Vitamin D: A New Promising Therapy for Congenital Ichthyosis

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Dr Sethuraman conceptualized and designed the study, supervised and coordinated the data collection, drafted the initial manuscript, and critically revised the manuscript; Dr Marwaha conceptualized and designed the study, drafted the initial manuscript, and critically revised the manuscript; Ms Challa carried out the biochemical assays; Dr Ramakrishnan supervised the biochemical assays and critically revised the manuscript; Dr Yenamandra supervised patient recruitment and critically revised the manuscript; Dr Sharma provided technical support; Dr Thulkar carried out the radiological evaluation; and all authors approved the final manuscript as submitted.

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Severe vitamin D deficiency and rickets are highly prevalent among children with congenital ichthyosis. We report an incidental observation of a dramatic and excellent clinical response with regard to skin scaling and stiffness in children with congenital ichthyosis after short-term high-dose vitamin D supplementation that has not been previously described. Seven children with congenital ichthyosis (5 with autosomal recessive congenital ichthyosis; 2 with epidermolytic ichthyosis) and severe vitamin D deficiency (and/or rickets) were given 60,000 IU of oral cholecalciferol daily for 10 days under supervision. All children were subsequently put on recommended daily allowance of 400 to 600 IU of cholecalciferol. The main outcome measures observed and studied were reduction in skin scaling and stiffness of the extremities. All cases had severe vitamin D deficiency (serum 25-hydroxyvitamin D < 4 ng/mL) and secondary hyperparathyroidism. Six patients had clinical and radiologic evidence of rickets. Significant improvement in scaling was noticeable by day 5, showing further improvement by day 10, in 6 of the 7 cases. At 1 month, the skin had become near normal in all the cases of autosomal recessive congenital ichthyosis. Remarkable reduction in stiffness was also observed in all children. Supplementation with high-dose vitamin D followed by recommended daily allowance appears to be an effective form of therapy in the management of congenital ichthyosis with vitamin D deficiency.

REPORT

Congenital ichthyoses are a group of Mendelian disorders of cornification that result in abnormal differentiation and desquamation of the epidermis. We earlier reported a high prevalence of vitamin D deficiency and rickets in children with congenital ichthyosis.1,2 Ichthyosis children with serum levels of 25-hydroxyvitamin D (25(OH)D) ≤ 8 ng/mL and parathyroid hormone (PTH) ≥ 75 pg/mL had significantly higher risk of developing rickets.3 The earlier practice of treating such cases in our department was to supplement with 60,000 IU of oral cholecalciferol weekly for 6 weeks followed by 60,000 IU once a month. The compliance to this treatment protocol was poor because of the inability of these cases to come for regular follow-up due to poor socioeconomic status and residing a long distance from the clinic. Hence, we decided to treat congenital ichthyosis and vitamin D deficiency, with oral cholecalciferol 60,000 IU daily for 5 days (stoss therapy).4 Incidentally, we noticed an excellent clinical response with regard to softening of skin and reduction in scaling by day 5, and therefore we continued with the same dose for another 5 days to observe whether there was further improvement in the skin.

In this initial observational case series, we describe our experience of short-term high-dose vitamin

abstract

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REPORT

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In this initial observational case series, we describe our experience of short-term high-dose vitamin
D supplementation in children of congenital ichthyosis with vitamin D deficiency and/or rickets.

METHODS

Seven consecutive cases of congenital ichthyosis with severe vitamin D deficiency (autosomal recessive congenital ichthyosis [ARCI] = 5; Epidermolytic ichthyosis [EI] = 2), aged 9 months to 8 years, were recruited in the outpatient dermatology clinic and admitted for treatment with oral cholecalciferol 60 000 IU daily for 10 days under supervision, with the exception of an infant who was given this dose for 5 days only. All children were subsequently put on recommended daily allowance (RDA) of 400 to 600 IU of cholecalciferol. In addition, 40 mg/kg/day of elemental calcium was given in all the cases. Serum biochemistry and urinary calcium-creatinine ratio were evaluated at baseline, 10 days, 1 month, and 3 months. Serum 25(OH)D and PTH were measured by chemiluminescence assay (Diasorin, Stillwater, MN). Calcium, phosphate, and alkaline phosphatase were estimated by auto-analyzer.

RESULTS

All children had severe vitamin D deficiency (serum 25(OH)D < 4 ng/mL) and secondary hyperparathyroidism. Six patients had clinical and radiologic evidence of rickets (mean rickets radiologic scores 4.2, range 1–10). Significant improvement in scaling was noticeable by day 5, showing further improvement by day 10, in all the cases except 1 (Figs 1, 2, 3, and 4) (Supplemental Figure 5). Remarkable reduction in stiffness was also observed in all children. At 1 month, the skin had become near normal. The overall response was significantly better on the face and trunk than the extremities. The child who was given only 5 days of oral vitamin D also showed an excellent response with normalization of ectropion by day 5 (Fig 3 A3).

