e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(2); 975-981

Original Research Article

Study of Vitamin D Deficiency in Patients with Congenital Ichthyosis in a Tertiary Care Hospital in South India

Priyanka Hemrajani[1], Sharath Kumar B. C.[2], Mona Sharma[3], Rajesh Somkuwar[4]

[1]Senior Resident, Dept. of Dermatology, ESIPGIMSR, New Delhi
[2]Professor & HOD, Dept. of Dermatology, Kempegowda Institute of Medical Sciences, Bangalore
[3]Postgraduate Resident, Dept. of Dermatology, ESIPGIMSR, New Delhi
[4]Consultant Dermatologist, Al Salaam International Hospital, Kuwait

Received: 30-12-2022 / Revised: 12-01-2023 / Accepted: 10-02-2023
Corresponding author: Dr Mona Sharma
Conflict of interest: Nil

Abstract

Vitamin D deficiency results in rickets in children and osteomalacia in adults. Skin is the major source of endogenous vitamin D and only 10% is derived from dietary sources. A prospective case control study was done in 50 clinically diagnosed cases of congenital ichthyosis attending dermatology outpatient department at a tertiary care centre in south India to determine the prevalence of vitamin D deficiency and rickets in patients with congenital ichthyosis.

Keywords: Endogenous Vitamin D, Osteomalacia, Dermatology, Rickets.

Introduction

Vitamin D is a pro-hormone that is essential for calcium and bone mineral homeostasis. Vitamin D deficiency results in rickets in children and osteomalacia in adults. This also has implications in several systemic illnesses such as diabetes mellitus, autoimmune diseases, cardiovascular diseases, microbial infections and malignancies. [1] Skin is the major source of endogenous vitamin D and only 10% is derived from dietary sources.[2] This study was done to determine the prevalence of vitamin D deficiency and rickets in patients with congenital ichthyosis. Levels of Vitamin D, parathyroid hormone and serum calcium levels were assessed in patients with congenital Ichthyosis and the incidence of rickets among those patients were determined.

Materials and Method

A prospective case control study with an analytical design was carried out on 50 clinically diagnosed cases of congenital ichthyosis (non-syndromic) with equal number of controls, attending dermatology outpatient department at a tertiary care centre in south India over a period of 18months.The study was conducted after taking approval from Institutional research and ethics committee (05/11/2016, Ref. No. KIMS/IEC/ D-38/ 2016). Convenient sampling was used to enroll the cases and controls. Serum levels of Vitamin D, parathyroid hormone and serum calcium levels were assessed in patients along with socio-personal characteristics.

Inclusion criteria for cases:

- Patients of congenital Ichthyosis
- Not on any calcium or vitamin D supplementation.

Exclusion criteria for cases:

- Acquired Ichthyosis

Inclusion criteria for controls

- Healthy age and sex matched volunteers
- Not on any calcium or vitamin D supplementation

Exclusion criteria for controls

- Patients on calcium or vitamin D supplementation

Results

During the study period, 50 patients of congenital ichthyosis were recruited. During the same period 50 healthy controls (age and sex matched) were recruited.

Table1: Age and gender-wise distribution of disease a group and control group

Characteristics					
	Disease Group(n=50)		Controls(n=50)		Total (n=100)
Age	**Males**	**Females**	**Males**	**Females**	
<15 years	19 (70.4)	7 (30.4)	18 (72.0)	8 (32.0)	52 (52.0)
15-18 years	8 (29.6)	16 (69.6)	7 (28.0)	17 (68.0)	48 (48.0)
Total	27 (100)	23 (100)	25 (100)	25 (100)	100 (100.0)

Most of the patients were less than 15 years of age (52.0%), followed by those between 15-18 years (37.0%). (Table 1). Mean age of patients in the case and control groups was 16.86 $\pm$ 10.57 and 16.9 $\pm$9.9 years respectively. (p-value>0.05%; non-significant

On exploring the history of the patients, it was observed that majority of the parents of the cases had a consanguinous marriage (78.0%), a positive history of collodion baby (13.0%), and more cases reported erythroderma, bullous lesion, recurrent infections (9.0%) compared to none in the control group.

