CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.7530368

Available online at: http://www.iajps.com *Review Article*

THE ROLE OF VITAMIN D SUPPLEMENTS IN BONE AND TEETH HEALTH AMONG CHILDREN: A SYSTEMATIC REVIEW

Dr.Faisal Ali alkhamisi,
Dr.faisalalkhamisi@gmail.com
Alhassan naif albarakaty,
Hsn@albarakati.net
Dr. Sarah talal musallem,
dr_sara_talal@hotmail.com
Raid hamid G almazrwai,
Xhero06@hotmail.com
SAAD ABDULLAH ALGHAMDI,
Have-moon2008@hotmail.com
SURRATI, AHMED WAFA ABDULAZIZ,
dr.ahmed.ws@gmail.com

Article Received: November 2022 **Accepted:** November 2022 **Published:** December 2022

Abstract:

Background: *In the literature, there are many studies that were conducted to assess the effect of vitamin D supplements on skeletal and non-skeletal functions however, most of these studies had focused on adult population with little is found among children and infant. Therefore, the aim of the current study was to systematically review the previous literature considering the role of vitamin D supplements in improving the bone and teeth health among children under the age of 18 years old.*

Methodology: *We searched Google Scholar, PubMed, The Cochrane Library, Web of Science databases using keywords related to vitamin D supplementation as "cholecalciferol" and "vitamin D supplement", to targeted population as "children", "infant", "school-aged" and "Pre-school age", to outcomes as "Rickets", "fracture", "serum vitamin D over 75 nmol/L", "dental caries", "bone health", and "Calcium content" and route of administration as "Oral", "Intramuscular (IM)" and "different concentration" and included all studies published between 2000 and 2022. Moreover, manual search through study identifiers or references from previous studies was conducted. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines*

Results: *The electronic search strategy conducted in this review ended in 875 hits which after removing of duplicated reduced to 360 studies. These 360 studies were considered eligible for further evaluation, from which 350 studies were excluded for different reasons as 245 studies based on title and abstract, 86 studies do not relevant to the subject of this study or sitting of this review, 17 consider replies of authors, 3 books, and 28 were reviews. At end, 10 articles were included in the qualitative synthesis of the present review*

Conclusion: *This systematic review has proven the importance of vitamin D supplements among children in improving their bone and teeth health and reducing the prevalence of rickets, fractures, teeth caries in children. More investigation of the possible mechanisms of these relations should be conducted.*

Corresponding author:
Dr.Faisal Ali alkhamisi,
Dr.faisalalkhamisi@gmail.com

Please cite this article in press Faisal Ali alkhamisi et al, ***The Role Of Vitamin D Supplements In Bone And Teeth Health Among Children: A Systematic Review.,*** *Indo Am. J. P. Sci, 2022; 09(12).*

INTRODUCTION:

Vitamin D is considered one of the essential vitamins for adequate growth of bone and development in children as well as for skeletal health in adults [1]. Vitamin D is associated with various biological functions that are related to is endocrine, autocrine, and paracrine activities [2]. Some of the reported functions of vitamin D include calcium regulation, metabolism of phosphate and their deposition in mineralized tissues [3,4]. Moreover, vitamin D is known for innating immune effectors [5], involvement in cognitive function, role in blood pressure maintenance and effects related to health outcomes as total mortality, aging and cardiometabolic conditions [6,7]. In general, functions of vitamin D are classified as skeletal related functions and non-skeletal functions [8,9]. There is a growing evidence suggesting that muscle strength and function are positively associated with status of vitamin D and they may optimized by vitamin D supplementation [10–12].

Rickets is considered rare in developed countries; however, it is considered one of the prevalent disorders in the developing countries. Many previous studies reported high prevalence of more subtle degrees of vitamin D insufficiency and deficiency in normal children and adolescents worldwide [13–15]. In general, having serum 25-hydroxy vitamin D [S-(25(OH)] levels lower than 30 nmol/l is considered sufficient for diagnosis with vitamin D deficient while 50 nmol/L is considered insufficient, and more than 75 nmol/L is suggested as optimal for health [16,17]. According to some epidemiological studies, insufficient levels of serum vitamin D are common among children and adolescents [18] particularly among those who are living in areas with less sunshine and in populations with protection against sun exposure or wit dark skin complexions [19,20].

