

Advances in Skin & Wound Care

Vitamin D Supplementation in congenital ichthyosis: a case series

--Manuscript Draft--

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Abstract:	<p>Ichthyosis is a group of genetic keratinisation disorders characterized by excessive scaling associated with hyperproliferative epidermis and/or cellular retention. Normal thickness of the outer epidermis is 25 µm while it can be 10 folds greater in patients with Ichthyosis which impairs photoactivation of 7-dehydrocholesterol causing systemic vitamin D deficiency.</p> <p>Material and Methods A case series of 25 patients of congenital ichthyosis with vitamin D deficiency (< 10ng/ml) were supplemented with 60000 IU of vitamin D3 for 10 days followed by daily allowance of 400 -600 IU of vitamin D3, and 40 mg/kg/day of elemental calcium. Improvement in cutaneous scaling and stiffness of the body were assessed. Testing of blood and urine samples on Day-1, Day-10, 1 month and 3 months was done. Documentation of Dermatology Life Quality index (DLQI) before and after treatment was done.</p> <p>Results Normal vitamin D levels were noted for all patients , although 2 patients showed 100 ng/ml level of Vitamin D within 10 days, hence supplementation was stopped. Subjective improvement of symptoms (dryness of the skin, allergic rhinitis, tightness of the skin and scaling) was observed. There was remarkable improvement in symptoms in severe Ichthyosis like lamellar ichthyosis (tightness of the skin and scaling).Marked improvement in DLQI was also noted.</p> <p>Discussion This study demonstrated remarkable symptomatic relief with Vitamin D supplementation in patients of congenital ichthyosis, however more studies with a bigger sample size should be conducted to support these findings.</p>
Response to Reviewers:	Reviewer comments with Author response

	<p>1)Rationale for choosing the amount of vit D supplementation in the study-Revised with relevant studies cited from literatures</p> <p>2)Limitations and strengths of the study must be a part of the discussion.-Limitations and strengths of the study added</p> <p>3)The dosage of 60 000 international units daily should be clearly statedrevised</p> <p>4) Add your list of QoL markersQOL discussed</p> <p>5) At what level of ng/ml Vit D did the positive changes started to occur in your study, and How does that compare to the current ng/ml levels recommended in literature. - Changes done</p> <p>Editorial comments noted and revised manuscript with changes .</p>
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To,

The Editor

Sub: Submission of Manuscript for publication

Dear Sir,

We intend to publish an article entitled “**VITAMIN D SUPPLEMENTATION IN CONGENITAL ICHTHYOSIS:A CASE SERIES**” in your esteemed journal as original article.

On behalf of all the contributors I will act and guarantor and will correspond with the journal from this point onward.

Conflicts of interest : nil

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Thanking you,

Yours’ sincerely,

Dr. Mona Sharma

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Type of article: Original research article

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Introduction

Ichthyosis is a group of genetic keratinisation disorders characterized by excessive scaling associated with hyperproliferative epidermis and/or cellular retention. Normal thickness of the outer epidermis is 25 µm while it can be 10 folds greater in patients with Ichthyosis, and which will impair photo activation of 7-dehydrocholesterol causing systemic vitamin D deficiency.

Material and Methods

- A case series of 25 patients of congenital ichthyosis with vitamin D deficiency (< 10ng/ml) were supplemented with 60000 IU of vitamin D3 for 10 days followed by daily allowance of 400 -600 IU of vitamin D3, and 40 mg/kg/day of elemental calcium.
- Documentation of cutaneous scaling and stiffness of the body
- Testing of blood and urine samples on Day-1, Day-10, 1 month and 3 months
- Documentation of Dermatology life quality index (DLQI) before and after treatment

Results

- Normal vitamin D levels for all patients, although 2 patients got 100 ng/ml within 10 days, so supplementation was stopped.
- Subjective improvement of symptoms (dryness of the skin, allergic rhinitis, tightness of the skin and scaling)
- Improvement of symptoms were remarkable in severe Ichthyosis like lamellar ichthyosis (tightness of the skin and scaling)
- Marked improvement in DLQI

Discussion

Our study demonstrated remarkable symptomatic relief with Vitamin D supplementation in patients of congenital ichthyosis, however more studies with a bigger sample size should be conducted to support these finding.

