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REVIEW ARTICLE

Interventions for Prevention and Control of Epidemic of Vitamin D Deficiency

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Abstract

Vitamin D deficiency (VDD) remains a significant health challenge globally with its overwhelming effects on skeletal growth and varied associations with extra-skeletal diseases. The last decade has reported a high prevalence of VDD in all age-groups across all zones of India. Children and adolescents are most vulnerable to ill-effects of VDD as peak linear growth and bone mass accrual occurs during these years. Vitamin D deficiency in mothers predisposes their infants to have low serum vitamin D levels. Indians have increased susceptibility to develop VDD due to predominant vegetarian dietary habits, high melanin skin content, atmospheric pollution, modest tradition of clothing and limited availability of fortified foods. Vitamin D supplementation during infancy and childhood has emerged as an effective strategy to combat VDD. However, effects of vitamin D supplementation are transient and are not cost-effective as a maintenance strategy. Fortification of foodstuffs has been adopted by many developed countries globally which has emerged as a safe, efficacious and cost-effective strategy to control VDD. A strong political will and support is required to sustain food fortification in India. The current review focuses on strategies to prevent and control the epidemic of VDD in children.

Keywords Sunlight · Vitamin D supplementation · Fortification · 25(OH)D · India

Introduction

Vitamin D has a profound effect on growth and development during childhood and on adult bone health. Optimal calcium and vitamin D nutrition are essential for bone mineral health during childhood and peak bone accrual during puberty that safeguards against osteoporosis and susceptibility to fractures in old age. Role of vitamin D in extra-skeletal diseases like infection, cancers, cardiovascular diseases, diabetes mellitus and immunological disorders is being investigated. Recent meta-analysis report an association between serum 25(OH)D and systemic diseases though its role in causality and prevention is still contentious [1, 2].

With timely realization of adverse effects of vitamin D deficiency (VDD) on skeletal health and extra-skeletal illnesses, industrialized countries had undertaken fortification of milk and other food products with vitamin D several decades back. In contrast, food fortification with vitamin D was never considered a 'felt–need' in India due to adequate sunlight available throughout the year (8.4^0 and 37.6^0N latitude). Contrary to this assumption, high prevalence (70–98%) of hypovitaminosis has been reported throughout the country affecting all ages–pregnant women, newborns, children, adolescence, young men, women and elderly [3–6]. The findings of a review on the global vitamin D status by the International Osteoporosis Foundation in 2009 underscore the fact that South Asia including India may be one of the worst affected regions in the World [6]. The increased susceptibility to develop VDD among Indians is predominantly due to vegetarian dietary habits, limited sun-exposure, high melanin skin content, atmospheric pollution, modest tradition of clothing and limited availability of fortified foods. This gets compounded in the absence of fortification of foods with vitamin D and low dietary intake of calcium.

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At present, there is no consensus regarding the levels of serum 25 hydroxy vitamin D (25(OH)D) that would be sufficient for optimal bone health in our population. The expert committee convened by Institute of Medicine in 2011 reported no additional benefits on bone health with serum 25(OH)D levels of 30 ng/ml over 20 ng/ml as recommended by Endocrine Society Task Force [7]. The dose-response relationship between serum 25(OH)D and bone mineral parameters showed that 97.5% of population would have optimum bone health at serum 25(OH)D of >20 ng/ml [8]. The current global and Indian guidelines on prevention of nutritional rickets in children also support a cut-off of serum 25(OH)D > 20 ng/mL for sound skeletal health [9]. Thus, children with serum levels of 25(OH)D < 20 ng/mg are diagnosed as vitamin D deficient and < 12 ng/ml as severely deficient [9, 10]. The current review will discuss the strategies for prevention and control of VDD in India.

Vitamin D Prevention Strategies During Prenatal Period: Infant and Maternal Vitamin D Interdependence

The postulated mechanism of antenatal vitamin D supplementation on newborn's health is contentious. Antenatal vitamin D supplementation has shown to affect DNA methylation which affects cell migration/motility and cellular membrane function at birth and cadherin signaling and immune function during postpartum period thereby regulating collagen metabolic processes and regulation of apoptosis in animal models [11]. Indian studies have shown significant correlation between vitamin D status of pregnant and lactating mothers and their infants [12, 13]. A study on dyads of lactating mothers and their breast infants observed that infants born to mothers with <10 ng/ml of serum 25(OH)D had four times higher risk of developing moderate to severe hypovitaminosis D than those with serum 25(OH)D levels of >10 ng/ml [13]. Infants born to vitamin D deficient mothers were at a significantly higher risk of developing hypocalcemic seizures [14].