In adolescents and children, there is an inverse relationship between serum vitamin D levels and PTH levels [14] and positive with bone mineral density [15]. Nutrition guidelines targeted to children and adolescents to optimize their bone health have focused on calcium intake and exercise with less interest in vitamin D supplements [13] because of the lack of evidence for the beneficial effect of supplementation in this age group. According to the scientific advisory committee on nutrition, the organization recommends that all individuals over the age of one years should take 400 IU of vitamin D3 supplement daily during the winter months [21] however, there is disagreement as to what the cut-offs should be [22].

In the literature, there are many studies that were conducted to assess the effect of vitamin D supplements on skeletal and non-skeletal functions however, most of these studies had focused on adult population [23–25] with little is found among children and infant. Therefore, the aim of the current study was to systematically review the previous literature considering the role of vitamin D supplements in improving the bone and teeth health among children under the age of 18 years old.

METHODOLOGY:

- **Search methods for identification of studies:**

We searched Google Scholar, PubMed, The Cochrane Library, Web of Science databases using keywords related to vitamin D supplementation as "cholecalciferol" and "vitamin D supplement", to targeted population as "children", "infant", "school-aged" and "Pre-school age", to outcomes as "Rickets", "fracture", "serum vitamin D over 75 nmol/L", "dental caries", "bone health", and "Calcium content" and route of administration as "Oral", "Intramuscular (IM)" and "different concentration" and included all studies published between 2000 and 2022. Moreover, manual search through study identifiers or references from previous studies was conducted. This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [26].

- **Eligibility criteria and study selection**

The studies were selected using the PRISMA flow diagram [12]. After removing duplicates, the titles and abstracts were screened to identify eligible studies for full-text review. Then, the authors surveyed the full text of the remaining studies based on inclusion and exclusion criteria and the eligible studies were identified. We excluded the articles which were topic to at least one of the following criteria:

- *Exclusion criteria:*
  - ✓ Unpublished studies
  - ✓ Non-original articles including reviews, protocols and editorials.
  - ✓ Animal studies
  - ✓ Adults' studies
  - ✓ Unsupported opinion of expert.
  - ✓ Clinical trials which were in progress without yet published results.
  - ✓ Replies to the author/editor.
  - ✓ Systematic reviews
  - ✓ Books'/conferences' abstracts.
  - ✓ Abstract papers, articles without obtainable full text
  - ✓ Published in any language other than English

- **Data analysis:**

In Several known database which was searched Ex: Google Scholar, PubMed, The Cochrane Library, Web of Science. We combined the search terms and limited the study to the English language. Depending on PRISMA checklist we removed duplicates, articles were screened based on title, abstract, and full text. We collected article information from each study, including the authors' details, study design, location, intervention, follow-up period, and study outcome.

RESULTS:

1. Study selection

The electronic search strategy conducted in this review ended in 875 hits which after removing of duplicated reduced to 360 studies. These 360 studies were considered eligible for further evaluation, from which 350 studies were excluded for different reasons as 216 studies based on title and abstract, 86 studies do not relevant to the subject of this study or sitting of this review, 17 consider replies of authors, 3 books, and 28 were reviews. At end, 10 articles were included in the qualitative synthesis of the present review (Figure 1).

2. General results:

In this review, we included 10 studies that had been conducted between 2000 and 2022. The studies included 1795 children with age between zero and 11 years old. Three studies were conducted in Canada [27–29], one study conducted in Egypt [30], one study in Louisiana [31], one study in Mongolia [32], one study in India [33], one study in Sweden [34], one study in Pakistan [35], and one study in New Zealand [36]. Four studies were case-control design [29–31,34] while two studies were randomized trial [28,33], two studies were survey depended studies [27,32], one study was prospective surveillance [36] and one study was cross-sectional study [35]. Moreover, five studies were conducted among normal health children [28,31,32,34,35], while three studies reported population of children diagnosed with rickets [27,33,36], and two studies were among fractured patients [29,30]. Three studies were interested in comparing the effect of using different doses and route of administration of vitamin D supplements on having normal concentration of serum vitamin D, while four studies aimed to assess the prevalence of children using vitamin D supplements among children diagnosed with rickets or fractures and two studies were conducted to assess the relation between vitamin D supplement and teeth health (Table 1,2).

