The Effects of Oral Vitamin D Supplement on Atopic Dermatitis: A Clinical Trial with *Staphylococcus aureus* Colonization Determination

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**Background:** An increase in *Staphylococcus aureus* skin colonization in atopic dermatitis patients resulted from the reduction of cathelicidin production in these patients. Recently, an in vivo study demonstrated that vitamin D could stimulate cathelicidin production. Oral supplements of vitamin D might be beneficial in atopic dermatitis.

**Objective:** To determine the effects of oral vitamin D supplements on clinical impact including *Staphylococcus aureus* skin colonization evaluation in atopic dermatitis patients.

**Material and Method:** Twenty-four atopic dermatitis patients were included in this double-blind, placebo-controlled study. They were randomly assigned into 2 groups for oral 2,000 IU/day of vitamin D$_3$ supplement and placebo. The lesional swab culture for *S. aureus* was done at week 0, 2 and 4. Clinical outcomes were assessed by SCORAD score, mexamer for erythema index and konometer for conductance were done at week 0, 2 and 4. Serum vitamin D levels were also determined at week 0 and 4.

**Results:** Twenty patients completed the protocol. *S. aureus* skin colonization, SCORAD score and erythema index were significantly reduced from baseline to week 4 for vitamin D treated group comparing with placebo ($p = 0.022, 0.028$ and $0.014$, respectively). There was an inverse correlation between serum vitamin D levels with *S. aureus* skin colonization and SCORAD score ($r = -1.0$, $p<0.001$).

**Conclusion:** Oral vitamin D supplement could reduce skin colonization of *S. aureus* and demonstrated the clinical improvement of patients with atopic dermatitis.

**Keywords:** Atopic dermatitis, Vitamin D supplementation, Cathelicidin, *S. aureus* colonization, SCORAD score

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Currently there are two upcoming interests concerning the pathogenesis of atopic dermatitis (AD)$_{11}$, The first is the dysfunction of skin barrier$_{21}$, The second is the immune dysregulation process which leads to the depletion of an innate immune response such as antimicrobial peptide molecules$_{35}$. Reduction of cathelicidin, one of the innate immune antimicrobial peptide, increases in *Staphylococcus aureus* skin colonization$_{3,5}$. It was reported that 90% of bacterial flora in AD patients were found with this organism$_{6}$. Therefore, an increase in *S. aureus* skin colonization's the one of the most important aggravating factors of this disease$_{7}$. 

Kedzierska et al found that colonization density of *S. aureus* was greater at lesional AD skin than non-lesional area with a statistically significant difference and directly correlated with disease severity$_{8}$. Gong et al reported that the lesional skin was commonly found with bacterial colonization especially *S. aureus*$_{9}$. 

Few studies reported that cathelicidin as the main target of vitamin D in this skin disorder$_{10,11}$ increased in lesional skin of moderate to severe AD patients who received oral vitamin D supplement$_{12,13}$. Recently, a few studies have showed that an oral vitamin D supplement could improve the clinical response of AD patients$_{14,15}$. However, there was no previous study demonstrating the effect of vitamin D.
on skin colonization with *S. aureus* and on objective measurements in AD patients.

The objective of this study was to evaluate the effect of oral vitamin D supplement on clinical outcome in AD patients and *S. aureus* skin colonization.

**Material and Method**

**Patients and methods**

The aim of this study is to compare the efficacy of vitamin D treated group with a control group in atopic dermatitis patients. Paired t-test was used to compare the outcome of interest and the decrease in SCORAD. From data obtained from the Javanbakht MH study\(^{(13)}\), the mean difference of the decrease in SCORAD between vitamin D treated group and the control group was 2.4 with the standard deviation of difference in the response of 1.8. The sample size of 20 patients is required with 95% confidence and 80% power. Sample size is calculated using the PS (Power and Sample Size Calculation) program version 3.0.34. With a dropout rate of 20%, samples of 24 patients have to be recruited, 12 in each group. A randomized, double-blind, placebo-controlled trial was conducted. There were 24 patients enrolled into the authors’ study. Eligible criteria included patients with mild to moderate atopic dermatitis assessed by SCORAD score (Scoring for Atopic Dermatitis)\(^{(1,7,18)}\), age between 1-18 years old. All patients were advised to take normal, dietary products and pursue their normal activities. They had been advised to discontinue at least 2 weeks topical corticosteroid or topical calcineurin inhibitor applications. The exclusion criteria included, patients with coexisting skin infection on top of AD lesions, known case of primary or secondary immune-compromised host, hepatic or renal disease, oral taking of vitamin D or nutraceutical supplement, continually taking antibiotics, corticosteroids, immunosuppressive agents, anti-epileptic drugs, thiazide diuretics, proton-pump inhibitors or histamine 2-receptor antagonists. Patients who used topical antiseptic or antibiotic products during the study period were also excluded.