Effect of antenatal vitamin D supplementation on reduction in maternal and fetal adverse outcomes like osteomalacia, preeclampsia and frequent cesarian sections, pre-term birth, low birth weight, small for gestational age (SGA), poor fetal bone development, craniotabes, increased risk of respiratory infections, abnormal enamel formation and dental caries, rickets in utero and neonatal hypocalcemic seizures has generated significant research interest globally. There are several observational studies indicating either linear relationship or lack of association between maternal vitamin D and birth outcomes such as SGA and anthropometry [15–17]. The meta-analysis of observational studies confirmed the benefits of supplementing pregnant mothers with vitamin D in terms of SGA, low birth weight and preterm birth [18–21]. Similarly, several randomized control trials from US and India showed beneficial effects on maternal 25(OH)D levels, cord blood alkaline phosphatase and infants' anthropometry [22–24]. In contrast, few studies report neutral effects of vitamin D on long term neurodevelopmental outcomes [25] and bone mineral content of babies [26]. Therefore, as of current available evidence, antenatal vitamin D supplementation may be a safer and healthier option for both mothers and babies even if it may not have proven health benefits.

Prevention Strategies in Childhood

In view of high prevalence of VDD among all age groups in India [3, 4, 13], suitable interventions are urgently needed to combat the major public health problem of vitamin D deficiency. A multi-pronged approach with advocacy for regular sun exposure, consumption of foods rich in vitamin D, daily or monthly vitamin D supplementation and food fortification would be ideal.

Dietary Intake of Vitamin D

Foods such as cod liver oil, fatty fish, like tuna, mackerel, and salmon and egg yolk that are rich in vitamin D are not regularly consumed by Indians. Moreover, majority of Indians being vegetarians, contribution of Indian diets towards providing vitamin D is minimal. The only report evaluating daily intake of vitamin D through Indian diets in children (using US Department of Agriculture Provisional tables on vitamin D content in foods) observed a maximum daily intake of only 60–110 IU/d [3, 27]. Furthermore, poor intake of calcium through diet increases vitamin D requirements of Indian children predisposing them to VDD [28]. In view of the above observations and limited availability of fortified foods at present, a strategy which focuses on dietary interventions alone will be futile, unless mandatory fortification of foods is enforced. Mandatory fortification of staple foods can be the only effective dietary approach which is discussed below.

Sunlight

Solar ultraviolet irradiation of the skin is the main source of endogenous vitamin D synthesis. About 90% of vitamin D is produced in the skin through ultraviolet-B light (wavelength 290–310 nm) mediated activation of 7 dehydrocholesterol present in the epidermis of the skin into previtamin D3. Vitamin D synthesis in the skin is determined by the quantity and quality of UV-B radiation reaching the earth's surface which in turn is governed by solar Zenith angle, latitude, season, atmospheric pollution and ozone layer *etc*. Personal host factors like clothing, time spent outdoors, use of barriers like sunscreens and lifestyle factors also determine the rate of this conversion.

Though poor sun exposure is an important contributing factor towards VDD, information with regard to the best time of the day for sun exposure, percentage body surface area (BSA) exposure and duration of exposure required for adequate synthesis of vitamin D is limited for Fitzpatrick type 4 & 5 skin that has high melanin content. The recent studies [27, 29, 30] have made the following important observations: (a) *Timing*– The mean UVB index measured by a solar meter was highest between 11 am to 1 pm throughout the year in all 4 different zones of the country, an observation reiterated by Harinarayan et al. in their laboratory based study [31]. (b) *Season*– Minimal synthesis of vitamin D was observed in extreme winter months. UVB irradiation reaching earth's surface was maximum in summer followed by autumn and winter [30]. (c) *Body surface area*– Children exposed for 4 wk in summer with 30% exposure had significantly greater rise in serum 25(OH) D than those with 15% BSA exposure. Similar significant correlation between estimated BSA exposure and serum 25(OH)D was observed by authors in one of their earlier studies [27]. Another prospective study on 100 infants from Northern India recommended minimum 30 min weekly sunlight exposure, between 10 am and 3 pm over 40% body area (infant clothed in diapers, in prone position) for at least 16 wk to achieve serum 25(OH)D > 20 ng/ml [32]. Thus, the present data to recommend minimum sunlight exposure (BSA and duration) to prevent VDD is heterogenous and is variable with respect to environmental and seasonal factors. Sunlight exposure alone, therefore, may not be a reliable strategy to address VDD in India. In view of limited information, more studies are required to establish Minimal erythematous dose (MED), % BSA exposure, and time of exposure in different seasons to achieve normal serum 25(OH)D levels.

