

# Assessment of Serum 25-Hydroxyvitamin D Levels in Children with Atopic Dermatitis: Correlation With SCORAD Index

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**Background:** Atopic dermatitis (AD) is a chronic inflammatory skin disorder with an immunologic basis. It may have negative medical and social impacts on a patient and his family.

**Objectives:** To assess serum level of vitamin D among children with AD and determine its association with AD severity using the AD Scoring System Index.

**Study Design:** A case-control study.

**Patients and Methods:** Twenty-nine patients with AD in the age group between 2 and 12 years were enrolled in the study. The severity of the disease was determined by the AD scoring system. Thirty controls were recruited. Serum levels of 25-hydroxyvitamin D3 [25(OH)D3] were tested using commercial automated chemiluminescent microparticle immunoassay.

**Results:** The mean value of vitamin D in children with AD was much lower than normal value, and there was a significant difference in the mean values of vitamin D between children with AD ( $5.4 \pm 1.9$  ng/mL) and the controls ( $28.9 \pm 2.4$  ng/mL). Serum 25(OH)D levels were found to be significantly higher in mild AD ( $14.6 \pm 3.5$  ng/mL) compared with moderate ( $5.5 \pm 3.1$  ng/mL) or severe AD ( $0.3 \pm 0.1$  ng/mL);  $P < 0.001$ .

**Conclusion:** Patients with AD have lower serum vitamin D levels than normal. Vitamin D deficiency might be related to the severity of AD.

Atopic dermatitis is a chronic relapsing inflammatory pruritic skin disease characterized by a defective skin barrier and increased propensity for colonization and infection by microbial organisms. Atopic dermatitis affects mainly children, but it may occur in adults.<sup>1</sup>

It is a genotypic diathesis in which minor skin stimulation is perceived as an itch that, when scratched or rubbed, elicits a heightened immune response. The heightened immune response leads to the development of eczema, which is the clinical syndrome of eczematous dermatitis; a group of inflammatory skin conditions characterized by pruritus; pale, erythematous, and violaceous hues; vesiculation; erosion; scaling; exudation; crusting; lichenification; and excoriations.<sup>2</sup>

Altered cell-mediated immunity has been noted in patients with AD; these patients exhibit both impaired skin barrier function

and defects in skin innate immunity.<sup>3</sup> Atopic dermatitis is often associated with elevated serum IgE levels and a personal or family history of type 1 allergies, allergic rhinitis, and asthma.<sup>4</sup>

Atopic dermatitis develops from a complex interplay between environmental, genetic, immunologic, and biochemical factors. Relevant to the amplification and persistence of inflammatory and immune responses in AD skin are keratinocytes, which can be induced to secrete proinflammatory mediators in response to a variety of stimuli, including epidermal barrier perturbation.<sup>5</sup>

Vitamin D is not a true vitamin for humans. The human body procures vitamin D through 2 independent pathways: the photochemical action of solar ultraviolet B (UVB) light (approximately 295 to 320 nm) in the skin and some limited dietary sources.<sup>6</sup>

Vitamin D3 is biologically inert and needs successive hydroxylation by 25-hydroxylase in the liver, a reliable indicator of vitamin D status, and is further hydroxylated in the kidney to yield the biologically active form of vitamin D3 (calcitriol); 1, 25-dihydroxyvitamin D3 [1, 25(OH)2D3]. In vitamin D target cells, calcitriol subsequently activates the vitamin D receptor, resulting in altered expression of genes involved in calcium metabolism, proliferation, differentiation, apoptosis, and adaptive immunity.<sup>7</sup>

The vitamin D level is regulated through the interaction of various factors, including intestinal absorption, renal function, serum level of calcium, and parathyroid hormone (PTH).<sup>8</sup> Skin

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pigmentation may play an important role in determining vitamin D levels as darker skin color may limit the amount of UVB light that penetrates, thereby reducing the cutaneous synthesis of vitamin D.<sup>9</sup>