All patients and their parents completed an informed consent. The clinical severity was assessed by using the SCORAD score, the objective skin evaluation for erythema by Mexameter (Cologne, Germany) and skin conductance by corneometer measurement (Cologne, Germany). The photographs of the skin lesions were taken by digital camera for pre-and post-treatment at week 0, 2 and 4. All of these measurements were done by dermatologist.

*S. aureus* culture was done from the skin lesions at week 0, 2, and 4. Quantitative method to determine total number of *S. aureus* were measured and reported with colony forming units per 1 ml (CFU/ml).

Serum 25-hydroxy vitamin D level (25 (OH) vitamin D) was measured at week 0 and 4. It was tested by chemiluminescence technique at Biochemistry Laboratory Center, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.

All patients were assigned by computerized blocked randomization (block of 4) method, which was performed by a third person and the encoding was disclosed at the end of the study. Twenty-four subjects were randomly assigned into two groups to receive either 2,000 IUs/day of vitamin D solution or placebo. The dose of 2,000 IUs/day of oral vitamin D supplement used in the study is safe because it is less than the tolerable upper intake level of vitamin D supplement. It is unlikely to cause adverse health effects and is recommended by Food and Nutrition Board at the Institute of Medicine of the National Academies of United State (FNB)\(^{(19)}\). The tolerable upper level dose is ranged from 2,500 IUs/day for 1-3 years old, to 4,000 IUs/day for >9 years old. All patients were allowed to take oral antihistamine (2 mg/kg/day, hydroxyzine) if clinically indicated, and providing them with the similar formulation of sunscreen, skin moisturizer and mild gentle cleanser (Physiogel\(^{®}\), Stiefel Laboratory, USA). This research was approved by Ethics Committee for Human Research, Faculty of Medicine, Srinakharinwirot University.

**Statistical analysis**

The demographic data was reported with proportion and percentage. Regarding the analysis of continuous data, the mean and standard deviation for normal distribution and Wilcoxon Signed Ranks test with data for non-normal distribution were used. Mann-Whitney U test was used to determine and compare between each variable. Spearman’s rho test was used to demonstrate the correlation between 25 (OH) vitamin D level with *S. aureus* colonization and SCORAD scores. Statistical significance was reported if \( p \) less than 0.05. Data software with SPSS program version 19.0 was used to analyze data in this study.

**Results**

Twenty patients completed the protocol, three of them were lost to follow-up and one patient was excluded due to secondary bacterial skin infection. Mean age was 8.28 years old (range = 1-18 years old).
There were 11 cases with mild AD and 9 cases with moderate AD. Baseline characteristics between groups had no statistically significant difference in term of gender, age, SCORAD score, *S. aureus* colonization, erythema index and skin conductance ($p = 0.64, 0.83, 0.83, 0.95, 0.95$ and $0.08$ respectively) (Table 1).

There was a decrease in SCORAD score from baseline to week 2 and 4 in both groups. At week 4, the decreased score of vitamin D group was statistically significantly different from the placebo ($p = 0.02$) (Fig. 1). It was shown that the vitamin D-treated group had lower colony count of *S. aureus* than those taking placebos at week 4 with statistically significant differences ($p = 0.03$) (Fig. 2).

Erythema index was decreased. At week 4, it was found that the erythema index of those with vitamin D supplement was statistically significant lower than those with placebo ($p = 0.01$) (Fig. 3). Skin conductance was not statistically significant difference between groups at each visit ($p = 0.08, 0.65$ and $0.55$ respectively) (Fig. 4).

