion: The current study proves the suggested role of calcidiol deficiency in AD especially in the pediatric group. In addition, it demonstrated the high efficacy of oral supplementation of calcidiol in the management of AD children that was comparable to documented results of NB-UVB.

Keywords: Atopic dermatitis; NB-UVB; Calcidiol

Introduction

Atopic Dermatitis (AD) is a common inflammatory skin disease characterized by immune activation, marked epidermal hyperplasia and defective barrier function, reflecting underlying alterations in kerationocyte differentiation [1,2].

Calcidiol is a fat-soluble prohormone steroid that has endocrine, paracrine and autocrine functions [3]. Its incrimination in skin diseases has been under the spot light in the recent years. Concerning its relation with AD, animal studies, case reports, and randomized clinical trials have suggested the role of calcidiol, through various mechanisms including immunomodulation [4]. Furthermore, an inverse relationship between the severity of AD and calcidiol levels has been previously suggested, and studies have shown that, in individuals with AD who are deficient in calcidiol, repletion of calcidiol results in improvement and decreased severity of the disease [5-7]; a notion that has been denied by others [8,9].

Despite the existence of numerous studies [5-12] tackling the connection that might exist between calcidiol and AD, the value of calcidiol in its treatment is far from clear. Adding to this, the proven existence of calcidiol receptor (VDR) polymorphism in the Egyptian population [13,14] gives more importance to studying the role of calcidiol and to assess its possible role in the treatment of AD in Egyptians; whether it is induced by phototherapy or given as an oral supplementation.

Patients and Methods

The current prospective randomized case-control study was conducted in the outpatient clinic Kasr Al-Ainy, Cairo University, after the approval of the ethical committee of the Dermatology department. A total of 30 children (4-18 years old) with a confirmed diagnosis of AD, and 20 age and sex matched controls were included in this study.

AD patients with other dermatological and/or systemic diseases were considered ineligible to be included. In addition, those patients with any contraindication to receiving phototherapy in the form of narrow band ultraviolet-B (NB-UVB) were also excluded. Oral supplementation of calcidiol within 3 months prior to the study was also considered an exclusion criterion. Patients were kept off any topical treatment for AD apart from bland emollients for at least 2 weeks, and systemic treatment for at least 4 weeks prior to inclusion.

After the signing of an informed consent by the parents/guardians, all included patients were subjected to history taking, physical examination and scoring of atopic dermatitis using the SCORAD index [15]. Skin lesions were photographed using Sony Cyber shot DSC-W570 Camera using the same settings for all patients.

A blood sample was retrieved from each patient for the measurement of the calcidiol level using ELISA. Afterwards, randomization using sealed envelope method was used to randomly divide the patients into 2 groups.

1-Group I (Nb-UVB)

It included 15 patients, 6 males (40%) and 9 females (60%), whose ages ranged from 5 to 14 years (mean of 8.00 years ± SD 2.51). Every patient received 24 sessions of NB-UVB (3 sessions per week) for 2 months.

NB-UVB was delivered by an UV cabin (Waldmann GmbH, Germany) equipped with an integrated UV photometer, having 16 TL-01/100W fluorescent lamps producing NB-UVB with a peak emission at 311 nm. Initial dosage and subsequent increments were dependent on the minimal erythema dose.

2-Group II (Oral calcidiol)

It included 15 patients, 8 males (53.3%) and 7 females (46.7%), whose ages ranged from 4 to 11 years (mean of 7.80 years ± SD 2.18). Every patient received oral calcidiol (600 IU/day orally) for 2 months, being the recommended daily allowance [16].

While on treatment, all patients were instructed to avoid any other topical or systemic therapy for AD apart from bland emollients and anti-histamines when needed.

At the end of the treatment plan (2 months), SCORAD index was re-evaluated for all patients in both groups. In addition, another blood sample was retrieved for the assessment of the calcidiol level after treatment.

Measurement of the calcidiol level

A blood sample was taken and the level of calcidiol was measured in serum using ELISA kit. The kit was provided by USCN life science Inc (Houston, USA).