Vitamin D Supplementation

Vitamin D supplementation is an effective alternate strategy to achieve optimum serum 25(OH)D levels in view of minimal intake through diet and poor endogenous synthesis through exposure to sun. It has greater specificity of intervention and permits dose adjustment. There are only limited studies assessing the efficacy of vitamin D3 supplementation in children and adolescents [33–41]. Furthermore, there are even fewer studies assessing the adequacy and efficacy of different daily doses of vitamin D3 supplementation in vitamin D deficient children and adolescents [35, 36, 39]. Duration of available studies in children varied from 8wk [35, 39] to one year [41] with supplemental doses ranging from 200 IU/d to 1,00,000 IU [41] administered either daily [33, 37, 38], weekly [35, 40] or bimonthly [34, 41]. Supplementation with lower doses of 200–600 IU/d did not achieve vitamin D sufficiency in majority of VDD subjects. Indian studies with monthly supplementation of children with 60,000 IU of oral vitamin D has been shown to be an effective intervention to achieve serum 25(OH)D > 20 ng/ml [42, 43]. It is important to remember that conventional preparations of vitamin D3 are fat soluble and are required to be given with a carrier containing fat such as milk or oil *etc*. This was documented in the first Indian study evaluating effectiveness of monthly and bimonthly supplementation of 60,000 IU of cholecalciferol with water in school girls given for a period of one year. A minimal rise of only 7.6 ng/ml in serum 25(OH)D as against rise of 21.1 ng/ml [42] and 23.7 ng/ml [43] with a similar dose and duration of supplementation when given with milk was postulated to better vitamin D3 absorption when given with a carrier containing fat such as milk than when supplemented with water.

The type of vitamin D preparation used also determines the absorption as it may vary with different preparations. In recent years, nanotechnology based nano-emulsion formulation of vitamin D3 (d < 200 nm) have been shown to be superior to the conventional coarse emulsions (d > 200 nm) in terms of bioavailability and homogeneity using simulated gastrointestinal tract system and in-vivo studies in mice [44]. The first open-label non-randomized pilot study in 180 healthy vitamin D deficient children [43] followed by a randomized controlled trial in adults comparing the efficacy of a recently developed nano technology based micellized formulation (DePura) over conventional fat soluble vitamin D3(Calcirol) (under communication), observed a significantly greater rise in serum 25(OH)D levels in those who received miscellized vitamin D than those supplemented with conventional cholecalcirol granules with milk.

Daily supplementation may be carried out with either ergocalciferol (D2) or cholecalciferol (D3) preparations. However, if supplementation is to be carried out weekly, fortnightly or monthly, only D3 preparations are used because of its longer half life. The major drawback of advocating supplementation is that the intervention needs to be continued on a constant basis to maintain normal serum 25(OH)D levels, resulting in poor compliance. The International guidelines therefore recommend daily supplementation of 400 IU of vitamin D upto 12 mo of age [9] and calcium supplementation at 150–200 mg/kg/d in preterm babies and 200 mg/d in term babies to prevent nutritional rickets till one year [10]. The daily recommended allowance for vitamin D for children aged 1–18 y is 600 IU/d along with 600–800 mg/d of calcium [7, 9, 10]. A recent study evaluating the impact of supplementing 600, 1000 and 2000 IU/d of vitamin D for 6 mo in VDD prepubertal girls observed that dose of 1000 IU/d is required to achieve serum vitamin D levels of >20 ng/ml in 97% of VDD subjects. Whether RDA of 600 IU of vitamin D per day would suffice for VDD prepubertal Indian girls to achieve normal serum 25(OH)D levels remains debatable [45].

