Vitamin D Deficiency Rickets in an Adolescent With Severe Atopic Dermatitis

Atopic dermatitis (AD) affects 10% to 20% of children worldwide. Its severity may be inversely correlated with 25-hydroxyvitamin D (25OHD) levels. Although low levels of vitamin D (VD) can cause rickets in infants, VD deficiency rickets is an unusual presentation in teenagers. We report the case of a 14-year-old girl with severe AD and fish allergy since early childhood. She lived at high latitude (with less sun exposure) and, because of her atopic disorders, avoided sunlight and fish. Laboratory studies showed elevated alkaline phosphatase and parathyroid hormone levels and low serum calcium; her serum 25OHD level was 12 nmol/L. A radiograph of the wrist showed a radiolucent band in the distal metaphysis of the radius with marginal sclerosis. She was diagnosed as having hypocalcemic rickets due to VD deficiency. Treatment with VD increased her 25OHD level to 44 nmol/L, with normalization of alkaline phosphatase, parathyroid hormone, and calcium. Moreover, we observed a dramatic improvement in her AD severity with VD treatment. This case demonstrates the complex interaction between VD deficiency, AD, and food allergy. We advise a high index of suspicion of VD deficiency rickets in children of all ages with AD, particularly during accelerated growth periods and in the presence of other risk factors such as darker skin, living at high latitude, sun avoidance, and low intake of VD-rich foods. The concomitant improvement in bone-related parameters and AD severity may reflect a double benefit of VD treatment, a possibility that warrants research on VD as potential treatment for AD.

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KEY WORDS
atopic dermatitis, rickets, latitude, vitamin D, food allergy

ABBREVIATIONS
25OHD—25-hydroxyvitamin D
AD—atopic dermatitis
SCORAD—severity scoring of atopic dermatitis
VD—vitamin D
VD3—cholecalciferol

Dr Borzutzky is the immunologist in charge of the patient’s care and drafted the initial manuscript; Dr Grob is the pediatric endocrinology fellow in charge of the patient’s care, wrote the case report, and reviewed and revised the manuscript; Dr Camargo assisted with the patient’s treatment assessment, drafted the case discussion with Dr Borzutzky, and critically reviewed the manuscript; Dr Martinez-Aguayo is the pediatric endocrinologist in charge of the patient’s care, collaborated in writing the manuscript draft, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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Atopic dermatitis (AD) is a chronic and relapsing inflammatory skin condition characterized by dry, itchy skin and immunologic hyperresponsiveness to allergens. AD affects 10% to 20% of children worldwide, constituting a serious public health concern, with increasing prevalence in industrialized countries. Severe AD adversely affects quality of life and may lead to significant morbidity due to skin infections and atopic comorbidity. However, other serious but less recognized AD complications may occur, including abnormalities in bone metabolism.

AD severity appears to be inversely correlated with serum 25-hydroxyvitamin D (25OHD) levels. The most severe form of vitamin D (VD) deficiency leads to rickets, a disorder of bone metabolism that causes failure of mineralization of the growth plate and osteoid matrix. This condition is most common in infancy but can also present during the adolescent growth spurt. The etiology of rickets is usually related to very low 25OHD levels, associated with low UV-B exposure, and to a lesser extent to low intake of VD or calcium. Rickets has been reported rarely in infants and toddlers with AD, but not in adolescents, in whom suspicion of rickets is generally low. We report on the case of an adolescent girl with severe AD and food allergies who was found to have hypocalcemic rickets due to VD deficiency. Treatment with cholecalciferol (VD3) normalized her bone-related parameters and was associated with a dramatic improvement in the severity of her AD.

**PATIENT PRESENTATION**

The patient was a 14-year-old Chilean girl with a history of severe AD since early childhood. She had no family history of AD, primary immunodeficiency, or bone metabolism abnormalities. Eczema involved most of her skin, causing intense pruritus and sleep disturbance, with poor response to several topical corticosteroids. She had a history of frequent staphylococcal skin infections (eg, every 1–2 months) but no skin abscesses or fungal infections. She also had recurrent ocular and nasal herpes, necessitating antiviral suppression with acyclovir. In addition, she had asthma and multiple food allergies (ie, egg, fish, and shellfish). She presented with high serum immunoglobulin E (9827 IU/mL) and eosinophilia (1524 cells/mm³) but normal immunoglobulins and lymphocyte counts.

