Original Article

Clinico-biochemical relation of Vitamin D3 with the severity of atopic dermatitis and response to supplementation of Vitamin D3: A randomized controlled trial

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ABSTRACT

Background: Atopic dermatitis (AD), also known as eczema, is one of the most common skin disorders among children and adults, with a steep rise in diagnoses among children. Many studies have investigated the relationship between Vitamin D3 (Vit D3) and AD. **Methods:** A randomized controlled trial was conducted among 60 children at SCB Medical College, Cuttack from August 2014 to November 2016. Children were randomly assigned to an intervention group that received 60,000 IU of Vit. D3 every week for 6 weeks in addition to regular treatment for AD and a control group that received same treatment of AD except for Vit. D3. Both the groups were followed up at 4 weeks and 8 weeks. **Results:** In 60 cases of moderate to severe AD, 70% of the patients were male. About 81.7% of patients were from urban areas and 56.7% belonged to a middle socioeconomic class. In 76.6% of cases, family history of atopy was present. At baseline, mean SCORAD was 47.8±7.5 in the intervention group, and 49.2±10.3 in the control group. At baseline, serum Vitamin. D3 level (ng/ml) was 17.6±1.8 in intervention and 17.3±3.5 in control group. After Vitamin. D3 supplementation, the SCORAD improved to 12.8±5.1 (75% reduction) at 4 weeks, and 3.6±2.1 (92% reduction) at 8 weeks in the intervention group. In the control group, the mean SCORAD was 18.8±9.1 (61% reduction) at 4 weeks, and 7.3±4 (85% reduction) at 8 weeks. **Discussion:** The improvement of serum 25-hydroxy Vit. D3 was 134% and 366% in the intervention group compared to 78% and 121% in the observation group after 4 weeks and 8 weeks respectively. The p-values at both the time points were significant (<0.05) for the intervention group as compared to the control group. **Conclusion:** Short-term therapeutic supplementation of Vitamin. D3 in children with moderate to severe AD improves the clinical score. There is an inverse relationship between serum Vitamin. D3 level and severity of AD.

Key words: Atopy, Eczema, Vitamin D3, SCORAD, Pediatric

Atopic dermatitis (AD), also known as Eczema, is one of the most common skin disorders among children and adults, with a steep rise in prevalence among children [1,2]. Up to 20% of children are now affected by AD in developing countries. AD is a chronic and relapsing disease that is associated with inflammatory processes often preceding asthma and allergic rhinitis with a prevalence of 9–20% worldwide [3]. AD is characterized by dry and extremely pruritic skin [4]. This leads to the appearance of erythematous scaly patches, excoriation, and lichenification of skin. Severity of AD can range from a few xerotic patches on the skin to involvement of the entire body causing intense psychological distress [5]. Due to defects in the innate immune system, patients with AD have a greater chance of acquiring infection by microbial organisms such as *Staphylococcus aureus* and herpes simplex virus.

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Treatment strategies have often focused on allergen avoidance and topical application of medications. But recently, research has focused on its connection with immune function and the skin's natural barrier function. AD is not only associated with defects in the immune system but also these defects worsening the inflammation [6]. Within the past 5 years, focus has moved from the known interactions of Vitamin D3 (Vit. D3), bone mineralization, and osteoporosis to a broader role including cardiovascular, endocrine, cancers, and chronic diseases such as hypertension [7].

Vit. D3 is a fat-soluble vitamin. Under ultraviolet rays' exposure, it is synthesized under the skin. It is also found in natural foods as well as supplemental diets. Vitamin. D3 also has an important role in immunity, as it improves innate and adaptive immune responses by altering local calcium balance and by binding to nuclear vitamin receptors, which regulate gene transcription [8]. Vitamin. D3 regulates the activity of various immune cells such as monocytes, dendritic cells, and lymphocytes as well as regulates the function of epithelial cells which are

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important in allergic inflammation [9]. The levels of Vit. D3 often varies among people of different skin shades, geographic locations, sun exposure, diet, and hereditary factors.

Many studies have investigated the relationship between Vitamin. D3 and AD. The severity of AD tends to increase in patients who have lower levels of Vitamin. D3 [10]. Pilot studies have revealed a possible correlation between the severity of AD and very low serum Vitamin. D3 levels. and. The severity of the disease improved after Vitamin. D3 supplementation, according to SCORAD.

MATERIALS AND METHODS

The study was conducted at SCB Medical College, Cuttack from August 2014 to November 2016. Ethical approval for the study was granted by the hospital ethics committee. An informed written consent was obtained from parents of all subjects prior to enrolment in the study.