Vitamin D Fortification

Food fortification has emerged as one of the most effective, sustainable, scalable and affordable way to address different micronutrient deficiencies like iron, iodine, vitamin A and recently, vitamin D. Food fortification refers to adding small quantities of vital micronutrients to edible substances to meet the daily nutritional needs of the population. Food fortification can be classified as *a) Mass fortification* which is usually mandatory and fortification is undertaken in foods that are widely consumed by the general population. It is the best option when majority of the population has an unacceptable risk, in terms of public health, of becoming deficient in specific micronutrients. *b) Target fortification* which may be mandatory or voluntary and foods aimed at specific population subgroups are fortified *e.g.*, young children/ elderly, pregnant women. *c) Market-driven fortification* that allows food manufacturers to voluntarily fortify foods available in the market place. It is always voluntary, but governed by regulatory limits [46, 47].

A systematic review evaluating several randomized interventions with vitamin D fortification in community dwelling adults shows that 14 out of 15 studies revealed significant effects of fortified foods on serum 25(OH) D levels [48]. The recent studies by authors' evaluating the impact of vitamin D fortified milk supplement on vitamin D status of healthy school children aged 10–14 y, have shown this to be an effective strategy [49, 50]. The randomized controlled trial showed significant improvement in serum 25(OH)D levels in children who consumed milk fortified with 600 and 1000 IU every day for 12 wk. The mean increase in serum vitamin D levels were 11.45 ng/ml and 15.72 ng/ml respectively while the percentage of subjects who achieved more than 20 ng/ml increased from 4.9% to 70% and from 12% to 81% in both groups respectively. No change was observed in the control group.

Currently 14 countries have adopted mandatory vitamin D fortification of milk while 11 among them also fortify it with vitamin A [47]. The common food stuffs fortified with vitamin D in North America are milk, dairy products like cheese, yoghurts, breakfast cereals, soy milk and orange juice (not to exceed 20 IU vitamin D per 100 cal) [46]. In view of the Indian studies and available world literature documenting the safety and efficacy of vitamin D fortification of milk, Food Safety and Standards Authority of India issued a notification on 06th December 2016 calling for voluntary fortification of toned, double toned and skimmed milk with 550 IU of ergocalciferol per litre and vegetable oils with 4.4–6.4 IU (0.11–0.16μg) of vitamin D per gram of cooking oil [47]. It is proposed that this approach will ensure intake of atleast 1/3 rd of RDA of vitamin D, assuming 400–500 ml of milk is consumed on daily basis.

India is the world's largest producer of dairy products by volume, accounting for more than 13% of world's total milk production. The per capita consumption of drinking milk is approximately 250 ml/d and 355 of dairy produce are handled by the organized sector. In 2010, Indian Govt and National Dairy Development board had drawn up a National Daily Plan (NDP) that proposes to really double India's milk production and increase distribution through organized sector. In view of this, mandatory fortification of milk with vitamin D, if undertaken through organized sector, could benefit a large section of Indian population [47]. The cost-benefit analysis shows food fortification as a cost-effective measure in India, for *example* milk fortification with vitamin D costs only additional 2 paise per litre incurred as cost of vitamin D [47]. Thus milk fortification will clearly emerge as a sustainable, convenient and cost-effective measure to control VDD in childhood provided there is political will, sustained support of the food industry, education of masses towards healthy eating, monitoring and evaluation on regular basis and effective legislation to ensure good quality fortified foods at minimal cost.

Conclusions

Vitamin D deficiency has emerged as a considerable concern for general population and the health industry. The menace of VDD is growing rapidly, prompting for immediate stringent actions to control and prevent its epidemic. Dietary substitution, sunlight exposure, supplementation and voluntary fortification measures may not be effective individually due to various associated confounding factors in the Indian region. A multiprong approach, may, therefore be an ideal strategy to deal with this important public health issue till legislation for mandatory fortifications of commonly consumed foods with vitamin D is passed by the Government. Strong political advocacy, increased consumer awareness, maintenance of strict quality standards and use of technology and marketing are key interventions required for successful fortification programme in India.

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Compliance with Ethical Standards

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