Table 2: Laboratory characteristics of disease age group and control group

Characteristics	Cases (n=50)	Control (n=50)	p-value
Serum calcium (mean+SD)	9.5+1.4	10.0+ 0.6	0.019
Serum phosphorus (mean+SD)	4.4 + 1.3	4.0 +0.6	0.022
25(OH)D (mean+ SD)	17.5 +13.5	38.4+ 16.5	0.147
PTH (mean+ SD)	35.94 +43.67	26.44 +32.47	0.099

It was observed that cases had a lower mean serum calcium (P<0.05; significant) and 25(OH)D(P>0.05; non- significant), but higher serum phosphorus levels (P<0.05; significant) and serum para thyroid levels (P>0.05; non- significant) as compared to the control group.

Table 3: Distribution of 25 (OH) Vitamin D(in ng/ml) amongst cases and controls

Level of vitamin D (ng/l)	Cases (n=50)	Control (n=50)	Total (n=100)
<5	10(20.0)	0	10(10.0)
5 - <9	3(6.0)	0	3(3.0)
>9- <20	21(42.0)	4 (8.0)	25(25.0)
>20 <30	9 (18)	13 (26)	22 (22.0)
>30	7 (14)	33 (66)	40(40.0)

It was observed that the frequency of biochemical rickets (moderate vitamin D deficiency, 25 (OH)D3 ≤9 ng/ml) found in the cases was significantly higher than those in the control. The prevalence of mild and severe vitamin D deficiency in the cases was also statistically significant than controls respectively [Table 3]. Ten cases (20%) had undetectable levels (<5) of 25 (OH) D3.($p<0.05$). A higher number of patients in the control group had sufficient levels of 25 (OH)D3 >20 ng/ml).

Table 4: Relationship of Vitamin D3 levels with sun exposure in patients

Sun exposure (In hours)	Mean Vitamin D3 Level
< 1 hour / day	4.12+ 2.63
1-2 hours /day	21.29+ 13.95
>2 hours /day	29.74 +17.34
p-value: 0.006	

The mean 25-(OH) D3 levels increased as a function of sun exposure time, and the difference was statistically significant on applying ANOVA.

Table 5: Distribution of Parathyroid levels (pg/ml) amongst cases and controls

Level of Parathyroid hormone (pg/ml)	Cases (n=50)	Control (n=50)		Total(n=100)	
Low (<10 pg/ml)	5 (10.0)	4	(8.0)	9	(9.0)
Normal (10-65 pg/ml)	42 (84.0)	46	(92.0)	88	(88.0)
High (>65 pg/ml)	3 (6.0)		0	3	(3.0)

Hyperparathyroidism was seen in 3(6.0%) cases while it was not seen in the control group.

Table 6: Distribution of calcium levels (mg/ml) amongst cases and controls

Calcium Levels (mg/dl)	Cases(n=50)		Control (n=50)	Total (n=100)	
<8.5	4	(8.0)	0	4	(4.0)
8.5 – 10.2	19	(38.0)	8 (16.0)	27	(27.0)
>10.2	33	(66.0)	36 (72.0)	69	(69.0)

Chi square: 7.28; df: 2 and p-value: 0.026

Most of the patients (n= 69) had hypercalcemia (Serum Ca^{++} more than 10.2 mg/dl) and the number was more in the control group (n=36) as compared to the cases (n=33). But, cases had a higher frequency of patients with hypocalcemia (Serum Ca^{++}less than 8.5 mg/dl).