Concerning the SCORAD score, there was a statistical significant group difference for erythema, edema, excoriations and pruritus at week 4; however, there was not statistically significant difference for skin lichenification, dryness and sleeplessness (Fig. 5).

Eight patients (4 for each group) were measured for serum 25(OH) vitamin D level in the serum. At baseline, the average mean of 25 (OH) vitamin D level of vitamin D treated group and placebo group was $18.55 \pm 2.68$ and $17.02 \pm 2.66$ ng/ml, respectively, which were lower than normal value (cut off point of normal value was 20 ng/ml). There was no significant group difference in vitamin D level at baseline ($p = 0.45$). At the beginning of the study, the 25 (OH) vitamin D level of the vitamin D treated group was range from $13.70-20.20$ ng/ml (the mean was $17.03$ ng/ml), by the end of week 4, it was range from $24.40-27.60$ ng/ml (the

![Fig 1](image1.png) **Fig. 1** To demonstrate the difference of SCORAD score between vitamin D and placebo group.

![Fig 2](image2.png) **Fig. 2** To demonstrate *S. aureus* colonization between vitamin D and placebo group.

![Fig 3](image3.png) **Fig. 3** To demonstrate erythema index between vitamin D and placebo group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Vitamin D (n = 10)</th>
<th>Placebo (n = 10)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male: female)</td>
<td>4:6</td>
<td>3:7</td>
<td>0.64</td>
</tr>
<tr>
<td>Age (year) (mean, SD)</td>
<td>8.59 (5.93)</td>
<td>7.90 (6.95)</td>
<td>0.83</td>
</tr>
<tr>
<td>SCORAD score (mean, SD)</td>
<td>18.23 (8.89)</td>
<td>19.21 (10.61)</td>
<td>0.83</td>
</tr>
<tr>
<td><em>S. aureus</em> colonization (CFU/ml) (mean, SD)</td>
<td>387.50 (246.22)</td>
<td>395.50 (276.91)</td>
<td>0.95</td>
</tr>
<tr>
<td>Erythema index (mean, SD)</td>
<td>563.40 (31.57)</td>
<td>564.40 (35.31)</td>
<td>0.95</td>
</tr>
<tr>
<td>Skin conductance (mean, SD)</td>
<td>18.49 (9.05)</td>
<td>26.77 (10.68)</td>
<td>0.08</td>
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</tbody>
</table>

SD = standard deviation

Table 1. Demographic data with SCORAD score and *S. aureus* colonization, erythema index and conductance at baseline.
mean was 25.06 ng/ml). The increment of 25 (OH) vitamin D level of the vitamin D treated group was significantly different from the placebo group, 8.03 ng/ml vs. 0.75 ng/ml (p<0.01). The correlation between serum vitamin D level of the patients with SCORAD score and *S. aureus* colonization were analyzed. It was discovered that the serum vitamin D level was inversely correlated with SCORAD score and *S. aureus* colonization with statistically significant differences (r = -1.0, p<0.01). No adverse effects were reported during the study period.

**Discussion**

Atopic dermatitis is a common chronic relapsing dermatitis with a complex of etiology. The standard management composes of anti-inflammatory agents, moisturizer and avoidance of aggravating factors. The role of vitamin D in the pathogenesis and treatment of AD was first elucidated by Schauber et al who demonstrated that vitamin D induced toll-like receptor 2 recognition of keratinocytes to microbes and led to cathecidin upregulation. Later, the study of Hata et al included patients with moderate to severe AD and volunteers with normal skin. All of them were orally given 4,000 IUs/day of vitamin D for three weeks. Then cathecidin expression from the patients’ skin was done on week 0 and week 3. It was found that patients with AD had statistically significant increase in cathecidin expression when compared with the baseline. Furthermore, volunteers with normal skin also had modest increased expressions of cathecidin. The researchers suggested that oral vitamin D supplement could significantly induce cathecidin expression in the skin of AD patients. Then the work of Peroni et al suggested that 25 (OH) vitamin D level of AD patients was inversely correlated with disease severity.