The family lived in southern Chile at latitude 41° south. Because of her severe AD, she had avoided sun exposure since early childhood. She did not eat fish, a VD-rich food, because of her known fish allergy. She experienced menarche at age 14 years, and her cycles were regular. The patient did not have bone pain or fractures but presented with proximal muscular weakness and difficulty walking.

On physical examination she had generalized eczematous skin with erythema, papules, lichenification, and xerosis, with greater involvement of the face, back, and forearms. She had oozing and crusting lesions on the face and scalp. Her Fitzpatrick skin phototype was type IV. Her height was 151 cm (z score −1.55 SD) and BMI 16.9 (z score −1.43 SD). Her dental enamel was normal, and she had no metaphyseal widening, rachitic rosary, or genu valgus. Her disease severity was assessed at each visit by the same physician by means of the Severity Scoring of AD (SCORAD) index (range, 0–103). At presentation, her SCORAD score was 92. She initially was started on immunosuppressive treatment with methotrexate (15 mg/m²) in addition to emollient creams and mild to moderate potency topical corticosteroids, with a gradual decrease in SCORAD score to 65 at 1-year follow-up.

Routine laboratory studies at a follow-up visit revealed elevated alkaline phosphatase level of 932 U/L (normal range 50–162 U/L); alkaline phosphatase isoenzymes showed that 87% were from bone, with other fractions within normal range. Serum 25OHD level was <12 nmol/L (normal range 50–125 nmol/L; chemiluminescence assay, DiaSorin, Saluggia, Italy). Additional laboratory investigations are shown in Table 1. Radiograph of the wrist showed a radiolucent band in the distal metaphysis of the radius with marginal sclerosis, suggestive of bone mineralization abnormalities.

At this point, she was diagnosed as having hypocalcemic rickets due to VD deficiency. She received intensive dietary counseling, improving the nutritional balance of her diet. Calcium supplements (20 mg/kg per day elemental calcium) and VD3 were prescribed. She received 1 VD3 dose of 150 000 IU, followed by 10 000 IU per week for 6 months. She was given advice about sunlight exposure at suberythematous doses. Six months later, we reassessed her VD status and biochemical markers of rickets. Although

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**TABLE 1** Laboratory Studies Performed in the Patient Before and After VD3 Supplementation

<table>
<thead>
<tr>
<th>Reference Range</th>
<th>At Diagnosis</th>
<th>After 6 mo of VD3 Supplementation</th>
</tr>
</thead>
<tbody>
<tr>
<td>25OHD, nmol/L</td>
<td>&lt;12</td>
<td>44</td>
</tr>
<tr>
<td>Alkaline phosphatase, U/L</td>
<td>932</td>
<td>275</td>
</tr>
<tr>
<td>Parathyroid hormone, pg/mL</td>
<td>50–162</td>
<td>654</td>
</tr>
<tr>
<td>Calcium, mmol/L</td>
<td>2.13–2.6</td>
<td>2.0</td>
</tr>
<tr>
<td>Phosphorus, mmol/L</td>
<td>0.9–1.52</td>
<td>0.97</td>
</tr>
<tr>
<td>Urinary calcium/urinary creatinine, mg/mg</td>
<td>&lt;0.21</td>
<td>0.07</td>
</tr>
<tr>
<td>Antiendomysial antibodies</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Eosinophil count, cells/mm³</td>
<td>&lt;500</td>
<td>1524</td>
</tr>
</tbody>
</table>
her 25OHD remained low, the VD$_3$ supplements increased her level to 44 nmol/L. Her serum calcium normalized, and alkaline phosphatase levels dropped to 275 U/L. Moreover, she presented with dramatic improvement in AD extent and intensity, minimal pruritus, and no sleep disturbance, with a decrease in SCORAD score to 18 (Fig 1) and a decrease in eosinophil count to 872 cells/mm$^3$. The patient had a 5-kg weight gain and increased muscle strength, and she reported feeling significantly better. Although ocular herpes recurred after transient discontinuation of her acyclovir suppressive therapy, she had no new staphylococcal skin infections over the 6-month period.