Table 7: Association of calcium levels with mean Vitamin D3 Levels and mean PTH Levels

Calcium Levels (mg/dl)	Mean Vitamin D3 Levels			Mean PTH Levels
	Case	Control	Case	Controls
<8.5	21.02+32.04	-	119.46+ 79.30	-
8.5 – 10.2	27.33+11.32	32.80+12.92	25.98 + 16.10	29.88 + 10.59
>10.2	37.30+ 25.76	42.60+17.07	16.23+ 8.75	23.29+ 9.5
p-value	0.007	0.033	0.000	0.208

The mean serum Vitamin D3 and serum Parathyroid levels were compared in the three groups with different serum Ca^{++} levels. Mean Vitamin D3 increased significantly with the serum calcium level, while PTH levels decreased significantly with increasing serum Calcium levels. It was seen that, Vitamin D3 levels increased as a function of serum Calcium levels in both the study groups. Whereas, the parathyroid levels decreased as the serum calcium increased in both the cases (p-value < 0.001) and controls (p-value>0.05).

Table 8: Frequency distribution of X-Ray findings of wrist joints in study patients.

	Case	Control	Total	
Normal	48 (96)	50 (100.0)	98	(98.0)
B/L cupping & fraying	1 (2.0)	0	1	(1.0)
Rare face of metacarpal & base of				
proximal phalangeal bones, mild	1(2.0)	0	1(1.0).	
Osteopenia				
Total	50 (100.0)	50 (100.0)	100	(100.0)

Chi square: 3.09 with df: 3 and p-value:0.378

It was observed that cases depicted most of the pathologies like bilateral cupping and fraying (2.0%), Rare face of metacarpal & base of proximal phalangeal bones, mild osteopenia (2.0%). Controls depicted no such findings. The association was statistically non-significant.

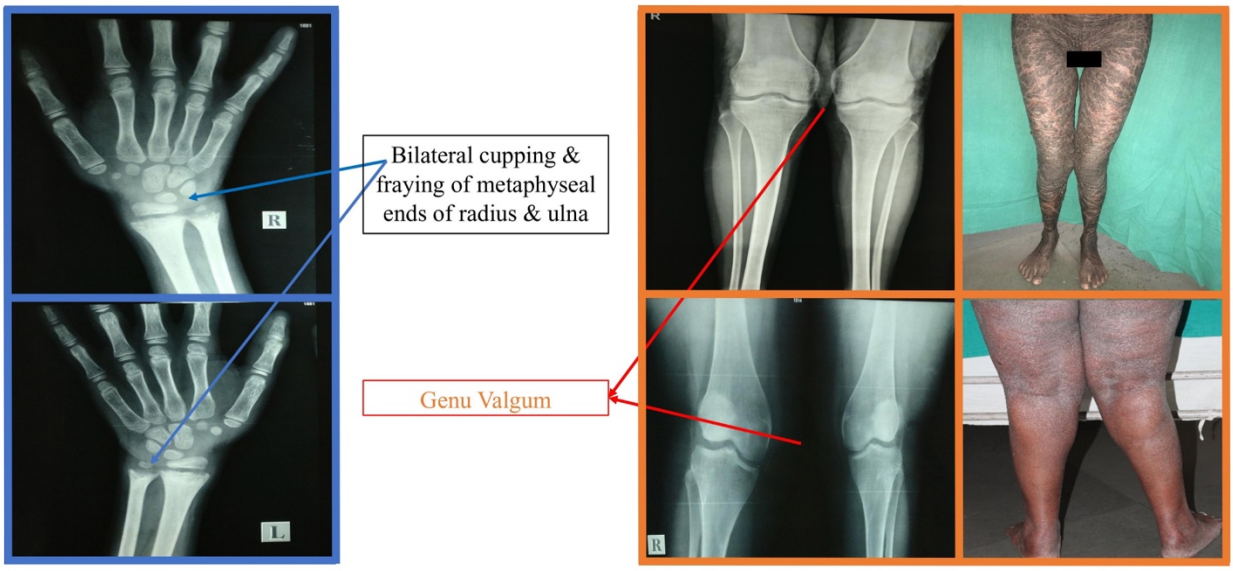

Figure 1: B/L cupping & fraying and Genu valgum in patients

Table 9: Other clinical characteristics observed in the cases and controls.

