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Systematic Review

Strategies to build stronger bones in Indian children: Challenges for implementation

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***Background & objectives*: Globally, vitamin D deficiency has been incriminated in poor bone health and growth retardation in children, impaired adult musculoskeletal health (classically described), increased risk of cardiovascular events, immune dysfunction, neurologic disorders, insulin resistance and its multiple sequelae, polycystic ovary syndrome (PCOS) and certain cancers. This review intends to holistically highlight the burden of vitamin D deficiency among children in India, the public health importance, and potential therapeutic and preventive options, utilizing the concept of implementation research.**

***Methods*: A systematic search was carried out on PubMed, Embase, China National Knowledge Infrastructure (CNKI) and Cochrane database, *clinicaltrials.gov*, Google Scholar, and *ctri.nic.in* with the keywords or MeSH terms namely 'vitamin D', 'cholecalciferol', 'ergocalciferol', 'children', connected with appropriate boolean operators.**

***Results*: Vitamin D deficiency/insufficiency prevalence varies from 70-90 per cent in Indian children. Rickets, stunting, impaired bone mineral health, and dental health are common problems in these children. Serum 25-hydroxy vitamin D (25(OH)D) should be maintained >20 ng/ml in children. Oral vitamin D supplementation has a high therapeutic window (1200-10,000 IU/d well tolerated). Fortification of grains, cereal, milk, bread, fruit juice, yogurt, and cheese with vitamin D has been tried in different countries across the globe. From Indian perspective, fortification of food items which is virtually used by everyone would be ideal like fortified milk or cooking oil. Fortification of "laddus" made from "Bengal gram" with vitamin D as a part of a mid-day meal programme for children can be an option.**

***Interpretation & conclusions*: There is enough evidence from India to suggest the importance and utility of food fortification with vitamin D to address the epidemic of vitamin D deficiency/insufficiency in children.**

Key words Children - fortification - osteomalacia - rickets - vitamin D

Vitamin D receptors are omnipresent in almost every human cell, highlighting this vitamin's ubiquitous role in maintaining homeostasis. Vitamin D is produced in the skin by exposure to solar ultraviolet B (UVB) radiation of a wavelength ranging from 290-320 nm. Exposure to sunlight is thus considered important for children, especially in tropical sunshine-rich countries such as India. However, lack of routine sun exposure due to our culturally sun-shy nature, indoor and sedentary lifestyles, increased skin pigmentation, and growing environmental pollution have contributed to highly prevalent vitamin D deficiency in growing peripubertal children in India. A systematic review[1] from Indonesia analyzing data from 5,870 children documented the prevalence of vitamin D deficiency (<50 nmol/l) to be 33 per cent. In another systematic review analyzing Asian data, >50 per cent of newborns were vitamin D deficient, underpinning prevalent maternal vitamin D deficiency[2].

The present study highlights the vitamin D deficiency burden among Indian children, underscores its public health importance, and potential therapeutic and preventive options. Further, it suggests practical solutions to handle this issue, which is critical for optimal musculoskeletal health in such children, focussing on the Indian perspective. The high prevalence of vitamin D deficiency in Indian children is well documented. Exposure to sunlight is not a pragmatic solution, since climatic conditions do not allow children across the country a 30 minute exposure to the UVB rays of the sun (ideally 10 AM and 3 PM) to allow enough cutaneous synthesis of vitamin D. Moreover, studies have shown insufficient amount of UVB rays reaching the skin due to environmental pollution that shows no signs of abating shortly.

Since around 25-30 per cent of total bone mass acquisition occurs during the peripubertal period, poor bone mass buildup during this critical phase leads to significantly low adult bone mass and a consequent increase in fracture risk due to fragility. Poor calcium, vitamin D and protein intake also contribute significantly to stunting in Indian children, as recorded in the latest National Family Health Survey (NFHS-5)[3]. In this context, it is to note that improvement in nutritional status has resulted in significant improvement in stunting in children in Japan, China and South Korea post second World War.