Recently, three studies demonstrated the beneficial effect of oral vitamin D supplement on the clinical manifestation of AD. Sidbury et al firstly conducted a clinical study of eleven AD patients with oral 1,000 IUs/day of vitamin D supplement. They reported 80% improvement of IGA (Investigator’s Global Assessment); however, there was no significant difference for EASI (Eczema area and severity index scale). The second study of Javanbakht et al was done to evaluate the effect of vitamin D and vitamin E supplements on the clinical outcome. The clinical result of SCORAD score with 34.80% improvement in vitamin D treated group was detected after 60 days of treatment. The third study by Amestrejani et al also demonstrated 38.30% improvement of SCORAD score with 1,600 IUs/day of oral vitamin D supplement. Moreover, the authors suggested that further studies with different doses of vitamin D would be better suited for approving this important issue. Since the dose of vitamin D used in all previous clinical studies was range from 1,000-1,600 IUs/day. Therefore, this study designed with higher doses of vitamin D (2,000 IUs/day) which was safe and lower than the tolerable upper intake level recommended by FNB.

The results of this study showed the highest...
Table 2. Comparison of this study with the others

<table>
<thead>
<tr>
<th></th>
<th>Sidbury et al[^6]</th>
<th>Javanbakht et al[^5]</th>
<th>Amestejani et al[^4]</th>
<th>This study</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>11</td>
<td>45</td>
<td>60</td>
<td>20</td>
</tr>
<tr>
<td><strong>Age (year)</strong></td>
<td>2-13 (median, 7)</td>
<td>13-45 (mean, 25.95)</td>
<td>Mean = 23.34 (SD = 2.10)</td>
<td>1-18 (mean, 8.28)</td>
</tr>
<tr>
<td><strong>Severity of disease</strong></td>
<td>Mild (EASI, range; 10 to 18.60)</td>
<td>Mild to severe (Mean SCORAD = 34.20)</td>
<td>Mild to severe (Mean SCORAD = 24.80)</td>
<td>Mild to moderate (Mean SCORAD = 19.50)</td>
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<tr>
<td><strong>Dose of vitamin (D/day)</strong></td>
<td>1,000 IU</td>
<td>1,600 IU</td>
<td>1,600 IU</td>
<td>2,000 IU</td>
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<tr>
<td><strong>Average follow-up (days)</strong></td>
<td>28</td>
<td>60</td>
<td>60</td>
<td>28</td>
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<td><strong>Clinical outcome:</strong></td>
<td></td>
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<tr>
<td><strong>Subjective assessment</strong></td>
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<tr>
<td>SCORAD</td>
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<td></td>
<td>34.8% improvement (p&lt;0.01)</td>
<td>55.8% improvement (p = 0.02)</td>
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<td>EASI</td>
<td>38.3% improvement (p = 0.01)</td>
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<td>EASI score</td>
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<td>TIS</td>
<td>45.7% improvement (p = 0.03)</td>
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<td></td>
<td>IGA</td>
<td>80% improvement (p = 0.04)</td>
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<td><strong>Objective assessment:</strong></td>
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<tr>
<td>Mexameter</td>
<td>12.2% improvement (p = 0.01)</td>
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<tr>
<td>Corneometer</td>
<td>48.2% improvement (p = 0.08)</td>
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<tr>
<td><strong>Laboratory assessment:</strong></td>
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<tr>
<td>S. aureus skin colonization</td>
<td>46% reduction (p = 0.03)</td>
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SCORAD = scoring for atopic dermatitis; EASI = eczema area and severity index scale; IGA = investigators' global assessment; TIS = three item severity score

improvement of SCORAD score (58%) compared with the other studies (Table 2). Nevertheless, this study can considerably compare only with Sidbury et al study because of the same age group of patients (pediatrics) and the same range of severity of atopic dermatitis (mild to moderate). Taken all together, the results implied that a higher dose of vitamin D usage might yield a higher clinical response. Regarding outcome assessment, not only the SCORAD score was used in our study, the objective measurements such as erythema index and skin conductance that represented the skin inflammation and moisturizing levels respectively were used. It was found that erythema index also improved significantly. However, the lichenification, dryness, sleeplessness and skin conductance score were not significant different from placebo. As a result, vitamin D had no effect on skin moisturizing property.