There is a growing body of evidence that vitamin D3 is an important regulator of cutaneous immunity in addition to its role in calcium homeostasis and bone metabolism.<sup>10</sup> In particular, vitamin D3 exerts pluripotent effects on adaptive immune functions such as T-cell activation and maturation of dendritic cells.<sup>11</sup> In addition, vitamin D3 has been suggested to increase innate immunity in skin and to enable efficient antimicrobial defense at epithelial surfaces.<sup>12</sup> Cells involved in innate and adaptive immune responses including macrophages, dendritic cells, T cells, and B cells express vitamin D receptor and can both produce and respond to vitamin D3. The net effect is an enhancement of innate immunity coupled with multifaceted regulation of adaptive immunity.<sup>13</sup>

In skin, the presence of vitamin D3 is essential for normal keratinocyte development and function. It regulates keratinocyte proliferation, differentiation, and the formation of an intact epidermal barrier. Alterations in local vitamin D3 concentrations and/or activation will likely affect normal cutaneous immune function, barrier function, and inflammation.<sup>14</sup> Moreover, it was found that the beneficial effect of low-dose UVB therapy in AD depends, at least in part, on activation of the cutaneous vitamin D system.<sup>15</sup>

Vitamin D3 stimulates the production of antimicrobial peptides (AMPs) by skin, which is a primary system for protection against infection. Cathelicidins were among the first families of AMPs discovered on the skin. They are now known to have 2 distinct functions: they have direct antimicrobial activity and will initiate a host cellular response resulting in cytokine release, inflammation, and angiogenesis. Dysfunction of cathelicidin is relevant in the pathogenesis of several cutaneous diseases including AD, where cathelicidin induction is suppressed; vitamin D3 was identified as a major factor involved in the regulation of cathelicidin expression.<sup>16</sup>

Another potential role for vitamin D3 is that it enables keratinocytes to recognize and respond to microbes through action on the Toll-like receptor 2 and leads to up-regulation of cathelicidin. Vitamin D deficiency might therefore be important in the predisposition of skin of patients with AD to superinfection by *Staphylococcus aureus*.<sup>17</sup>

Serum 25(OH)D levels are collectively constituted by 25(OH)D2 from nutritional sources and by 25(OH)D3 from both cutaneous

**TABLE 2. Sociodemographic Distribution of the Studied Samples (Cases Versus Controls)**

|              | Cases (n=29) | Controls (n=30) | P      |
|--------------|--------------|-----------------|--------|
| Age, mean±SD | 6.1±2.7      | 6.5±2.9         | >0.05* |
| Sex, n (%)   |              |                 |        |
| Boys         | 14 (48.3)    | 16 (53.3)       | >0.05† |
| Girls        | 15 (51.7)    | 14 (46.7)       |        |

Significance level is considered when  $P < 0.05$ .

\*Student *t* test was used to compare the mean difference between the 2 groups.

† $\chi^2$  analysis was used to compare the difference in proportions.

sources and nutritional sources. 1,25(OH)D2 levels, unlike 25(OH)D levels, are well maintained until the extremes of vitamin D deficiency because of secondary hyperparathyroidism and so do not provide a useful index for assessing vitamin D deficiency at least at the initial stages.<sup>18</sup>

In children, severe vitamin D deficiency (25[OH]D <10 ng/mL) manifests as rickets, and vitamin D inadequacy (25[OH]D, 10–29 ng/mL) can impair or retard attainment of peak bone mass.<sup>19</sup>

Although there is currently no consensus for optimal levels, most experts define vitamin D deficiency as levels of 25(OH)D less than 20 ng/mL; optimal levels greater than 30 ng/mL and that levels ranged from 20 to 30 ng/mL was defined as vitamin D insufficiency.<sup>20</sup>

## The Aim of This Study

Assess the serum level of vitamin D among children with AD and determine its association with AD clinical severity using AD scoring system (SCORAD) index.