Table 1: The general characteristics of the included study (N=10)

No.	Authors	Study design	Setting	Year of publication	Total number	Age
1	Ward L [27]	Survey based study	Canada	2007	104	0-7 Y
2	Ponnapakkam T [31]	Case-control study	Louisiana	2010	25	0-6 M
3	Uush T [32]	Survey based study	Mongolia	2013	524	6–59 M
4	Gallo S [28]	Randomized Controlled Trial	Canada	2013	132	1-2 M
5	Mondal K [33]	Randomized Controlled Trial	India	2014	71	0.5-5 Y
6	Wheeler B [36]	Prospective surveillance	New Zealand	2015	58	0.3-11 Y
7	El-Sakka A [30]	Case-control study	Egypt	2016	46	3-10 Y
8	Anderson L [29]	Case-control study	Canada	2017	549	< 6 Y
9	Gyll J [34]	Case-control study	Sweden	2018	206	8 Y
10	Nusrat Ali [35]	Cross sectional study	Pakistan	2017	80	2-8

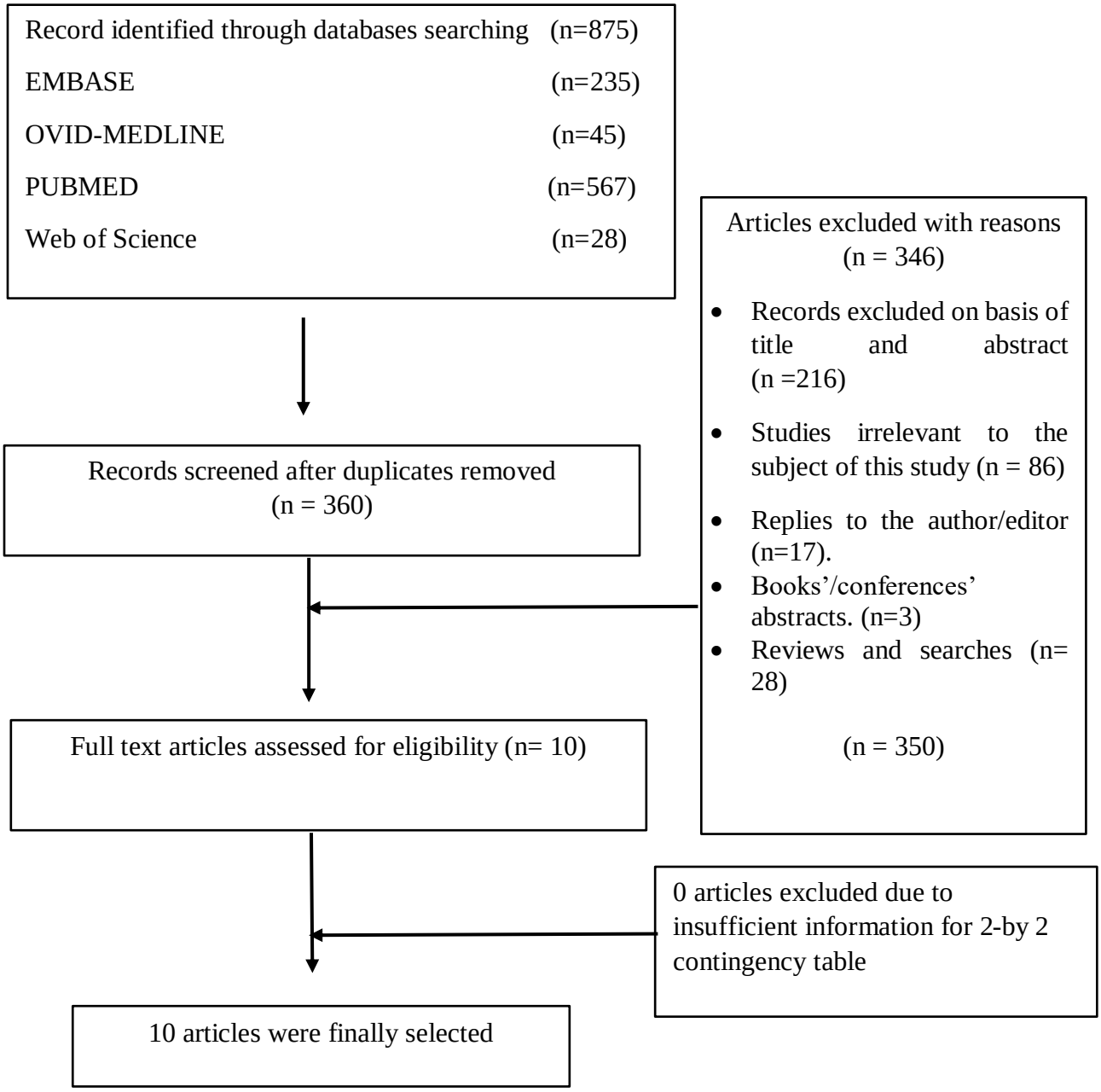

Figure 1The PRISMA figures showing the steps to choose the studies for systematic review.