Methods

A systematic search was carried out on MEDLINE (PubMed) Embase, Cochrane and CKNI (China National Knowledge Infrastructure) databases using appropriate keywords or MeSH terms namely ‘vitamin D’, ‘cholecalciferol’, ‘ergocalciferol’, ‘children’ connected with appropriate boolean operators. A preliminary search was also done on *ctri.nic.in*, *clinicaltrials.gov*, and Google Scholar to ensure no relevant articles were missed. The search was restricted to English language literature for the papers published between January 1, 1922 and March 31, 2024. No ethical approval was required for this review based on secondary data comprising articles published in peer-reviewed journals. Only those studies which focussed on the different aspects of vitamin D metabolism in children were included for analysis. Studies focussing on data from India were given special emphasis. The flow of studies reviewed in this article has been elaborated in the Figure showing the systematic search sequence followed to select articles for inclusion for review.

Results

The initial search resulted in 15,532 articles (Figure); following the removal of duplicates (230 publications), the number was reduced to 15,302 publications. Following screening titles and abstracts, we further narrowed our focus to 2037 publications, which were evaluated in detail for potential inclusion in this review.

Indian children & vitamin D deficiency: In a study of apparently healthy 3127 school-going girls from New Delhi, the prevalence of vitamin D deficiency (25(OH) D<50 nmol/l) was 90.8 per cent[4]. Rana *et al*[5] recorded a high prevalence of vitamin D deficiency among Indian children based on the analyses of data from the Comprehensive National Nutrition Survey for 2016-2018. They documented Vitamin D deficiency, defined as a serum 25(OH)D <12 ng/ml (<30 nmol/l), in 14, 18, and 24 per cent of children aged 1-4, 5-9, and 10-19 yr, respectively[4]. Greater household income, urban residence, greater Body Mass Index (BMI), school attendance, winter sampling, less than 3 h of physical activity per week, female sex, and a vegetarian diet[5] were associated with vitamin D deficiency in children. In another study on 338 healthy children from India, vitamin D deficiency/insufficiency was documented in 65.8 per cent of children[6]. Studies from eastern India witnessed a similarly high prevalence of vitamin D deficiency/insufficiency (>70%)[7]. In Kangra and Kullu districts, Himachal Pradesh, the prevalence of vitamin D deficiency (<20 ng/ml; <50 nmol/l), through population-level screening in 1222 healthy children was noted to be 81 and 80 per cent, respectively[8]. Vitamin D deficiency, compounded by poor dietary calcium intake, is the major cause of rickets in children. The