## MATERIALS AND METHODS

The study design was cross-sectional case-control study. Twenty-nine patients (15 girls and 14 boys) with AD enrolled in the study

**TABLE 1. Classification of the Severity of AD for the SCORAD Index, the (Objective) SCORAD, and TIS**

|                    | Classification of Severity of AD |          |          |
|--------------------|----------------------------------|----------|----------|
|                    | Mild                             | Moderate | Severe   |
| SCORAD index       | 0–24                             | 25–50    | 51–103   |
| (Objective) SCORAD | 0–14                             | 15–40    | 41–83/93 |
| TIS                | 0–2                              | 3–5      | 6–9      |

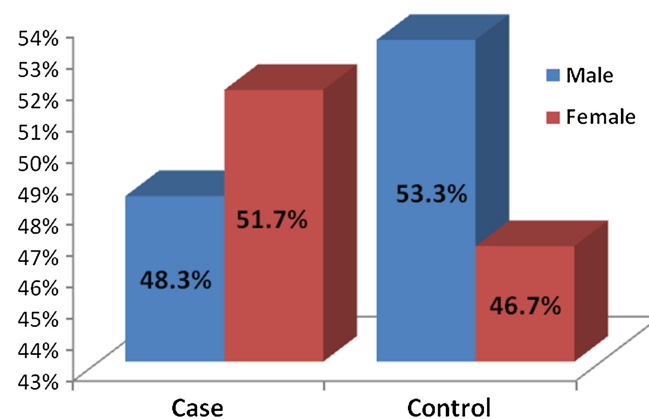


**Figure 1.** Sex distribution of cases versus controls.

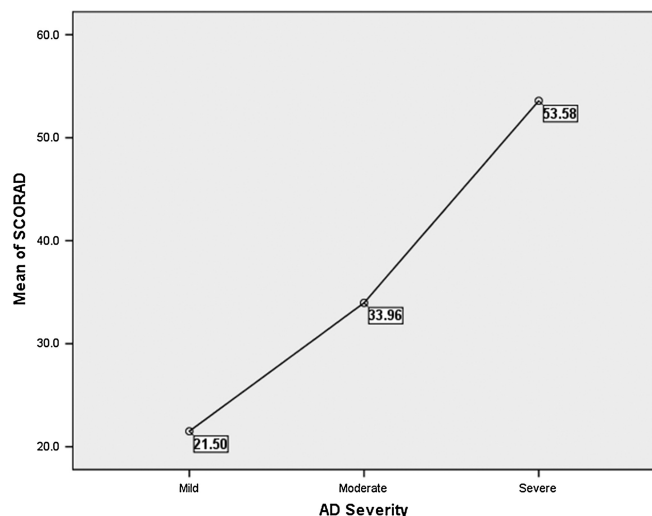


**Figure 2.** Mean SCORAD index for AD severity categories.

with ages from 2 to 12 years. Patients recruited from patients with AD presented to the outpatient's clinic at the department of dermatology, venereology and andrology, Qena University Hospital, South Valley University, Egypt, in the period between September 2012 to February 2013. All patients were graded as Fitzpatrick skin type III. Thirty healthy controls with age- and sex-matched groups with exclusion of allergic diseases. Written consents were taken from all patients and controls.

## Diagnosis of AD

Diagnosis of patients with AD was based on the criteria of Hanifin and Rajka.<sup>21</sup> The SCORAD index consists of the interpretation of the extent of the disorder, that is, the intensity, composed of 6 items (erythema, edema, papules, effect of scratching, oozing, crust formation, lichenification, and dryness), and 2 subjective symptoms (itch and sleeplessness); the maximum score is 103 points. The Three-Item Severity score (TIS) is the sum of the 3 items: erythema, edema, and excoriations (scored on a scale from 0 to 3); each item should be scored on the most representative lesion, that is, a lesion that represents the mean intensity for that item. The TIS items are identical to their SCORAD counterparts (Table 1).<sup>22</sup>