Subjects between the age group of 1–14 years diagnosed with AD by a dermatologist as per Hanifin and Rajka criteria and subjects willing to give blood for estimation of Vitamin. D3 levels were included in the study. The SCORAD was divided into three grades of severity: mild (<25 points), moderate (25–50 points), and severe (>50 points) [11]. Only moderate to severe cases of AD as per SCORAD were eligible for inclusion in this study. Serum Vitamin. D3 levels were measured in children with moderate to severe AD, and categorized as: sufficient (>30–40 ng/ml), insufficient (20–30 ng/ml), and deficient (20 ng/ml). Subjects with other atopic conditions (asthma, allergic rhinitis, conjunctivitis) or other skin diseases, syndromes, underlying systemic co-morbidity, and severe malnutrition were excluded from the study.

The intervention group received 60,000 IU of Vitamin. D3 supplementation every week for 6 weeks in addition to the standard treatment of AD as advised by a dermatologist. Control group received the same treatment of AD except for Vitamin. D3. Both groups were followed up at 4 weeks and 8 weeks to measure the response. Baseline data and socio-demographic parameters were recorded in a pre-designed data collection form. The following outcomes were measured in both the groups;

1. Serum 25-dihydroxy cholecalciferol level (Vit. D3)
2. Response to Vitamin. D3 supplementation in children with moderate to severe AD.

Children were randomly divided into two groups (intervention and control group) by a computer-generated random number table. Allocation concealment was done by the use of sealed, opaque envelopes. Patients and investigators were blinded to the identity of the study drug.

Data were entered into Microsoft excel sheet 2016 version. Statistical analysis was carried out using STATA software version 16.0 (USA). Data were analyzed using Shapiro–Wilk test for normality distribution. Continuous data were analyzed using "t-test," and categorical data using "Chi-square test." A $p<0.05$ was considered to be statistically significant.

RESULTS

A total of 86 children were assessed for eligibility. After excluding 22 subjects not meeting the inclusion criteria, 60 children with moderate to severe AD were finally randomized into two groups: intervention and control group (30 in each group) (Fig. 1). The baseline parameters of the two groups were comparable (Table 1). Out of all the subjects, 70% were male. About 81.7% of patients were from urban areas and 56.7% belonged to a middle socioeconomic class. In 76.6% of subjects, family history of atopy was present. At baseline, mean SCORAD was 47.8±7.5 in the intervention group, and 49.2±10.3 in the control group. At baseline, serum Vitamin. D3 level (ng/ml) was 17.6±1.8 in the intervention and 17.3±3.5 in the control group.

After Vitamin. D3 supplementation, the SCORAD improved to 12.8±5.1 (75% reduction) at 4 weeks, and 3.6±2.1 (92% reduction) at 8 weeks in the intervention group. In the control group, the mean SCORAD was 18.8±9.1 (61% reduction) at 4 weeks, and 7.3±4 (85% reduction) at 8 weeks. The improvement of serum 25-hydroxy Vit. D3 was 134,366 in the intervention group compared to 78,121 in the observation group after 4 weeks and 8 weeks respectively. The p-value at both the time points was significant (<0.05) for the intervention group compared to the control group (Table 2 and 3). There was no report of any adverse event in either of the groups.

DISCUSSION

AD is a chronic, pruritic disease of the skin which is relapsing in nature. There is a steep rise in incidence of AD during the past 2 decades, more so in children. Various studies have been conducted to examine the incidence and epidemiological profile of AD in different geographies with respect to gender, rural and urban distribution, socio-economic status, and family history of atopy. Recent studies have highlighted the relationship of AD with that of Vitamin. D3. An inverse relationship between the severity of AD and serum Vitamin. D3 has been shown by many studies.

In the present study, we found a significant improvement in the SCORAD after supplementation with Vitamin. D3 in children with moderate to severe AD. There was no report of any adverse events. The male-to-female ratio was 3:1 in our study. In a study

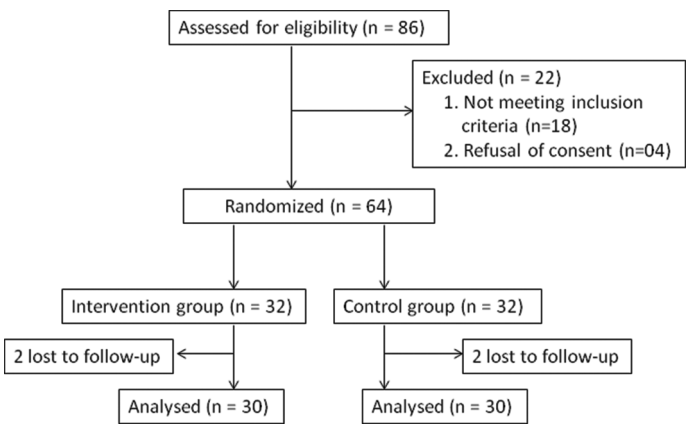

Figure 1: Study flow chart showing patient flow in the study

Table 1: Baseline characteristics of study children with moderate to severe AD as per SCORAD