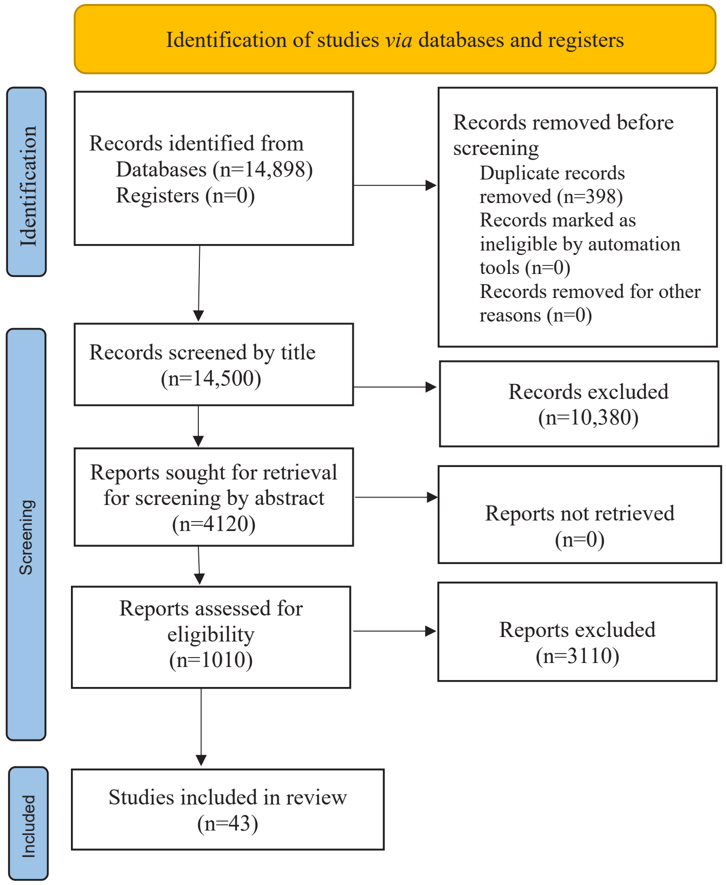

Figure. PRISMA flow diagram showing literature search.

Comprehensive National Nutrition Survey recorded that 40 per cent of school-aged children did not consume curd or milk at least once weekly and only six per cent of the children aged 6-23 months were on a minimum acceptable diet[9].

In a large multicentric study involving 2500 school children from six different States in India, the mean 25(OH)D was noted to be 45.8±23.9 nmol/l, with only 36.8 per cent of children having sufficient serum levels of 25(OH)D (>50 nmol/l)[10]. A study from Delhi identified atmospheric pollution as an independent risk factor for high vitamin D deficiency in infants, toddlers and children[11]. With an exponential increase in urbanization across the country, this problem is expected to worsen. The zenith angle of the sun and the latitudes also have a major role in determining the efficacy of sunlight in forming vitamin D in the exposed skin[12]. Although we are exposed to UVB rays at a favourable zenith angle owing to our proximity to the equator, not enough UVB rays reach the skin due to environmental pollution. Vitamin D deficiency is as prevalent in Swedish children as in their Indian counterparts, albeit for a different reason; the Swedish are at a latitudinal disadvantage, unlike us and get exposed to UVB rays at 30 degrees inclination, which is not ideal for cutaneous vitamin D synthesis[13]. Moreover, their exposure to sunlight is less compared to that of Indians. All these studies highlight the public health problem of vitamin D deficiency among children in India, contributing to poor bone health and stunting. A study even highlighted vitamin D deficiency in physicians in India, which was of an equally serious nature[14].

Vitamin D deficiency & bone health: In a systematic review[15], data analyses from 44,992 mother-offspring pairs revealed that vitamin D supplementation to mothers resulted in improved birth length and future growth in under-five children. Another systematic review[16] (7655 children from 7 studies) suggested vitamin D deficiency could lead to dental caries in children. Reportedly, vitamin D deficiency among children also indicated a 22 per cent higher risk of acquiring dental caries as compared to those without[17]. A study from Romania evaluating 688 children, revealed that each unit increase in 25(OH)D level significantly reduced the chances of middle third and distal third forearm fractures (OR 1.07 and 1.06, respectively)[18].

A recent systematic review[19] analyzing participant-level data from 120 studies with 5412 children underlined that keeping serum 25(OH)D levels to more than 28 nmol/l (11.2 ng/ml) would offer a protective effect against nutritional rickets for children taking adequate calcium.

Calcium supplementation, exercise & bone health: Apart from ensuring vitamin D sufficiency in children, ensuring adequate daily calcium intake is equally important for children to attain their optimal peak bone mass. In an Randomized Controlled Trial (RCT) from Switzerland, Bonjour *et al*[20] demonstrated that pre-pubertal girls on two food products containing 850 mg of calcium supplements daily for one yr had significantly higher bone mineral density at the radial and femoral bone ends and lumbar spine as compared to the girls receiving placebo. A study from a Canadian University in 1999 demonstrated 9 and 17 per cent greater total body bone mineral content (TB-BMC) for actively exercising boys and girls, respectively, compared to their inactive peers post one year age of peak bone mineral content velocity (PBMCV)[21].