Cases were assessed clinically and categorized according to the clinical severity score of AD using the SCORAD index<sup>22</sup> as follows:

**TABLE 3.** SCORAD Index Among AD Cases

| AD       | SCORAD Index |          | P*     |
|----------|--------------|----------|--------|
|          | n (%)        | Mean±SD  |        |
| Mild     | 3 (10.3)     | 21.5±1.3 | <0.001 |
| Moderate | 20 (69)      | 33.9±5.1 |        |
| Severe   | 6 (20.7)     | 53.6±1.4 |        |

\*One-way analysis of variance test was used to compare the mean difference between groups.

**TABLE 4.** Percentage of Subjects in Each Category of Vitamin D

| 25(OH)D (ng/mL)          | Girls      | Boys       |
|--------------------------|------------|------------|
| <3 Below detection limit | 8 (72.7%)  | 3 (27.3%)  |
| <10                      | 13 (54.2%) | 11 (45.8%) |
| 10–20                    | 2 (40%)    | 3 (60%)    |
| 20–30                    | 10 (55.6%) | 8 (44.4%)  |
| >30                      | 4 (33.3%)  | 8 (66.7%)  |

3 patients with mild AD (<25), 20 patients with moderate AD (25–50), 6 patients with severe AD (>50) (Table 3).

Patients with the following criteria were excluded from the study: patients with other chronic, systemic diseases other than asthma or environmental allergies, hyperimmunoglobulin E or Job syndrome, ichthyosis disorder other than ichthyosis vulgaris, prior systemic therapy or phototherapy for AD, ongoing or prior treatment for known vitamin D deficiency, history of delayed teething, delayed growth, bone pain or unexplained bone fractures, history of rickets, history of hyperparathyroidism, history of renal impairment and patients on long-term systemic corticosteroids for asthma.

## Assessment of 25-Hydroxyvitamin D [25(OH)D]

Two milliliters of blood was withdrawn from patients and controls, allowed to clot, and then centrifuged at 3000 rpm for 15 minutes and serum separated for quantitative determination of 25-hydroxyvitamin D [25(OH)D] using commercial automated chemiluminescent microparticle immunoassay (Architect, Abbott Diagnostics, New Cairo, Egypt).

It is a delayed one-step immunoassay including a sample pretreatment using 6-point calibration. In the first step, the sample is pretreated to dissociate the vitamin from its binding sites. An aliquot of the pretreated sample then reacts with paramagnetic antihuman 25(OH)D IgG (sheep, polyclonal) coated microparticles. After incubation, a biotinylated 25(OH)D IgG (mouse, monoclonal) antibiotin-acridinium-labeled conjugate complex is added to the reaction mixture and binds to unoccupied binding sites of the antivitamin D-coated microparticles. After washing, pretrigger and trigger solutions are added to the reaction mixture to produce a chemiluminescent reaction and relative light units are measured. An indirect relationship exists between the amount of 25(OH)D in the sample and the relative light units detected.

**TABLE 5.** Vitamin D (Sufficient vs Insufficient) Status by Sex

|       | Vitamin D Level |            |
|-------|-----------------|------------|
|       | Insufficient    | Sufficient |
| Boys  | 22 (73.3%)      | 8 (26.7%)  |
| Girls | 25 (86.2%)      | 4 (13.8%)  |
| Total | 47 (79.7%)      | 12 (20.3%) |

**TABLE 6. Vitamin D Status by AD Disease Status**

| AD       | Vitamin D |         | <i>P</i> * |
|----------|-----------|---------|------------|
|          | <10       | 10–20   |            |
| Mild     | 0 (0%)    | 3 (60%) | <0.001     |
| Moderate | 18 (75%)  | 2 (40%) |            |
| Severe   | 6 (25%)   | 0 (0%)  |            |

Significance level is considered when  $P < 0.05$ .\* $\chi^2$  analysis was used to compare the difference in proportions.