	Cases (n=50)		Controls (n=50)	Total (n=100)	
Nil	25	(50)	50 (100)	75 (75)	
Keloid	1	(2)	0	1	(1)
Alopecia areata with Corneal Deposit	1	(2)	0	1	(1)
Asthma	1	(2)	0	1	(1)
Atopy	5	(10)	0	5	(5)
Bathing Suit ichthyosis	1	(2)	0	1	(1)
Breast Cancer	1	(2)	0	1	(1)
Genu valgum	2	(4)	0	2	(2)
Hyper linearity of palm	3	(6)	0	3	(3)
Juvenile plantar dermatosis	4	(8)	0	4	(4)
Keratosis Pilaris	1	(2)	0	1	(1)
Osteopenia	1	(2)	0	1	(1)
Refractive errors	2	(4)	0	2	(2)

Rickets	1	(2)	0	1	(1)
Vitiligo	1	(2)	0	1	(1)
Total	**50 (100)**		**50**	**100**	**(100)**

It was observed that most of the clinical findings were present in the cases only. Atopy of muscles was the most common finding in the cases (10%), followed by juvenile palmar dermatosis (8%) and hyper-linearity of palms (6%). Controls on the other hand has no such associated complaints

Discussion

Vitamin D deficiency results in abnormalities of calcium and bone mineral homeostasis. With normal serum 25-hydroxyvitamin D level, dietary calcium absorption is approximately 30–40% in comparison to only 10–15% in vitamin D deficient subjects. [3] This low absorption leads to low serum calcium levels which results in secondary hyperparathyroidism which in turn increases the generation of active vitamin D by conversion of the available 25-hydroxyvitamin D to 1,25-hydroxyvitamin D until the serum 25-hydroxyvitamin D reaches the minimal threshold limit. With further decrease in serum 25-hydroxyvitamin D levels, the parathyroid hormone tries to maintain the serum calcium levels in the normal range by mobilizing calcium from the skeleton and decreasing phosphate reabsorption in the proximal renal tubules. This result in inadequate calcium phosphorus product causes poor mineralization of bones resulting in rickets in children. Also parathyroid hormone mediated bone resorption causes generalized decrease in bone mineral density and weakening of bone. [3] Rickets in children is a major global health concern with Vitamin D deficiency and dietary calcium deficiency being the most important causes in several studies.[4,5] Some studies have reported that children with congenital ichthyosis, especially those with the pigmented skin types, are more prone to develop vitamin D deficiency and rickets.[6-8]

Vitamin D deficiency is a major health problem in India. In the largest study of clinical evaluation for evidence of vitamin D deficiency in 5137 healthy school children (from Delhi, India) aged 10-18 years, hypovitaminosis D was seen in 92.6% of the lower socioeconomic status (LSES) group (severe: 11.2%; moderate: 39.5%; and mild: 42.1%) and 84.9% of the upper socioeconomic status (USES) group (severe: 4.9%; moderate: 25.5%; and mild: 57.6%). 42.3% children in the LSES group had biochemical rickets compared to 27% in the USES $p < 0.01$). Ichthyosis a genetic disorder of keratinization is characterized by excessive scaling associated with epidermal hyperproliferation and/or cellular retention. [9] This generalized thick scaling that may act as physical sunscreen preventing ultraviolet B rays from penetrating the epidermis fully, resulting in inadequate activation of the precursor molecule leading to poor vitamin D formation. Besides this, these children avoid sunlight because of heat intolerance and social stigma due to the abnormal scaling and the appearance. [10] Rickets in a patient with disorder of keratinization may occur due to alterations in epidermal cholesterol metabolism. Low vitamin D levels in these children are also because of consuming food low in vitamin D.