Vitamin D deficiency & extra-skeletal impact: Gan *et al*[22] in their review, noted a significantly increased likelihood of children having a urinary infection when their serum 25(OH)D was <20 ng/ml[22]. Moreover, vitamin D deficiency in children has been associated with autoimmune disorders like inflammatory bowel disease (IBD)[23], immune dysfunction and increased risk of infection of the lower respiratory tract[24]. In a systematic review[24] analyzing data from 11 cross-sectional studies (22,196 children), Rouhani *et al*[25] underscored a 50 per cent significant reduction in odds of Metabolic Syndrome (MetS) in children to be associated with the highest vitamin D concentration compared to their counterparts having the lowest concentration of the vitamin. However, it was unclear from the study whether this was a true association or reverse causation.

Vitamin D supplementation & skeletal/extra-skeletal outcomes: In a cohort of 203 underprivileged children and youths with type-1 diabetes (T1DM) from Maharashtra, a western State of India, 200 ml of daily milk supplementation fortified with 1000 IU of vitamin D3 or a daily intake of 500 mg of calcium carbonate tablet along with 1000 IU of vitamin D3 for a year was associated with significantly higher whole body bone mineral content (BMC). The cortical thickness of bones, especially in girls, also increased compared to standard care of no supplementation[26]. In a systematic review[27] (1439 children from 11 studies; 86 per cent female; baseline 25(OH)D 36.3 nmol/l), vitamin D supplementation for a year was associated with an overall improvement in total hip areal bone mineral density (BMD).

Typically the estimated average requirement (EAR) is used to calculate the most likely requirement of a given population, however, the recommended daily allowance (RDA) is used to determine the estimated requirement for individuals at the highest end of the distribution. Hence EAR is always slightly lower than RDA[28]. Vitamin D supplementation (400 IU/day) is recommended during infancy as the RDA[29]. The RDA in older children and adolescents is 400-600 IU/day[29]. A RCT showed that the children with vitamin D deficiency benefited maximum from the daily supplementation of 2000 IU of vitamin D3[30], which was four to five times higher than the dose recommended by the Indian Council of Medical Research (ICMR), Indian Academy of Paediatrics (IAP) or Institute of Medicine (IOM, USA) and thus raised a question about such recommendations. The current guidelines suggest that serum 25(OH)D >20 ng/ml should be maintained in children, especially in high-risk conditions for vitamin deficiency, *i.e.*, chronic kidney or liver disease, and intake of anti-epileptic medications or steroids[29]. The role of vitamin D as a stand-alone supplement, without adequate calcium and protein intake, remains controversial.

Oral vitamin D supplementation has a high therapeutic window of safety in children. This is of vital importance if we are considering vitamin D fortification. A systematic review[31] based on analysis of 32 RCTs (8400 children; 0-6 yr) suggested that supplementing vitamin D daily in the range of 1200 to 10,000 IU was well tolerated without any side effects.

Hypervitaminosis D: Hypervitaminosis D and vitamin D intoxication is defined as serum 25(OH)D levels >100 ng/ml and >150 ng/ml, respectively[32]. Hypervitaminosis D has been seen primarily with parenteral supplementation of supraphysiologic doses of vitamin D[32]. In contrast with the recommended oral dose, unmonitored and prolonged supplementation with vitamin D with a non-standardized regimen mostly leads to hypervitaminosis D[31].

Evidence of the impact of vitamin D fortification: A recently published systematic review[33] suggests that adherence to vitamin D supplementation guidelines is challenging in children under five. This highlights the implementation challenges around vitamin D fortification to address the epidemic of vitamin D deficiency in children.