Keywords- congenital ichthyosis, vitamin D3 deficiency, vitamin D3 supplementation

Vitamin D Supplementation in congenital ichthyosis: a case series

RESPONSE TO REVIEWER COMMENTS -

<u>Reviewer comments</u>	<u>Author response</u>
1)Rationale for choosing the amount of vit D supplementation in the study	Revised with relevant studies cited from literatures
2)Limitations and strengths of the study must be a part of the discussion.	Limitations and strengths of the study added
3)The dosage of 60 000 international units daily should be clearly stated	<u>revised</u>
4) Add your list of QoL markers	<u>QOL discussed</u>
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Ichthyosis is a group of genetic keratinisation disorders characterized by excessive scaling associated with hyperproliferative epidermis and/or cellular retention. Normal thickness of the outer epidermis is 25 µm while it can be 10 folds greater in patients with Ichthyosis which impairs photoactivation of 7-dehydrocholesterol causing systemic vitamin D deficiency.

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Discussion

This study demonstrated remarkable symptomatic relief with Vitamin D supplementation in patients of congenital ichthyosis, however more studies with a bigger sample size should be conducted to support these findings.

Keywords- congenital ichthyosis, vitamin D3 deficiency, vitamin D3 supplementation

Introduction

Ichthyosis is a group of genetic keratinisation disorders characterized by excessive scaling associated with hyperproliferative epidermis and/or cellular retention. Normal thickness of the outer epidermis is 25µm while it can be 10 folds greater in patients with Ichthyosis, which impairs photoactivation of 7-dehydrocholesterol causing systemic vitamin D deficiency. Vitamin D is a pro-hormone that is highly essential for calcium and bone mineral homeostasis. Vitamin D deficiency causes rickets in children and osteomalacia in adults besides its association with several systemic conditions like diabetes mellitus, autoimmune diseases,

1 cardiovascular diseases, microbial infections, and malignancies.¹ Skin is the major source of
2 endogenous vitamin D and only 10% is derived from dietary sources. This study was done to
3 assess the role of Vitamin D supplementation in congenital ichthyosis.
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6 **Material and methods:**

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8 A case series of 25 patients of congenital ichthyosis with vitamin D deficiency (<10ng/ml)
9 were included in the study. Participation was voluntary and written informed consent was taken
10 from the guardians of each child. Also, necessary approval from Institutional research and
11 ethics committee (05/11/2016, Ref. No. KIMS/IEC/ D-38/ 2016) was taken. All the cases were
12 enrolled by convenient sampling method, and were supplemented with Vitamin D3 60000 IU
13 daily for a period of 10 days under medical supervision. Daily allowance of 400 -600 IU of
14 vitamin D3 and 40 mg/kg/day of elemental calcium was given after 10 days till 3
15 months. Improvement was documented by using parameters like scaling, stiffness of the body,
16 clearance of scales and assessment of quality of life in patients. Blood tests and urine samples
17 were evaluated on Day -1, Day -10, after 1 month and 3 months. DLQI was measured before
18 starting the therapy and after 3 months.
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23 **Inclusion criteria:**

24 Patients with congenital Ichthyosis with no H/O calcium or vitamin D supplementation
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27 **Exclusion criteria:**

28 Acquired Ichthyosis.
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30 Patients with normal Vitamin D levels
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41 **Results:**

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43 Total 25 cases with severe vitamin D deficiency (serum 25(OH) D < 10 ng/mL) were included
44 in the study comprising of 10 males (40 %) and 15 females (60%). Out of these 11 (44%)
45 patients had Ichthyosis vulgaris, 7 (28%) had X-linked recessive Ichthyosis, 5 (20%) had
46 lamellar Ichthyosis while 2 (8%) suffered from non-bullous congenital ichthyosiform
47 erythroderma. Most of the patients were in the age range of 12-18 years (48%). [Table 1]
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51 Serum vitamin D levels improved in almost all patients with supplementation. 01 patient had a
52 value of 99 nmol/L of Vitamin D after 10 days of supplementation, hence further therapy was
53 stopped, while one patient was lost to follow up. 07 patients of Ichthyosis vulgaris were
54 associated with atopy which improved after vitamin D supplementation. Clinical improvement
55 amongst the patients of Ichthyosis vulgaris and X-linked recessive ichthyosis was noted in terms
56 of reduction in itching, skin tightness and clearance of scales by Day-5 which was further
57 appreciable by Day-10 .All cases of Lamellar Ichthyosis and Non bullous ichthyosiform
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erythroderma improved symptomatically with significant difference in tightness of the skin and mild to no improvement in clearance of scales. At 1 month, the skin was almost normal in less severe ichthyosis patients with remarkable improvement on the face and trunk compared to extremities.