Two of the children with ARCI, who had completed 6 months of follow-up with daily allowance of vitamin D, maintained the same status in
skin condition. However, in 1 of these cases, the caregiver stopped the RDA for 4 weeks, resulting in reappearance of scaling on the trunk, which subsequently started clearing within 2 weeks of restarting the RDA of vitamin D.

In 1 case of EI, the response was not satisfactory despite adequate levels of serum 25 (OH) D. Serum 25(OH) D > 150 ng/mL was observed in 2 cases on day 10, and hence the RDA was not given until day 30, after which serum 25(OH)D levels normalized. No clinically evident adverse side effects were seen except for hypercalcemia in 1 case, which normalized during follow-up.

Serum 25 (OH) D, PTH, calcium, phosphate, and alkaline phosphatase levels at different points of time during follow-up are shown in Tables 1 and 2.

**DISCUSSION**

Our report clearly shows that correction of severe vitamin D deficiency with short-term high-dose cholecalciferol (vitamin D₃) in children with congenital ichthyosis (ARCI and EI) results in significant reduction in skin scaling. Keratinocytes possess the entire vitamin D metabolic pathway, including the 25(OH) D-1α-hydroxylase resulting in production of 1,25 dihydroxy vitamin D₃, which is responsible for the autocrine or paracrine functions. It may be hypothesized that correcting vitamin D deficiency with high-dose vitamin D₃ might have resulted in an increased keratinocyte production of 1,25(OH)₂D₃, which has antiproliferative and prodifferentiating actions leading to normalization of keratinization and clearance in skin scaling.6,7 This hypothesis has been supported by the in vitro observation by Lu et al,8 who have shown that 1,25 dihydroxy vitamin D₃ regulates the expression of a number of genes that are involved in the terminal differentiation and desquamation of keratinocytes. These are collectively called as vitamin D–responsive genes, which include involucrin (that is involved in cornified envelope formation), peptidylarginine deiminase (a family

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**TABLE 1** Biochemical Profile of Ichthyosis Children: 25(OH)D and PTH

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Radiologic Rickets Scoresa</th>
<th>Day 0</th>
<th>Day 10</th>
<th>Day 30</th>
<th>Day 3 mo</th>
<th>Day 0</th>
<th>Day 10</th>
<th>Day 30</th>
<th>Day 3 mo</th>
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<tr>
<td>1</td>
<td>3</td>
<td>M</td>
<td>ARCI</td>
<td>4</td>
<td>&lt;4.0</td>
<td>47</td>
<td>31.8</td>
<td>23.8</td>
<td>26.1</td>
<td>20.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>F</td>
<td>ARCI</td>
<td>8</td>
<td>&lt;4.0</td>
<td>23.3</td>
<td>63.6</td>
<td>584</td>
<td>70</td>
<td>166</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
<td>M</td>
<td>ARCI</td>
<td>1</td>
<td>&lt;4.0</td>
<td>55.3</td>
<td>37.4</td>
<td>13.1</td>
<td>152</td>
<td>23.8</td>
<td>11.2</td>
<td>18.8</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>M</td>
<td>EI</td>
<td>10</td>
<td>&lt;4.0</td>
<td>150</td>
<td>37.4</td>
<td>36.7</td>
<td>398</td>
<td>70</td>
<td>166</td>
<td>41.3</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>M</td>
<td>ARCI</td>
<td>4</td>
<td>&lt;4.0</td>
<td>119</td>
<td>37.2</td>
<td>38.4</td>
<td>584</td>
<td>34.2</td>
<td>45.3</td>
<td>64.7</td>
</tr>
<tr>
<td>6</td>
<td>3.5</td>
<td>F</td>
<td>EI</td>
<td>Normal</td>
<td>&lt;4.0</td>
<td>101</td>
<td>63.6</td>
<td>55.6</td>
<td>55.6</td>
<td>22</td>
<td>26.5</td>
<td>21.6</td>
</tr>
<tr>
<td>7</td>
<td>0.75</td>
<td>M</td>
<td>ARCI</td>
<td>2.5</td>
<td>&gt;150</td>
<td>75</td>
<td>38.4</td>
<td>144</td>
<td>6.52</td>
<td>20.8</td>
<td>21.6</td>
<td>15.5</td>
</tr>
</tbody>
</table>

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7 From Thatcher et al.5. Pt, patient number.
8 Normal: 30–100 ng/mL.
9 Normal: 15–85 pg/mL.
of calcium-dependent enzymes required for protein deimination during the final stages of epidermal differentiation, transglutaminase 1 (that is involved in cross linking of cornified envelope proteins with keratins), kallikrein (serine proteases that helps in shedding of old corneocytes), serine proteinase inhibitors B (important for negative feedback regulation of stratum corneum serine protease activity), cystatin EM, small proline rich protein 1 B, Kruppel-like factor 4 and c-fos. The excellent clinical response to vitamin D in our series might be related to the vitamin D-mediated epidermal differentiation network.