This assay is a competitive inhibition enzyme immunoassay procedure. The microplate was coated by monoclonal antibody specific to hydroxycalcidiol3. There is competitive inhibition reaction between biotin labeled HVD3 analogues and unlabeled antigen (Standards or samples) with the pre-coated antibody. Avidin conjugated to Horseradish Peroxidase is added. After addition of the substrate solution, the intensity of color is reverse proportional to the concentration of HVD3 in the sample.

Statistical methods

Data were statistically described in terms of mean ± standard deviation (± SD), median and range or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test for independent samples in comparing 2 groups when normally distributed and Mann Whitney U test for independent samples when not normally distributed. Comparison of normally distributed numerical variables between more than two groups was done using one way analysis of variance (ANOVA) test with post hoc multiple 2-group comparisons. Non-normal numerical variables between more than two groups were compared using Kruskal Wallis test with post hoc multiple 2-group comparisons. For comparing gender, Chi square (χ^2) test was performed. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

The current study included 30 AD patients and 20 age and sex matched controls. Their demographic and clinical data are summarized in Table 1.

Baseline evaluation

Prior to therapy, there was no significant difference in the SCORAD index assessment between both groups (P=0.6) (Table 1).

The mean level of calcidiol was significantly lower in the AD patients (mean 92.53 ng/ml ± SD 22.42 ng/ml) in comparison to the controls (mean 132.18 ng/ml ± SD 48.27) (P=0.005). However, there was no statistically significant difference between both AD groups regarding the baseline mean level of calcidiol (P=0.86) (Table 1).

	Group I Nb-UVB (n=15)	Group II Oral vitamin D (n=15)	Controls (n=20)
Age (years) Range	5-14	4-11	4-16
Sex (number)			
Males	6	8	9
Females	9	7	11
Calcidiol level (ng/ml) Mean ± SD	89.41 ± 21.63	96.23 ± 29.92	132.17 ± 48.26 *
SCORAD Mean ± SD	48.7 ± 12.42	40.53 ± 7.88	

Table 1: Demographic and clinical data of included subjects before treatment (*; Calcidiol level is significantly lower in AD patients in comparison to controls (P=0.005)).

Post-treatment evaluation

Two months after treatment, the SCORAD index significantly decreased in both AD groups to reach 17.06 ± 10.94 in the NB-UVB receiving group (P=0.001), and 11.17 ± 12.063 in the oral calcidiol receiving group (P=0.001). There was no significant difference between both groups regarding the final SCORAD index evaluation (P=0.172) and the mean % of change in SCORAD index (P=0.548) (Tables 2, 3 and Figures 1, 2).

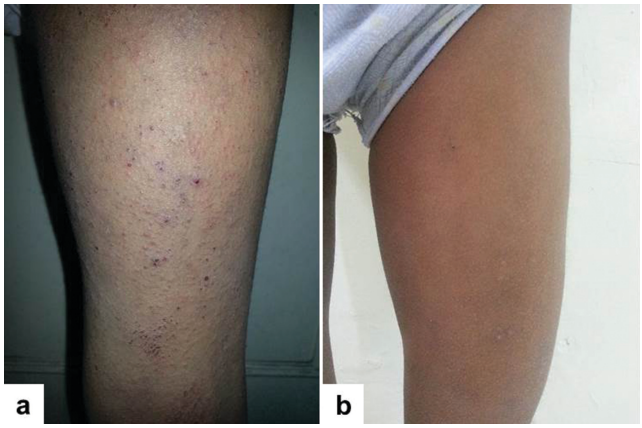

Figure 1: AD patient (A), showing improvement after 2 months of NB-UVB treatment (B).

In addition, the mean calcidiol level significantly increased in both AD groups to reach 118.73 ± 27.59 ng/ml in group I (P= 0.001), and 146.48 ± 38.60 in group II (P=0.003). There was no statistical significant difference between post-treatment mean calcidiol level in both groups and that of the controls (132.18 ± 48.27 ng/ml), (P=0.666, P=0.709) respectively. There was no significant difference between both groups regarding the final mean calcidiol level evaluation (P=0.094) and the mean % of change in mean calcidiol level (P=0.141) (Table 2).