In our study on exploring the history of the patients, it was observed that majority of the parents of the cases had a consanguinous marriage (78.0%), had a positive history of collodion baby (18.0%), and more cases reported Erythroderma, Bullous lesion, recurrent infections (9.0%) compared to none in the control group. Hypovitaminosis D (25

(OH) D3 < 25nmol/L) has been reported in a series of 9 patients (Europeans 6, Africans 3) with congenital ichthyosis. This was more severe in African children which explain pigmentation as one of the predisposing factors in rickets with type IV-VI skin.

Various studies from India have also reported vitamin D deficiency rickets in children with different types of ichthyosis.[11-13] Mean levels of 25(OH)D in diseased group in this study was 17.5 $\pm$ 13.5 ng/ml as compared to 38.4$\pm$ 16.5ng/ml in control group. About 62% subjects in diseased group had 25(OH)D levels <20 ng/ml whereas in control group only 8% subjects had vitamin D levels <20 ng/ml. Other studies have also reported low levels of Vitamin D in patients with ichthyosis.

About 6% cases in the present study were having parathyroid levels >65 pg/mL. The correlation between 25-(OH) D and PTH levels shown by various studies, suggesting that secondary hyperparathyroidism is linked to Vitamin D deficiency. Serum 25-hydroxyvitamin D ≤8 ng is the threshold value for secondary hyperparathyroidism.[8] This is in contrast with the results of the series by Milstone *et al*. who demonstrated that patients suffering from ichthyosis associated with secondary hyperparathyroidism did not have any vitamin D deficiency. Another study done by Sethuraman *et al* with a sample size of 119 children with ichthyosis concluded that forty-seven children with Ichthyosis had either clinical or radiological evidence of rickets. The correlation between serum 25(OH)D and PTH showed that a serum level of 25(OH)D 8 ng mL^{-1} was associated with a significant increase in PTH.

In several studies, X-ray of the limbs depicted marked cupping and fraying of the distal metaphysis with coarse tubercular pattern and osteopenia in patients with vitamin D deficiency.[14] Similar findings were present in cases of our study. Bilateral cupping and fraying (2.0%), rare face of metacarpal & base of proximal phalangeal bones, mild osteopenia (4.0%) was observed in x rays of limbs. On X-Rays of knee joints early osteoarthritic changes (2.0%) and genu valgum (2.0%) was observed. Another study from north-eastern part of the India also presented similar case of ichthyosis with genu valgum.[15] Other clinical findings present in the cases were atopy (10%), juvenile palmar dermatosis (8%) and hyper-linearity of palms (6%). Vitamin D and Serum Calcium showed statistically positive correlation (at the 0.05 level). Serum calcium depicted statistically significant (at the 0.01 level) negative correlation with PTH. Another important additional point that needs to be discussed is the impact of sun avoidance on vitamin D level in ichthyosis. It is known that because ichthyosis is a stigmatizing condition, affected individuals may remain largely indoors and avoid social gatherings and are therefore probably less exposed to the sun. Moreover, many have heat intolerance that further induces them to avoid exposure to sunlight. In our study the relationship of Vitamin D3 levels with Sun exposure have shown that the mean 25-(OH) D3 levels increased as a function of sun exposure time, and the difference was statistically significant.

Conclusion

The present study concludes that patients with congenital ichthyosis are at an increased risk of developing vitamin D deficiency and clinical rickets. Hence all children with different types of ichthyosis and other keratinizing disorders should be screened and given lifelong rickets prophylaxis with vitamin D along with vitamin D rich diet, in order to prevent the occurrence of clinical rickets and advanced irreversible skeletal changes. The most important factor causing rickets in these patients the thick scaly skin which acts as physical sun block/sunscreen

that considerably reduces the synthesis of vitamin D in the epidermis. The other possible etiological factors include background prevalence of vitamin D deficiency, and decreased exposure time to sun light due to heat intolerance and social stigma.

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