Variables	Intervention group (n=30)	Control group (n=30)	p-value
Age, year (mean±SD)	7.4±5.8	7.7±5.6	0.24
Male sex, n (%)	17 (56.7)	16 (53.3)	0.53
Urban area, n (%)	14 (46.7)	15 (50)	0.78
H/o atopy in family, n (%)	11 (36.7)	10 (33.3)	0.47
Lower socio-economic status, n (%)	9 (30)	7 (23.3)	0.29
Moderate malnutrition, n (%)	6 (20)	5 (16.7)	0.18
H/o exclusive breast feeding, n (%)	19 (63.3)	21 (70)	0.17

AD: Atopic dermatitis

Table 2: Vitamin D3 level and SCORAD in both groups at various time points

Time points	Intervention group (n=30)		Control group (n=30)		p-value
	SCORAD, mean±SD	Vitamin D3 level (ng/ml), mean±SD	SCORAD, mean±SD	Vitamin D3 level (ng/ml), mean±SD	
At admission	47.8±7.5	17.6±1.8	49.2±10.3	17.3±3.5	0.26
At 4 weeks	12.8±5.1	41.3±6.4	18.8±9.1	30.8±10.6	0.03*
At 8 weeks	3.6±2.1	83.1±8.8	7.3±4.0	38.3±13.6	0.01*

***p<0.05, SD: Standard deviation**

Table 3: Percentage (%) reduction of SCORAD in intervention and control group at various time points

Time points	Intervention group (n=30)	Control group (n=30)	p-value
At admission	100	100	0.26
At 4 weeks	75	61	0.04*
At 8 weeks	92	85	0.012*

***p<0.05**

from North India, the male-to-female ratio was 1.6:1 [12]. Our study also revealed an increased prevalence of AD in males in accordance with a study from China which also indicated male dominance [13]. In our study, urban children constituted 81.7% and rural children constituted 18.3% with the ratio being 4.45:1. In another study, the prevalence of AD as per ratio of urban to rural was found to be 5:1 [14]. The cause of this high variation was depicted as rapid industrialization, change in lifestyle, and dietary habits.

We also found out in our study that 33% of children had a positive family history of atopy (eczema, asthma, or allergic rhinitis). According to a previous study, AD is 2.9 times more likely to occur in children of atopic parents than those of non-atopic parents [15]. This study also depicted maternal atopy having the strongest (20–26%) influence on childhood AD. When both the parents are affected, the odds ratio increases to 1.75. Nearly 27% of children belonged to lower socioeconomic status. This is in line with a previous systematic review that showed AD is more common among people with higher economic status [16]. The possible reason being hygiene hypothesis which states that higher exposure to infection in early life is a protective factor for AD. Therefore, the prevalence of AD with relation to socio-economic status remains controversial.

In our study, the intervention group showed both improvements in SCORAD and Vit. D3 compared to observation group with $p<0.05$. An earlier randomized clinical trial on the effectiveness of Vitamin. D3 supplementation in the treatment of AD found significant improvements in SCORAD across all the severity of AD [1]. The authors used Vitamin. D3 supplementation for 60 days compared to 6 weeks in our study. However, our findings were in accordance with this study.

Our study has an important implication, as a long-term supplementation might increase the risk of Vit. D3 toxicity without any additional benefits. Albenali *et al.* reported an improvement in SCORAD after taking Vit. D3 for 2 months by increasing IL-37 level [17]. SCORAD was also found to be improved upon supplementation with Vit. D3 in another study [18]. Contrastingly, one study found a link between elevated intake of Vit. D3 during infancy and increased incidence of AD in children younger than 6 years [11].

Though our study has several strengths, it has few limitations also. The limitations were: (a) small sample size, (b) the dose and duration of Vit. D3 was arbitrary; (c) neither allergic nor immunological parameters were studied to determine the mechanism of Vit. D3 action in AD.

CONCLUSION

Short-term therapeutic supplementation of Vit. D3 in children with moderate to severe AD improves the clinical score. There is an inverse relationship between serum Vit. D3 level and severity of AD. However, it remains to be seen if further studies examining different doses and duration regimens will confirm or refute the current study findings.

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