**DISCUSSION**

VD deficiency or insufficiency affects 1 billion people worldwide.$^{10}$ Extremely low levels of 25OHD (<12 nmol/L) are associated with development of rickets or osteomalacia, but insufficient levels (<75 nmol/L) are linked to a wide variety of nonskeletal diseases including infections and allergies.$^{11}$ Adequate sunlight exposure is the most cost-effective means of obtaining VD, because most VD in humans is synthesized from precursors in the skin to VD$_3$. Some foods such as oily fish also contain VD$_3$. VD$_3$ is metabolized in the liver and kidney to produce 1,25-dihydroxyvitamin D (calcitriol), the active hormone, which acts as regulator of mineral homeostasis and exerts multiple biological actions because most tissues have calcitriol receptors.$^{10}$ Synthesis of VD is lower in children with greater skin pigmentation, in whom melanin functions as a natural sunscreen; in children who stay primarily indoors; in those who live at high latitudes; and in those who use artificial sunscreens.$^{12}$ Other factors can affect 25OHD levels, such as obesity and gastrointestinal malabsorption.

Rickets due to VD deficiency typically presents in infants and toddlers, when growth rate is high. In adolescence, a period of accelerated skeletal growth, rickets requires a high index of suspicion because obvious clinical signs are very uncommon at this age and appear slowly and progressively.$^{6}$ Symptoms such as tiredness, muscle weakness, and fatigue are nonspecific, and the differential diagnosis includes a variety of endocrine and rheumatologic diseases. Our patient had several risk factors that led to the development of VD deficiency and, secondarily, to rickets. First, because of her severe AD she usually covered her skin with clothing and emollient creams, and she had dark skin. Moreover, she lived at high latitudes with low solar radiation$^{13}$ and had fish allergy, severely limiting her oral intake of this VD-rich food. The severe VD deficiency together with increased bone mineralization needs due to her growth spurt combined to generate rickets. This scenario has been reported in young children with AD who also had food allergy–related nutritional restrictions but not during adolescence.$^{14,15}$ An association between VD deficiency and allergic diseases has been suggested.$^{16,17}$ Epidemiologic data have shown a higher prevalence of allergic diseases, including AD, food allergy, and anaphylaxis, at higher latitudes, used as a proxy of sun exposure.$^{11,18,19}$ Lower 25OHD levels also appear to correlate with AD severity, which suggests a potential role of VD in the pathogenesis of AD.$^5$ A prospective birth cohort study supported this association by showing that infants born with cord blood 25OHD levels of <50 nmol/L had a higher risk of AD at 12 months of age.$^{20}$

VD has widespread effects on the immune system and skin integrity. VD has been shown to induce tolerogenic dendritic cells and regulatory T cells and is able to suppress T-cell–mediated immunity.$^{21}$ VD also modulates innate immunity, particularly boosting immunity to *Staphylococcus aureus*, the major skin pathogen of patients with AD.$^2^2$ In addition, VD is relevant for epidermal differentiation and skin barrier permeability, essential factors that are altered in patients with AD.$^2^3$

Current treatments of AD are focused on decreasing skin inflammation and improving barrier function, but no safe and effective oral treatment has been demonstrated. VD is a low-cost intervention that is safe and easy to administer in any setting and at any age. However, there is conflicting evidence about the effect of VD supplementation on AD severity. A recent systematic review did not find a significant difference.

![FIGURE 1](http://pediatrics.aappublications.org/)

*The patient’s SCORAD index after different treatments for her severe AD.*
in AD severity after VD supplementation compared with placebo. Nonetheless, a pilot study showed an important difference in change of AD scores after treatment and a subsequent study revealed a significant difference in SCORAD reduction in comparison with baseline in the VD group. A larger trial also showed a significant reduction in SCORAD after VD supplementation but not after placebo. Our patient experienced a dramatic improvement of her AD after treatment with VD. Improvement may be larger when VD deficiency is severe, as observed in our patient. Additional studies to evaluate the effect of VD supplementation on the clinical severity and immunity of AD patients are ongoing.

CONCLUSIONS
This case demonstrates the complex interaction between VD deficiency, AD, and food allergy. With this case report, we stress that a high index of suspicion of VD deficiency rickets is needed in children of all ages with AD, particularly during periods of accelerated growth and in the presence of other risk factors such as darker skin, living at high latitude, sun avoidance, and low intake of VD-rich foods. In addition, our report suggests that VD supplementation in affected patients may improve AD severity. Our patient’s concomitant improvement in bone-related parameters of rickets and AD severity score may reflect a double benefit of VD treatment, a possibility that warrants additional research on VD as potential treatment of AD.

REFERENCES
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