3. The results of individual studies:

A. Impact of vitamin D supplements on improving serum vitamin D concentration over 75 nmol/L:

Ponnapakkam T et al., compared between vitamin D supplementation (at birth and after two months of birth) with placebo as control in southern Louisiana on the serum 25 OH D at birth, 2 months, 4 months, and 6 months. At 6 months, 62.5 % of children using vitamin D supplements at birth had serum 25 OH D over than 75 nmol/L (Low risk for rickets) compared with 77.78 % of children taken vitamin D supplements at 2 months of birth and 87.5 % of control groups (Placebo group). In general, Ponnapakkam et al, found no evidence that vitamin D supplementation reduced rickets risk [31]. In comparison between different doses of vitamin D supplements, Gallo S et al., compared between four doses of vitamin D supplements (400 IU/day, 800 IU/day, 1200 IU/day, and 1600 IU/day) with main outcome of having plasma 25(OH)D concentration of 75 nmol/L or greater in 97.5% of infants at 3 months. By 3 months of the study, 55 % of

infants in the 400 IU/day group achieved a 25(OH)D concentration of more than 75 nmol/L in comparison with 81 % in the 800 IU/day group, 92 % in the 1200 IU/day and 100 % in the 1600 IU/day. At 12 months, the concentration of 25 (OH) D was not sustained over 75 nmol/L in 97.5 % of the infants in any of the groups. Therefore, Gallo S et al showed that among health breasted infants, only vitamin D supplement dosage of 1600 IU/day was associated with increasing of the plasma 25 (OH) D concentration to 75 nmol/L in 97.5 % of the infants at 3 months [28]. Mondal et al, compared between two administration routes of vitamin D (oral dose, and intramuscular) among pediatric patients with rickets. The authors reported that there is no difference between the two administration routes on biochemical and radiological parameters. Seventy percent of the IM group had developed Serum concentration of 25 (OH) D over 75 nmol/L compared with 22.9 % in oral group. Moreover, both routes are equally effective and safe in treatment of nutritional rickets [33].

Table 2: The relation between administration of vitamin D supplement and outcomes

No.	Authors	Condition of the cases	Intervention	Outcomes	Results
1	Ward L [27]	Patients with rickets	No intervention	Rickets	14 patients were diagnosed with rickets and received vit D supplement (13 %)
2	Ponnapakkam T [31]	Breast-fed infants	I1: 200 IU vitamin D per day starting at birth I2: 200 IU vitamin D per day starting at 2 months of age C: Placebo	Having 25-Hydroxy Vitamin D > 75 nmol/L (at 6 months)	62.5 % of I1 group achieved the outcome compared with 77.78 % of I2 group and 87.5 % of control.
3	Uush T [32]	Normal children	I1: vitamin D supplement C: no intervention	Developing rickets	18.8 % of children at I1 group developed rickets compared with 23.1 % of the control group
4	Gallo S [28]	Breast-fed infants	I1: Different four doses of Vit D supplement	Having 25-Hydroxy Vitamin D > 75 nmol/L (at 3month)	55 % of infants in the 400 IU/day group achieved a 25(OH)D concentration of more than 75 nmol/L in comparison with 81 % in the 800 IU/day group, 92 % in the 1200 IU/day and 100 % in the 1600 IU/day.
5	Mondal K [33]	Patients with rickets	I1: IM vitamin D I2: Oral vitamin D	Having 25-Hydroxy Vitamin D > 75 nmol/L (at 3month)	70.9 % of I1 group reached the outcomes compared with 22.9 %
6	Wheeler B [36]	Patients with rickets	No intervention	Rickets	5 patients were diagnosed with rickets and received vit D supplement (8.6 %)
7	El-Sakka A [30]	Children with fractures	I1: children with fracture C: No fracture	Receiving vitamin D supplement	47.8 % of both intervention and control groups were received vitamin D supplement
8	Anderson L [29]	Children with fractures	I1: children with fracture C: No fracture	Receiving vitamin D supplement	16 % of the intervention group had received vitamin D compared with 31 % of control group
9	Gyll J [34]	Normal children	Vitamin D intervention	Developing caries	There is weak inverse association between vitamin D status at 6 years of age and caries 2 years later
10	Nusrat Ali [35]	Normal children	Vitamin D intervention	Developing caries	There is association between Vitamin D levels in children and early childhood caries