In group I, there was no significant correlation between the cumulative dose of NB-UVB and both the SCORAD index and the calcidiol level after treatment. Furthermore, no significant correlations were detected between the severity of AD in the form of the SCORAD index and the calcidiol level, whether before or after therapy in both groups.

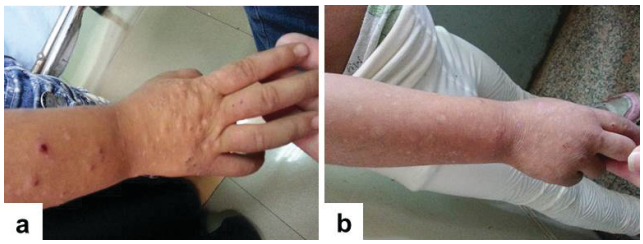

Figure 2: AD patient, showing improvement after 2 months of oral calcidiol (B).

Discussion

The current study conducted on 30 AD patients and 20 age and sex matched controls highlights the possible role played by calcidiol in the complexity of AD. This incrimination has been shown by 2 ways, first the significantly decreased level of calcidiol in AD patients in comparison to the controls during the baseline assessment. Secondly, 2 months after therapy (NB-UVB or oral calcidiol supplementation), all AD patients showed improvement that was evident *via* the significant decrease in their SCORAD, along with the significant up rise in their calcidiol levels.

	Group I Nb-UVB (n=15)	Group II Oral vitamin D (n=15)	p value
Calcidiol level (ng/ml) Mean ± SD	118.73 ± 27.59	146.48 ± 38.60	0.09
% of Change in Cacidiol level	36.16 ± 32.34	68.36 ± 58.69	0.141
SCORAD Mean ± SD	17.06±10.93	11.17±12.06	0.172
% of change of SCORAD	65.8 ± 16.89	67.87 ± 22.59	0.548

Table 2: Clinical data of included patients after treatment.

A recent meta-analysis handling 35 studies [2], demonstrated that the depressed level of calcidiol in all age groups of AD patients particularly in pediatric patients is a constant finding, a notion that our study on AD Egyptian children comes in agreement with. The consistency of such a finding in a large number of studies [5-7,17-22], confirms that the low level of calcidiol in such a disease is not a coincidence, and that calcidiol deficiency has a possible role in the pathogenesis of AD.

The controversy in the serum level of calcidiol in AD patients is mainly viewed among adult AD patients, where several studies showed the non-significant alteration of calcidiol levels among patient and control groups [8,9]. This raises the attention that pediatric AD patients are more prone to be worsened with depressed calcidiol level being the age group that may have an increased risk of allergen penetration through the skin, specially that most allergies are initiated in childhood [2].

Taking a step further, our study demonstrated that the elevations of calcidiol, together with the improvement of the SCORAD, even though not statistically correlated, were noted in our patients after 2 months of therapy. Interestingly, this elevation and improvement was noted in both groups (NB-UVB and oral calcidiol), with no significant differences between them. This is of special importance as for the first time oral supplementation of calcidiol was compared to NB-UVB in the treatment of AD. It puts forefront the possibility of using oral calcidiol in the management of AD patients, as it yielded results that appeared to be comparable to that of NB-UVB that is regarded as the most efficacious, well-tolerated treatment option for AD [2,23]. This could be of particular value as it overcomes the compliance problem that is commonly faced while using phototherapy [24], and has a higher safety profile when the side effects of phototherapy [25], or even topical steroids [26] are considered.

	Calcidiol level Before	Calcidiol level After	p value	SCORAD Before treatment	SCORAD After treatment	p value

	Treatment (ng/dl)	Treatment (ng/dl)				
Group I: Nb-UVB (n=15)	89.41 ± 21.63	118.73 ± 27.59	0.001	48.7 ± 12.42	17.06 ± 10.93	0.001
Group II: Oral vitamin D (n=15)	96.23± 29.92	146.48 ± 38.60	0.003	40.53 ± 7.88	11.17 ± 12.06	0.001

Table 3: Comparison between calcidiol level & SCORAD before & after treatment.