Vitamin D fortified fruit juice has been found to be effective in improving vitamin D deficiency in children with cerebral palsy when administered over four wk[34]. Serum 25(OH)D in these children improved from 54.1 to 110.3 nmol/l over four wk and was well tolerated without hypercalcemia[34]. In a systematic review evaluating the impact of food fortification with vitamin D on outcomes in children, the authors analyzed data from 20 different RCTs[35]. The fortification of grains, cereals, juices, milk, bread, cheese, and curd with vitamin D was compared with no fortification[36]; food fortification was associated with improvement in 25(OH)D levels by 15.51 nmol/l, with a mean increase of 3 nmol/l for every 100 IU of vitamin D[35]. In an RCT from the USA involving young children, 12 wk of daily consumption of orange juice providing 200 IU vitamin D and 12 IU vitamin E was effective in increasing 25(OH)D and α-tocopherol concentrations[36]. Consumption of fortified milk in Morocco was associated with improvement in circulating 25(OH)D levels in children during winters[37]. Iron and vitamin D status of healthy young European children[38] improved in an RCT through micronutrient-fortified young-child formula, and a systematic review[39] (5 RCTs, 792 children; 2-11 yr) showed improvement in circulating 25(OH)D levels with dairy products fortified with vitamin D; none experienced hypervitaminosis D or vitamin D intoxication.

Vitamin D fortification: Against the background of the high population prevalence of vitamin D deficiency, particularly in children, there is a strong case for food fortification with the vitamin in India. Fortification of commonly consumed staple foods with vitamin D could be most effective, as evidenced by data from the Western world[40,41]. Of note is a recent RCT conducted in New Delhi, where 200 ml milk was fortified with around 240 IU vitamin D2 (ergocalciferol) and supplemented for three months, along with adequate sunlight exposure during winter. However, this did not achieve the sufficient serum 25(OH)D levels particularly in children with vitamin D deficiency[42]. Ergocalciferol was used in this study instead of cholecalciferol as it has a plant-based origin, in contrast to the animal origin of cholecalciferol, which may be an issue with certain sections of the Indian population who are vegans/vegetarians, although cholecalciferol is known to produce better results in terms of serum 25(OH)D levels achieved. This study underpins the importance of using a higher dose of vitamin D (using cholecalciferol rather than ergocalciferol) to mitigate vitamin D deficiency in at-risk children. In a cohort of 290 healthy school girls from Delhi (93.7% having 25(OH)D<50 nmol/l), only 47 per cent were vitamin D sufficient at the end of one year of cholecalciferol supplementation at 60,000 IU monthly or two-monthly, which translated into 1000-2000 IU/day[43]. These studies highlight that if sufficient doses of vitamin D are not used, the supplementation/ fortification may not be effective.

Vitamin D fortified food for children - way forward: Energy and micronutrient-dense food is needed for children to meet their daily nutritional requirements[44]. Government programmes, especially midday meal programmes in schools, could serve as an indigenous means to provide them with food fortified with vitamin D and other micronutrients. Longer shelf life, ease of preparation and economic considerations will remain central while adopting such an approach. *Sattu*, a protein-rich Indian food, which is made from roasted flour of cereals and legumes would serve as an ideal candidate for vitamin D fortification from such perspectives[44]. Multicentric pilot studies targeting school-going children supplementing them with vitamin D fortified milk, milk products, or Bengal gram-based laddus, therefore, need to be undertaken urgently to decide upon India specific regimens under such initiatives.

Conclusions

Vitamin D deficiency is highly prevalent in Indian children. Exposure to sunlight is not a pragmatic solution, since climatic conditions do not allow children across the country a 30 minute exposure to the UVB rays of the sun between 10 AM and 3 PM to allow enough cutaneous synthesis of vitamin D. Moreover, studies have shown insufficient amounts of UVB rays reaching the skin due to environmental pollution that shows no signs of abating shortly. There is enough evidence from India to suggest the importance and utility of food fortification with vitamin D for addressing the epidemic of vitamin D deficiency in Indian children. The key would be to identify an ideal vehicle that, on fortification, will take care of the calcium, vitamin D and protein intake of growing children. The fortified food must have universal acceptance and should be made accessible to all children, ideally through programmes such as the midday meal scheme.

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