B. The role of vitamin D supplements in preventing developing of rickets:

Considering the relation between administration of vitamin D supplements and reducing the risk of rickets, Uush T et al, reported that 18.8 % of normal children (6-59 months) who depending on vitamin D supplements developed rickets compared with 23.1 % of those who did not receive any type of vitamin D supplements. Therefore, the study showed that there is no significant difference between two groups in developing rickets [32]. Moreover, both of Ward L et al and Wheeler B et al reported that 13 % and 8.6 % of children (0-11 years) who were diagnosed with rickets had been received vitamin D supplements before diagnosis [27,36]. Using the pooled results of the three studies [27,32,36], the prevalence of rickets among children using vitamin D supplement was 28.2 % compared with 44.2 % of those did not receive any type of vitamin D. Vitamin D supplement was found to reduce the risk for developing rickets by the half (RR:0.497, 95 % CI: 0.331: 0.728, P=0.0003).

C. The role of vitamin D supplements in reducing the prevalence of fractures:

Considering the relation between vitamin D supplements and fracture rate among children, two studies conducted by Anderson L et al, and El-Sakka A et al [29,30] investigated this relation. Anderson L et al showed that the prevalence of using of vitamin D supplements among children with fractures was significantly lower than that reported among control groups (16 % vs 31%) [29] while El- Sakka et al did not reported this difference between cases and control where 47.8 % of both groups had adequate vitamin D administration [30]. Using pooled results of both studies showed that using of vitamin D supplements reduce the risk of fracture in children by the half (RR: 0.49, 95 % CI: 0.33, 0.74, P=0.0006) where 18 % of those having fracture were found to have vitamin D supplement compared with 31.7 % among those did not have any fractures.

D. The role of vitamin D supplements in improving teeth health:

Among 206 children, Gyll J et al reported that using of vitamin D supplements in children at age of six year was associated with reducing the prevalence of children with low serum vitamin D levels from 28 % at baseline to 11 % after intervention. Gyll et al showed that there is weak significant inverse association between vitamin D status at 6 years of age and caries 2 years later (odds ratio 0.96; $p = 0.024$). Moreover, Vitamin D status at 6 years of age was unrelated to enamel defects but was positively associated with saliva LL37 levels [34]. Ali N et al, reported that there is a significant correlation between vitamin D levels in children and early childhood caries. Having serum 25 (OH) D lower than 75 nmol/L is associated significantly with total decayed, missing, filled primary teeth caries score. Vitamin D supplement was associated with improved serum concentration of 25 (OH) D and improved teeth health [35].

DISCUSSION:

In the current systematic review, it was reported that administration of vitamin D supplements among children under the age of 11 years old was associated with lower risk for rickets and fractures as well as better results considering oral health. The positive role of vitamin D supplements in reducing fractures and improvement of rickets was extensively discussed among adult population [37–39], however, little is known about children and adolescent population. The role of vitamin D in reducing rickets could be due its close correlation between lean mass, bone mass and muscle mass with serum 25 (OH) D [40,41]. In this review, we found that only vitamin D supplements with dose over 1600 IU /day was associated with increasing the serum concentration of more than 75 nmol/L in 97 % of the children. However, high concentrations of vitamin D supplements in younger children were found to be associated with increased risk for hypercalcemia [42,43]. However, in a recent systematic review conducted among 32 randomized clinical trials with 8400 unique participants, the authors found that there is no increased in the overall serious adverse effects of using high- doses of vitamin D and there is no increased risk for hypercalcemia [44]. The authors reported that vitamin D supplementation in the dose ranges of 1200 to 10 000 IU/d and bolus doses to 600 000 IU to young children may be well tolerated [44].

Moreover, previous studies showed that severe chronic vitamin D deficiency (having serum concentration of 25 (58) D of lower than 12 nmol/L) leads to overt skeletal abnormalities in children with is typically known as rickets [45,46]. According to many previous studies, vitamin D deficiency and low vitamin D reserve among children was significantly correlated with classical signs of rickets [47,48]. Many studies conducted in different regions showed high vitamin D deficiency and insufficiency were found in children and mothers as those conducted in Iran [49–51], China [52], Egypt [53], India [54], Turkey [55], and Pakistan [56]. These studies showed that there is a need to find and regulate the use of medications that are associated with increasing the serum concentration of 25 (OH) D in children in order to reduce the impact of

Vitamin D insufficiency among children on their health.