The use of oral calcidiol in the management of AD has been proven before to be successful [9,22,27-30]. Two studies [29,30] enrolled pediatric patients who had a history of AD, and both studies showed that eczema area and severity index (EASI) was decreased after calcidiol supplementation. Similar findings were shown by the others [9,22,27,28] but with using the SCORAD.

Although this improvement was not correlated to calcidiol level in our study, no other treatment lines were used, so it could be assumed that the clinical improvement was related to the administration of calcidiol. This lack of correlation could be explained by the multifactorial nature of the disease, and the small sample size, or calcidiol deficiency could be simply related to the disease pathogenesis but not necessarily to disease severity as previously suggested [31].

Several ways could elucidate the value of calcidiol in improving AD. First, Calcidiol decreases local and systemic inflammation, thus modulating cytokine production and inhibiting T-helper cell (Th1) proliferation, as well as Th17 cells [32]. Calcitriol, the active form of calcidiol, seems to significantly decrease the secretion of IL-2, TNF-α and IFN-γ by Th1 cells and that of IL-4 by Th2 cells [33]. Moreover, the IFN-γ reduction would lead to a decreased expression of other cytokines such as IL-31 and IL-33 and to the improvement of clinical features such as spongiosis [34]. In fact IFN-γ is implicated in keratinocyte apoptosis which leads to eczema and spongiosis in patients with AD [35].

In addition, at the skin level, calcidiol acts through the suppression of the inflammatory response, increasing anti-microbial peptides, and promoting the integrity of the cutaneous barrier [36]. Furthermore it reduces Toll-like receptor activation [37]. Therefore, calcidiol deficiency might exacerbate AD *via* disturbed epidermal barrier function and immunologic dysregulation with subsequent impaired defense against infections [38].

Regarding the nb-UVB, and its well documented efficacy in the treatment of AD [2,23], this study could not offer proof that the up-rise of calcidiol is a direct mechanism by which this improvement in AD is achieved by this phototherapeutic machine. This is because of the lack of a correlation between the calcidiol level and the SCORAD of NB-UVBreceiving patients. Still, non-existence of a correlation does not necessarily mean its absence, and it could be attributed again to the multifactorial nature of the disease, and the small sample size.

The improvement of clinical signs of atopic dermatitis by the NB-UVBtreatment is well documented in literature [2,23,39,40] and is explained by the different mechanisms of actions of nB-UVB. UVB can improve the barrier function through increased expression of terminal differentiation proteins (filaggrin and involucrin) and antimicrobial peptides (AMPs) [41]. In addition, UVB has been shown to induce T-cell apoptosis in atopic skin lesions [42], and to suppress major T-cell pathways involved in AD pathogenesis namely the TH17/IL-23 and Th1 pathways [43-46].

UVB also suppresses the pro-inflammatory cytokines IL-12, IL-2 and IFN-γ, and to a lesser extent TNF-α [44]. Furthermore, it has immunomodulatory effects that lead to improvement of the inflammatory skin diseases as AD [47]. Ultraviolet-B also induces activation of AMPs, and induces calcidiol synthesis and subsequent cathelicidin expression in skin [48] that protects the skin from microbial infection.

In conclusion, the current study offers proof that supports the postulated role of calcidiol deficiency in AD especially the pediatric group. In addition, the current study demonstrated the high efficacy of oral supplementation of calcidiol that approached that of the well documented NB-UVB in the management of AD children. This opens the door for such an affordable, easy to adhere to, safe line of treatment to be used for such cases. Nevertheless, larger-scale clinical trials are further needed to assess the effect of calcidiol treatment on AD outcomes, and thereby reach a clear consensus. Furthermore, combined treatments using both lines of therapy seem to be prudent to be evaluated.

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