The reference ranges used in our laboratory for 25(OH)D were as follows: sufficient ( $>30$  ng/mL), insufficient (20 to  $<30$  ng/mL), mild deficiency (10–20 ng/mL), and severe deficiency ( $<10$  ng/mL).

### Statistical Analysis

Statistical Package for the Social Sciences version 19.0 for Windows (SPSS Inc, Chicago, IL) software package was used to analyze the data of various parameters. Normally distributed quantitative variables (parametric data) expressed as mean, SD, and range.  $\chi^2$  was used to compare qualitative variables between the groups, the Spearman rank correlation test ( $r$ ) was used to assess the strength of the correlations between the SCORAD index and disease duration with the vitamin D values, analysis of variance test for comparison of serum vitamin D3 levels among groups presenting different AD severity assessed by SCORAD index.  $P < 0.05$  was considered significant.

## RESULTS

In the current study, 48.3% of the patients with AD and 53.3% of the controls were boys. The mean  $\pm$  SD age in years for AD was ( $6.1 \pm 2.7$ ) versus ( $6.5 \pm 2.9$ ) for the controls. Age and sex distribution for the patients and the controls are summarized in Table 2 and Figure 1.

Using SCORAD index, 6 children (20.7%) with AD were classified as having severe AD with a SCORAD value of ( $53.6 \pm 1.4$ ), 20 children (69%) were classified to have a moderate disease with a SCORAD value of ( $33.9 \pm 5.1$ ), and 3 children (10.3%) had mild AD with a SCORAD value of ( $21.5 \pm 1.3$ ) (Table 3, Fig. 2).

Serum concentrations of 25(OH)D were found to be sufficient, insufficient, and deficient, respectively, in 12 (20.3%), 18 (30.5%), and 29 (49.2%) in all study subjects; age and sex distribution of serum concentrations of 25(OH)D are summarized in Tables 4 and 5.

**TABLE 7. Vitamin D Status by AD SCORAD Severity Index**

|       | 25(OH)D<br>(ng/mL) | Classification of Severity of AD |            |           | <i>P</i> * |
|-------|--------------------|----------------------------------|------------|-----------|------------|
|       |                    | Mild                             | Moderate   | Severe    |            |
| Boys  | $18.8 \pm 12.1$    | 1 (7.1%)                         | 12 (85.8%) | 1 (7.1%)  | <0.001     |
| Girls | $15.9 \pm 12.9$    | 2 (13.3%)                        | 8 (53.4%)  | 5 (33.3%) |            |
| Total | $17.4 \pm 12.5$    | 3 (10.3%)                        | 20 (69%)   | 6 (20.7%) | <0.001     |

\* $\chi^2$  analysis was used to compare the difference in proportions.**TABLE 8. Mean Serum 25(OH)D Levels Among AD Cases**

| Serum 25(OH)D levels |          |        |
|----------------------|----------|--------|
| AD                   | Mean±SD  | P*     |
| Mild                 | 14.6±3.5 | <0.001 |
| Moderate             | 5.5±3.1  |        |
| Severe               | 0.3±0.14 |        |

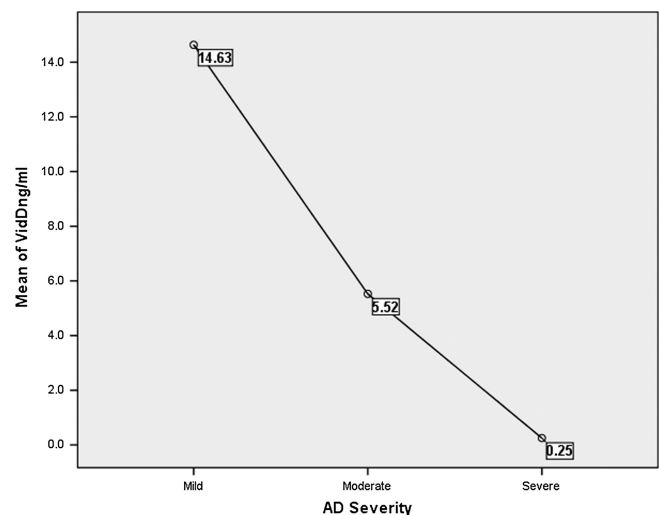
\*One-way analysis of variance test was used to compare the mean difference between the groups.

