Editorial

# Vitamin D, bone health and congenital ichthyosis

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Vitamin D is a prohormone that is essential to maintain the bone mineral homeostasis and many cellular and immunological functions. Vitamin D deficiency leads to rickets in children and osteomalacia in adults besides being implicated in several systemic illnesses such as diabetes mellitus, autoimmune diseases, cardiovascular diseases, microbial infections and malignancies.[1] Hence, maintaining adequate levels of circulating 25-hydroxyvitamin D is crucial for good health.

Solar ultraviolet B irradiation (290–320 nm) of skin accounts for approximately 90% of vitamin D synthesis through the activation of its precursor molecule, 7-dehydrocholesterol present in the epidermis. Only 10% is derived from dietary sources.[2] The amount of vitamin D synthesis in the skin is primarily determined by the quantity and quality of the ultraviolet B irradiation reaching the earth's surface which in turn is dependent on the solar zenith angle, latitude, season, atmospheric pollution and ozone layer.[3] Melanin, the natural (pigment) sunscreen in the skin can reduce the cutaneous synthesis of vitamin D by preventing the ultraviolet B radiation from reaching the basal and spinous cell layers of the skin which have the highest concentrations of 7-dehydrocholesterol.[2,3] Regular use of sunscreens can reduce the vitamin D synthesis in the skin by more than 95%.[1]

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Vitamin D deficiency results in abnormalities of calcium and bone mineral homeostasis. The dietary calcium absorption with normal serum 25-hydroxyvitamin D level is approximately 30–40% in comparison to only 10–15% in vitamin D deficient subjects.[4] The resulting low calcium levels lead to 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. The resultant inadequate calcium phosphorus product causes poor mineralization of bones resulting in rickets in children. In addition, the parathyroid hormone mediated bone resorption causes generalized decrease in bone mineral density and weakening of bone.[4]

Rickets in children is a persistent global health concern. Though vitamin D deficiency remains a major cause of rickets in most countries, dietary calcium deficiency alone has also been shown to be responsible for causation of rickets in Nigerian children.[5,6] This observation was further supported by the fact that calcium supplementation with or without vitamin D was superior to vitamin D supplementation alone in the treatment of rickets.[5] Limited data from India also reinforces the importance of dietary calcium in the prevention of rickets.[7]

Recently, it has been reported that children with congenital ichthyosis, especially those with the pigmented skin types, are more prone to develop



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vitamin D deficiency and rickets.[8-10] Clinical and/or radiological evidence of rickets have been observed in 41% of children with congenital ichthyosis as against clinical evidence of vitamin D deficiency in 10.8% of apparently healthy children.[10,11] This is probably due to the fact that congenital ichthyosis is a disorder of keratinization, characterized by generalized thick scaling that may act as physical sunscreen preventing ultraviolet B rays from penetrate the epidermis fully, resulting in inadequate activation of the precursor molecule leading to poor vitamin D formation. In addition, these children avoid sunlight because of heat intolerance and social stigma due to the abnormal scaling and the appearance. Even if they try and expose themselves to sunlight, in particular, during winter months, they may not synthesize adequate vitamin D due to low ultraviolet B index as reported in our recent studies.[12,13] Low vitamin D levels in these children are also because of consuming food low in vitamin D.

The relationship between vitamin D-parathyroid hormones-calcium axis in children with congenital ichthyosis has revealed several interesting observations. There is a threshold level for parathyroid hormone that increases significantly only below a serum 25-hydroxyvitamin D level of 8 ng/ml, suggesting that serum 25-hydroxyvitamin D ≤8 ng is the threshold value for secondary hyperparathyroidism. In the same way, a significant rise in alkaline phosphatase level is noted when the serum parathyroid hormone exceeds 75 pg/ml, indicating that a parathyroid hormone level of ≥75 pg/ml is the threshold level for increasing serum alkaline phosphatase and bone resorption. Of the different combinations of the identified threshold levels of serum 25-hydroxyvitamin D and parathyroid hormone, the increased risk of developing rickets in children with congenital ichthyosis is among those with serum threshold levels of 25-hydroxyvitamin D ≤8 ng/ml and parathyroid hormone ≥75 pg/ml.[10]

Among the different types of congenital ichthyosis, proliferative types of ichthyosis such as autosomal recessive congenital ichthyosis and epidermolytic ichthyosis are significantly predisposed to the development of rickets compared to the retention types (ichthyosis vulgaris and X-linked recessive ichthyosis).[10]

Children with congenital ichthyosis should routinely be evaluated for clinical, biochemical (serum calcium, phosphate, alkaline phosphatase and urinary calcium creatinine ratio), hormonal (serum 25-hydroxyvitamin D, parathyroid hormone) and radiological (X-ray-wrists and knees and dual-energy X-ray absorptiometry scan) parameters. The treatment would depend on whether children have vitamin D deficiency (serum 25-hydroxyvitamin D <20 ng/ml) with or without rickets. Those with rickets should be corrected with weekly cholecalciferol of 60,000 IU for 10 weeks along with elemental calcium of 50–75 mg/kg/day, till radiological and biochemical healing of rickets occur.[14,15] Children should be reviewed at 12 weeks with all the baseline investigations except dual-energy X-ray absorptiometry scan. Those who have not healed completely may need further treatment till radiological healing occurs. This should be followed by daily maintenance of 400 and 600 IU of cholecalciferol for infants and children above 1 year of age, respectively, along with 30–75 mg/kg/day (depending on the age) of elemental calcium (including daily dietary intake).[14,15] It would be pertinent to estimate the serum 25-hydroxyvitamin D and parathyroid hormone levels after 3 months of of administering the maintenance dose to see whether the levels are within normal limits or not. If levels are normal, the maintenance dose may be continued lifelong with yearly evaluation of bone mineral metabolic parameters.

Children with only low vitamin D levels (without rickets) should be supplemented with cholecalciferol 60,000 IU once a week for 4 weeks followed by monthly maintenance of 60,000 IU or daily maintenance of 400 IU for infants and 600 IU for children above 1 year of age along with calcium supplementation.[16]

Stoss therapy for vitamin D deficiency rickets consists of administration of 100,000–600,000 IU of vitamin D orally over a period of 1–5 days followed by 400–1000 IU of vitamin D daily or 50,000 IU of vitamin D weekly for 8 weeks.[2] This therapy is particularly helpful for patients who are unable to come for regular follow-up because of poor socioeconomic status or because they live in far off places. We have used modified stoss therapy (60,000 IU oral cholecalciferol daily for 10 days) that not only helped in healing of severe clinical rickets, but also proved to be effective in reducing the stiffness, clearing of skin scaling and normalization of ectropion in children with congenital ichthyosis (autosomal recessive congenital ichthyosis and epidermolytic ichthyosis).[17] Hence, vitamin D may be considered as a sole alternative therapy in

congenital ichthyosis.[17] Vitamin D regulates a number of genes involved in the terminal differentiation and desquamation of epidermal keratinocytes and the excellent treatment response may be related to vitamin D-mediated epidermal differentiation network.[18]

To conclude, a high prevalence of vitamin D deficiency rickets has been observed in children with congenital ichthyosis. Children having a serum level of 25-hydroxyvitamin D ≤8 ng/ml and parathyroid hormone ≥75 pg/ml are predisposed to developing rickets. Vitamin D seems to be an effective form of therapy in congenital ichthyosis.

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