We changed the regular treatment protocol of weekly dose of vitamin D followed by monthly maintenance to a short-term high-dose supplementation, owing to poor compliance associated with staggered regular protocol. Several investigators have evaluated the safety of high-dose vitamin D. Hackman et al.6 used similar high-dose therapy (oral cholecalciferol 50 000 IU daily for 10 days) for vitamin D-deficient population without significant adverse effects. They concluded that the high-dose regimen might be an effective and cheap alternative for patients with vitamin D deficiency. Mondal et al.9 in their randomized trial, compared the safety and efficacy of cholecalciferol 600 000 IU single intramuscular high dose with staggered oral dose in children with rickets and concluded that both are safe and effective. The short-term high-dose therapy in our series seems to work well in congenital ichthyosis. This is in contrast to the observation by Thacher et al.,5 who despite treating a case of lamellar ichthyosis and rickets with intramuscular vitamin D$_3$ 600 000 IU showed no improvement in skin scaling. The same study also showed no improvement after 6 weeks of topical calcipotriene. Okano et al.11 also reported ineffectiveness of oral 1α-hydroxyvitamin D$_3$ in ichthyosis. Our observations suggest that high-dose therapy in our series seems to work well in congenital ichthyosis but should be used with caution, particularly in younger children, due to their potential side effects, especially skeletal toxicity. With retinoid therapy, the improvement in skin thickness and scaling begins in ~1–2 weeks of starting the treatment in ARCI.14

Retinoids have been the mainstay of treatment in moderate to severe ichthyosis but should be used with caution, particularly in younger children, due to their potential side effects, especially skeletal toxicity. With retinoid therapy, the improvement in skin thickness and scaling begins in ~1–2 weeks of starting the treatment in ARCI.14

The response, however, is variable and does not lead to near complete clearance of scaling (personal observation), as reported in the present case series with vitamin D supplementation. In all our cases, the parents noticed reduction in stiffness within 2 to 3 days of vitamin D supplementation, indicating an immediate response. Importantly, the sustained near-normal skin was observed in 2 children with ARCI, who were on RDA for 6 months. In 1 of the cases of EI, even the thick, scaly plaques significantly cleared by the 10th day. Because this child had serum 25(OH)D > 150 ng/mL, on day 10, we stopped all treatment for the next 3 weeks, and sustained clinical response was noticed even at 1 month. Later, at 3-month follow-up, he continued to have good clinical response, but with reappearance of minimal scaling, which significantly cleared on resuming the RDA of vitamin D 800 IU.

Our observations suggest that vitamin D may be considered as an alternative therapy in younger children with congenital ichthyosis and vitamin D deficiency, especially in pigmented skin types. In view of widely reported vitamin D deficiency across the globe, vitamin D therapy could possibly be used in other skin types with ichthyosis, even in the absence of rickets.

In view of 1 case developing hypercalcemia after 10 days of therapy and good response with normalization of ectropion even after 5 days of therapy in another child, we feel cholecalciferol 60 000 IU per day for 5 days followed by RDA may be adequate for good clinical response. Additional long-term

### TABLE 2 Additional Biochemical Profile

<table>
<thead>
<tr>
<th>Pt</th>
<th>Calcium (mg %)$^a$</th>
<th>Phosphate (mg %)$^b$</th>
<th>Alkaline Phosphatase (IU)$^c$</th>
<th>Urinary Calcium/Creatinine Ratio (Spot)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 0</td>
<td>Day 10</td>
<td>Day 30</td>
<td>3 mo</td>
<td>Day 0</td>
</tr>
<tr>
<td>1</td>
<td>10.3</td>
<td>10</td>
<td>10.4</td>
<td>3.72</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>9.9</td>
<td>6.1</td>
<td>4.8</td>
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<tr>
<td>3</td>
<td>9.97</td>
<td>10.82</td>
<td>11.2</td>
<td>10.2</td>
</tr>
<tr>
<td>4</td>
<td>6.7</td>
<td>9.6</td>
<td>9.7</td>
<td>10.2</td>
</tr>
<tr>
<td>5</td>
<td>9.12</td>
<td>9.3</td>
<td>9.5</td>
<td>9.8</td>
</tr>
<tr>
<td>6</td>
<td>8.1</td>
<td>9.2</td>
<td>9.7</td>
<td>5.1</td>
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<tr>
<td>7</td>
<td>10.5</td>
<td>10</td>
<td>9.3</td>
<td>10.4</td>
</tr>
</tbody>
</table>

$^a$Normal: 8.1–10.4 mg %.
$^b$Normal: 2.5–4.5 mg %.
$^c$Normal: 240–840 IU.
follow-up and randomized controlled studies are needed to understand the efficacy of varying dosing schedules, safety, and duration of therapy in different types of congenital ichthyosis with or without rickets. In addition, molecular studies with gene expression profile will be an important step in delineating the role of vitamin D in congenital ichthyosis.

The limitations in this study were poor follow-up for clinical and biochemical evaluation after 1 month of starting supplementation with vitamin D.

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REFERENCES


ABBREVIATIONS

25(OH)D: 25-hydroxyvitamin D
ARCI: autosomal recessive congenital ichthyosis
EI: epidermolytic ichthyosis
PTH: parathyroid hormone
RDA: Recommended Daily Allowance

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