18(72%) out of 25 patients started to show improvement in symptoms after day 10 of supplementation. Average Vitamin D level was 39 IU.

No clinically evident adverse side effects were observed. Serum calcium, phosphate, parathyroid hormone, and urine analysis were normal throughout the duration of study. Details of Vitamin D supplementation are mentioned in Table 2.

QoL was measured using an standard DLQI questionnaire. It includes 10 questions comprising of 6 areas of the patients' lives: "symptoms and feelings," "school or holidays," "leisure," "sleep," "personal relationships," and "treatment." Each question has four different responses: "not at all," "a little," "a lot," and "very much" with corresponding scores as 0, 1, 2, and 3, respectively. The final score is determined by adding up scores of individual questions ranging from 0 to 30. Higher the score, higher is the impairment in the QoL of patients/parents. The assessment questionnaire was filled before starting and after finishing the treatment i.e 3months. Hence, in this study it was observed that quality of life score amongst the patients with less severe ichthyosis (Ichthyosis vulgaris, X-linked recessive ichthyosis) was lesser compared to more severe ichthyosis (Lamellar Ichthyosis and Non bullous Ichthyosiform Erythroderma).

Discussion:

Vitamin D metabolic pathway takes place in cutaneous keratinocytes with formation of 1,25 dihydroxy vitamin D₃ which has both autocrine or paracrine functions. Sethuraman et al hypothesized that correction of vitamin D deficiency with high-dose supplementation therapy may result in increased keratinocyte production of 1,25(OH)₂ D₃ which has known antiproliferative and pro-differentiating actions leading to repair in keratinization process and clearance of skin scaling.¹ This hypothesis was supported by Lu et al, who observed 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.² These vitamin D-responsive genes include involucrin (that is involved in cornified envelope formation), peptidylarginine deiminase (a family of calcium-dependent enzymes required for protein deamination 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).

Several investigators have evaluated the safety of high-dose vitamin D in the management of ichthyosis. In this study, patients were supplemented with 60000 IU of vitamin D₃ for a period of 10 days. As mentioned by Hackman et al, high dose therapy (oral cholecalciferol 50 000 IU daily for 10 days) for vitamin D-deficient population was used without any significant adverse effects. Hence, it was observed that high-dose regimen might be an impactful and cost effective alternative for patients with vitamin D deficiency.³ In a randomized trial by Mondal et al, safety

1 and efficacy of cholecalciferol 600 000 IU single intramuscular high dose was compared with
2 staggered oral dose in children with rickets and it was found that both the regimes were safe
3 and effective. The short-term high-dose therapy used in this series seems to work well in
4 congenital ichthyosis.⁴

5 Retinoids have been prescribed more often for moderate to severe ichthyosis. However, owing
6 to their potential side effects especially skeletal toxicity, particularly in younger children
7 cautious use is advised. With retinoid therapy, the improvement in skin thickness and scaling
8 begins in ~1–2 weeks of starting the treatment but complete clearance is not achieved.⁵ In our
9 study, stiffness was reduced within 2-3 days of vitamin D supplementation, indicating an
10 immediate response. Observations suggest that vitamin D may be considered as an alternative
11 therapy in younger children with congenital ichthyosis and vitamin D deficiency. It has been
12 suggested that vitamin D therapy could possibly be used in ichthyosis, even in the absence of
13 rickets as vitamin D deficiency is quite common across the globe.⁶⁻⁷

14 Vitamin D deficiency is a major health problem in India as well. In one of the largest study of
15 clinical evaluation for evidence of vitamin D deficiency in 5137 healthy school children (from
16 Delhi, India) aged 10-18 years, hypovitaminosis D was seen in 92.6% of the lower
17 socioeconomic status (LSES) group (severe: 11.2%; moderate: 39.5%; and mild: 42.1%) and
18 84.9% of the upper socioeconomic status (USES) group (severe: 4.9%; moderate: 25.5%; and
19 mild: 57.6%). 42.3% children in the LSES group had biochemical rickets compared to 27% in
20 the USES (p < 0.01).