The mean value of serum vitamin D in AD was much lower than the normal value, and there was a significant difference found in the mean values of vitamin D between AD ( $5.4 \pm 1.9$ ) and the controls ( $28.9 \pm 2.4$ ),  $t(57) = 23.3$ ;  $P < 0.001$ . The difference in proportions of mean serum 25(OH)D levels in the patients and the controls are shown in Tables 6 and 7.

Mean serum 25(OH)D levels were found to be significantly higher in the patients with mild AD ( $14.6 \pm 3.5$  ng/mL) compared with those with moderate ( $5.5 \pm 3.1$  ng/mL) or severe AD ( $0.3 \pm 0.1$  ng/mL),  $f(26) = 19.6$ ;  $P < 0.001$  (Table 8). There was a highly significant inverse correlation between the severity of AD and serum 25(OH)D levels ( $P < 0.001$ ) (Figs. 3, 4). The individual SCORAD values showed also a significant inverse correlation with serum 25(OH)D levels ( $r = -0.88$ ,  $P < 0.001$ ) (Fig. 5).

## DISCUSSION

Vitamin D has an important role in both innate and acquired immune response.<sup>11</sup> It also has a role in the cutaneous immune response, keratinocyte development, and functions and integrity of skin barrier.<sup>14</sup> Vitamin D deficiency has been implicated in several allergic disorders and immune system dysregulation.<sup>23</sup>

**Figure 3.** Mean serum vitamin D levels for AD severity categories.

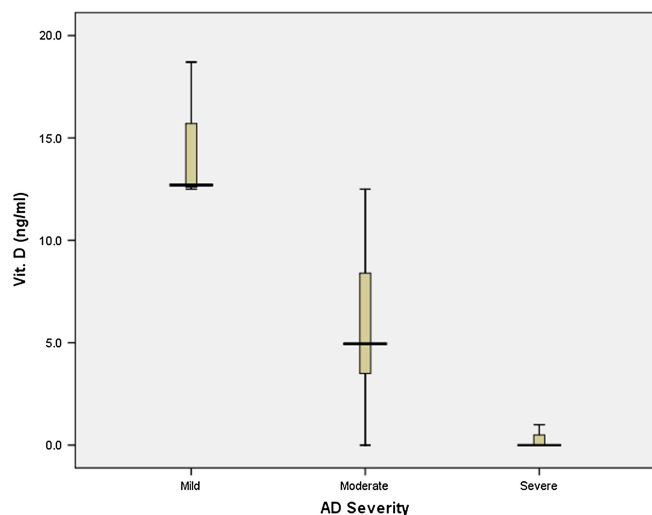


**Figure 4.** Correlation between serum vitamin D levels and the AD severity categories.

In our study, we found that the mean serum levels of 25(OH)D in children with AD were much lower than those of the controls. We found a high significant negative correlation between serum levels of 25(OH)D and AD disease severity as evaluated by the SCORAD index; higher levels of 25(OH)D were detected in the patients with mild disease than in those with moderate and severe disease, respectively. These results agree with the previous studies that correlated vitamin D levels with AD. Peroni et al<sup>24</sup> found a negative correlation between serum levels of 25(OH)D and severity of AD in children. Akan et al<sup>25</sup> found that vitamin D was not correlated with total IgE and eosinophil percentage in patients with AD, but they found that vitamin D level negatively correlates with and may affect the severity of AD, especially in children with allergic sensitization.