Regarding the role of vitamin D on the pathogenesis of AD, it was hypothesized that an oral vitamin D supplement increased cathelicidin expression on AD patient skin, which in turn could inhibit the growth of S. aureus. This study demonstrated that oral vitamin D supplement could cause statistically significant reduction of S. aureus skin colonization in AD patients and lead to the improvement of subjective and objective clinical outcomes. Finally, it also determined the inverse correlation between serum 25 (OH) vitamin D level and S. aureus colonization.

Concerning the side effects of oral vitamin D supplement, the FNB suggested that serum 25 (OH) vitamin D level above 50 ng/ml should be avoided. Since it could be associated with an increase in side effects such as cancer in some areas like the pancreas, greater risk of cardiovascular events, and more fractures in the elderly. It was found from the researches that vitamin D intakes of 5,000 IU/s/day achieved serum 25 (OH) vitamin D levels between 40-60 ng/ml. Utilizing an uncertainty factor of 20% to this intake dose gave a
4,000 IU/day, which is the lower FNB recommended dose for younger children aged 9 or older. The dose used in the previous studies was ranging from 1,000-1,600 IU/day and the maximum dose of 4,000 IU was used to determine the correlation between vitamin D supplement and cathelicidin expression. The dose of 2,000 IU/day used in the present study was safe because it was lower than the recommended dose and the serum 25 (OH) vitamin D level in this study was in the range of 22.40 to 27.60 ng/ml (mean = 26.53 ng/ml), which was much lower than the critical serum level (40-60 ng/ml).

In conclusion, the results of this study supported that oral daily vitamin D supplement of 2,000 IU might decrease in S. aureus skin colonization and provide clinical improvement especially the inflammatory parameters, but not for a moisturizing effect in mild to moderate pediatric AD patients. However, concerning the side effects of vitamin D supplement, further studies on different doses, not to exceed 2,000 IU/day in long-term follow-up and an increase in sample size should be conducted.

What is already known on this topic?

Staphylococcus aureus plays an important role in atopic dermatitis (AD) exacerbation of the eczema owing to a reduction in the cathelicidin production in the patients. Oral vitamin D supplement in the volunteers demonstrated an increase in the cathelicidin production. A few clinical studies shown that vitamin D supplement had beneficial effects on AD patients.

What this study adds?

The authors’ study demonstrated the additional evidence to support that vitamin D supplement in AD patients might improve the clinical severity and objective measurements. It also decreased the Staphylococcus aureus skin colonization. Moreover there was an inverse correlation between serum vitamin D levels with Staphylococcus aureus skin colonization and SCORAD score.

Acknowledgement

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Potential conflicts of interest

None.

References


การศึกษาผลของการให้วัคซีนตับคินือศรับประทานในผู้ป่วยเด็กกับผู้ใหญ่: ผลด้านอาการทางคลินิกและ Staphylococcus aureus colonization

ผู้ป่วย: การศึกษา Staphylococcus aureus colonization เป็นปัจจัยหนึ่งในโรคอิดีเนซีของโรค atopic dermatitis โดยพบว่ามีสาเหตุจากมีการสร้าง cathelicidin ลดลงในบริเวณผิวที่มีการเกิดกระดูกรุ้งการสร้าง cathelicidin ได้คัดลонтการให้รับประทานวัคซีนตับคินือจะช่วยให้อาการของ atopic dermatis ดีขึ้น

วัสดุและวิธีการ: เพื่อศึกษาผลของการรับประทานวัคซีนตับคืออาการทางคลินิกแล้ว S. aureus colonization ในคนไข่ atopic dermatitis.

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ผลการศึกษา: เมื่อสุ่มการศึกษาพบว่า S. aureus colonization, คะแนน SCORAD ต่ำ erythema index ลดลงอย่างมีนัยสัมพันธ์ทางสถิติไม่ต่ำกว่า 0.05 ในกลุ่มที่ให้วัคซีนตับคินือศรับประทาน (p = 0.022, 0.028 และ 0.014 ตามลำดับ) และพบจากนี้เห็นความสัมพันธ์ระหว่างระดับวัคซีนตับคินือศรับประทานและ SCORAD (r = -0.1, p<0.001)

สรุป: วัคซีนตับคินือศรับประทานสามารถลด S. aureus colonization และช่วยให้อาการทางคลินิกของผู้ป่วย atopic dermatitis ดีขึ้น.