21 Strengths and limitations

22 The strength of the study was that it proved the efficacy of high-dose Vitamin D
23 supplementation regimen as an effective, less time consuming and cost effective alternative for
24 patients with vitamin D deficiency ,specially amongst the patients with less severe forms of
25 ichthyosis (Ichthyosis vulgaris, X linked recessive ichthyosis). Although a prospective work with
26 a robust design, this work has several limitations such as inclusion of small sample size
27 conducted at a single centre. With high of Vitamin D, rare complications like hypercalcemia,
28 hypervitaminosis D and hypercalciuria are possible and therefore it is recommended that larger
29 sample size would be more appropriate in determining their incidence in such studies.

30 Conclusion:

31 This study concluded that short-term, high-dose vitamin D3 supplementation was effective
32 in reducing scaling in patients with congenital ichthyosis and in ameliorating the associated
33 vitamin D deficiency. Further research with long-term randomised clinical studies is
34 essential to assess the safety and efficacy of vitamin D supplementation in children with
35 congenital ichthyosis.

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TABLE -1 : DEMOGRAPHIC PROFILE AND CLINICAL FEATURES

	Frequency, n (%)
Forms of ichthyosis	
Ichthyosis vulgaris	11 (44)
X-linked recessive ichthyosis	7 (28)
Lamellar ichthyosis	5 (20)
Nonbullous ichthyosiform erythroderma	2 (8)
Age group (years)	
1-3 years	01(4)
3-6 years	03(12)
6-12 years	09 (36)
12-18 years	12(48)
Duration of ichthyosis (months)	
0-12	9 (36)
>12	16 (64)
Gender	
Male	10 (40)
Female	15 (60)
Demographic profile and clinical features	
History of consanguineous marriage	14 (56)
History of hyperlinearity of palms	1 (4)
History of rickets/genu valgum/bone involvement	3 (12)
History of pruritus	18 (72)
History of atopy	7 (28)
H/O alopecia areata with corneal deposits	1 (4)

Table 2: Response of Vitamin D supplementation

#Patient	Day of Administration				After 10 Days		After 1 Month		After 3 Months	
	Clinical Inspection	Bio-chemical Inspection			Clinical Inspection	Bio-Chemical Inspection	Clinical Inspection	Bio-Chemical Inspection	Clinical Inspection	Bio-Chemical Inspection
	Type of Ichthyosis	Vit D	Calcium	Urine Analysis	Findings(improvement +/-)	Findings(Vit.D)	Findings	Findings	Findings	Findings
1	Ichthyosis Vulgaris	9.87	10.2	N	-	45.09	+	64.54	+	89.72
2		3.89	9.8	N	+	25.8	+	55.90	+	65.90
3		7.80	10.5	N	-	30.98	+	49.68	+	59.82
4		5.8	8.5	N	-	29.89	+	33.5	+	40.90
5		4.2	9.67	N	+	33.45	+	76.94	+	89.80
6		6.6	8.7	N	+	100	STOPPED			
7		3.7	7.8	N	+	23.90	+	55.78	+	74.93
8		9.5	10.1	N	+	40.56	-	78.0	+	82.90
9		7.8	9.4	N	+	39.05	+	53.89	+	67.93
10		8.3	8.8	N	+	22.1	+	56.94	+	60.87
11		4.4	9.0	N	-	27.4	-	53.89	+	68.97
12	NBCIE	3.8	8.5	N	+	26.4	+	44.90	+	56.65
13		4.5	10.3	N	-	34.9	+	50.98	+	59.78
14	X-Link	7.67	9.8	N	+	29.78	+	50.78	+	69.89
15		5.89	10.9	N	-	28.90	+	47.89	+	73.87
16		8.68	11	N	+	99.01	STOPPED			
17		6.89	9.6	N	+	30.90	+	55.76	+	64.90
18		3.09	4.92	N	<u>didn't follow up</u>					
19		8.32	10.03	N	+	32.08	+	68.45	+	77.90
20		5.98	11.0	N	+	40.58	+	49.78	+	53.67
21	Lamellar	4.87	9.9	N	+	39.78	+	46.89	+	62.78
22		3.23	8.9	N	+	21.90	+	55.89	+	77.64
23		4.78	10.03	N	+	27.67	+	49.89	+	60.89
24		5.02	8.5	N	+	31.89	+	53.89	+	78.32
25		3.78	9.03	N	+	39.63	+	45.67	+	67.78

(+) denotes improvement in symptoms

(-) denotes no improvement in symptoms

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