In contrast to our findings, Chiu et al<sup>26</sup> found that vitamin D was not correlated with the severity of AD but with black race, age younger than 3 years, and winter season. Hata et al<sup>27</sup> found that vitamin D was not correlated with the severity of AD but negatively correlated with Fitzpatrick skin type (ie, darker skin types) and elevated body mass index. Samochocki et al<sup>28</sup> found that frequency of bacterial skin infections was higher in patients with AD who had lower 25(OH)D3 levels.

Vitamin D deficiencies have been listed as risk factors in development of allergic and immunological disorders.<sup>23</sup> Food intake during pregnancy and vitamin deficiency have been stated to have a role in development AD and other allergic disorders.<sup>29–32</sup>

Several clinical studies show that skin inflammation in AD can be ameliorated by UVB irradiation.<sup>33</sup> So far, the positive effect of this therapy was attributed to the effect of UVB on T cells. However, the beneficial effects could also be a result of the UVB-induced activation of AMPs and/or the UVB-induced vitamin D3 synthesis and subsequent cathelicidin expression in the skin.<sup>33–36</sup>

In addition, Mallbris et al<sup>36</sup> showed that the vitamin D3-activated pathways leading to induced cathelicidin in keratinocytes in atopic

skin are functional. In addition, Hata et al<sup>37</sup> showed increased cathelicidin in skin biopsies in patients experiencing atopic eczema after a course of oral vitamin D supplementation. Thus, increasing vitamin D3 synthesis and elevating vitamin D3 levels in the serum could help to strengthen the innate defense barriers to prevent cutaneous infections that trigger skin inflammation in AD.

Results were obtained by evaluating children of different ages with a wide range of disease severity from mild to severe AD. Our data, showing a correlation between vitamin D deficiency and severity of AD in children, seem to support previous epidemiological observations suggesting a possible inverse association between vitamin D nutritional intake and exposure to the sun and AD disease prevalence. Further studies considering more patients and evaluating other confounding variables, such as race, age, atopy, sex, and family atopic diseases, are required.

## CONCLUSION

Our data suggest that vitamin D deficiency may be related to the development and severity of AD and advocate the need for studies evaluating the use of vitamin D, either by nutritional supplementation or by sun exposure, as a potential treatment in patients with this disease. Further studies on larger numbers of patients and evaluating other variables, for example, age, sex, and other atopic diseases, are required. Finally, longitudinal studies on oral vitamin D supplementation in large cohorts of patients are necessary to establish the optimal doses and actions to be taken as potential treatment.

## Study Limitations

The current study encountered the following limitations: the small number of participants and absence of a regression model (ie, we could not adjust for type of skin, time of year, or sex). We did not evaluate other confounding variables such as sex. We also did not include TIS in our SCORAD evaluation.

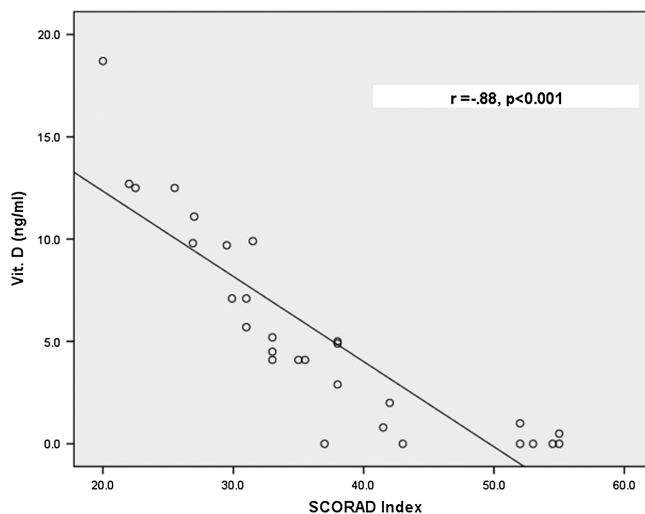


**Figure 5.** Correlation between serum vitamin D levels and the individual SCORAD values.

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