Regular examination of vitamin D levels in children is important in order to early diagnosis of vitamin D insufficiency and starting treatment. Vitamin D affects many important hormones and proteins in the body of the children and thus is associated with many functions however, in the current study, we focused on the skeletal functions of the vitamin D supplement in children.

This systematic review had some limitations. One of these limitations is the lack of studies that conducted in Saudi Arabia however the extensive search over the literature review where most of the studies in Saudi Arabia focused on knowledge, and prevalence of use. Moreover, small size of the studies was another limitation of this systematic review however, this is because the little studies published among the targeted population in the targeted duration.

In conclusion, this systematic review has proven the importance of vitamin D supplements among children in improving their bone and teeth health and reducing the prevalence of rickets, fractures, teeth caries in children. More investigation of the possible mechanisms of these relations should be conducted.

REFERENCES:

1. World Health Organization, Food and Agriculture Organization of the United Nations. Human Vitamin and Mineral Requirements. *Hum Vitam Miner Requir*. Published online 2001:303. http://www.fao.org/3/y2809e/y2809e.pdf
2. Reichrath J, Saternus R, Vogt T. Challenge and perspective: the relevance of ultraviolet (UV) radiation and the vitamin D endocrine system (VDES) for psoriasis and other inflammatory skin diseases. *Photochem Photobiol Sci*. 2017;16(3):433-444. doi:10.1039/C6PP00280C
3. Svensson D, Nebel D, Nilsson B-O. Vitamin D3 modulates the innate immune response through regulation of the hCAP-18/LL-37 gene expression and cytokine production. *Inflamm Res*. 2016;65(1):25-32. doi:10.1007/s00011-015-0884-z
4. Davideau JL, Lezot F, Kato S, Bailleul-Forestier I, Berdal A. Dental alveolar bone defects related to Vitamin D and calcium status. *J Steroid Biochem Mol Biol*. 2004;89-90:615-618. doi:10.1016/j.jsbmb.2004.03.117
5. Raftery T, Martineau AR, Greiller CL, et al. Effects of vitamin D supplementation on intestinal permeability, cathelicidin and disease markers in Crohn's disease: Results from a randomised double-blind placebo-controlled study. *United Eur Gastroenterol J*. 2015;3(3):294-302. doi:10.1177/2050640615572176
6. Skaaby T, Husemoen LLN, Pisinger C, et al. Vitamin D status and incident cardiovascular disease and all-cause mortality: a general population study. *Endocrine*. 2013;43(3):618-625. doi:10.1007/s12020-012-9805-x
7. Abhimanyu A, Coussens AK. The role of UV radiation and vitamin D in the seasonality and outcomes of infectious disease. *Photochem Photobiol Sci*. 2017;16(3):314-338. doi:10.1039/C6PP00355A
8. White Z, White S, Dalvie T, Kruger MC, Van Zyl A, Becker P. Bone health, body composition, and vitamin D status of black preadolescent children in South Africa. *Nutrients*. 2019;11(6):1-12. doi:10.3390/nu11061243
9. Ong YL, Quah PL, Tint MT, Aris IM, Wei L. Europe PMC Funders Group The association of maternal vitamin D status with infant birth outcomes , postnatal growth and adiposity in the first two years of life in a multi-ethnic Asian population : the GUSTO cohort study. *Br J Nutr*. 2016;116(4):621-631. doi:10.1017/S0007114516000623.The
10. Al-Jwadi RF, Jespersen E, Dalgård C, Bilenberg N, Christesen HT. S-25OHD Is Associated With Hand Grip Strength and Myopathy at 5 Years in Girls: An Odense Child Cohort Study. *J Clin Endocrinol Metab*. 2018;103(7):2630-2639. doi:10.1210/jc.2018-00281
11. Minshull C, Biant LC, Ralston SH, Gleeson N. A Systematic Review of the Role of Vitamin D on Neuromuscular Remodelling Following Exercise and Injury. *Calcif Tissue Int*. 2016;98(5):426-437. doi:10.1007/s00223-015-0099-x
12. Tomlinson PB, Joseph C, Angioi M. Effects of vitamin D supplementation on upper and lower body muscle strength levels in healthy individuals. A systematic review with meta-analysis. *J Sci Med Sport*. 2015;18(5):575-580. doi:10.1016/j.jsams.2014.07.022
13. El-Hajj Fuleihan G, Nabulsi M, Tamim H, et al. Effect of Vitamin D Replacement on Musculoskeletal Parameters in School Children: A Randomized Controlled Trial. *J Clin Endocrinol Metab*. 2006;91(2):405-412. doi:10.1210/jc.2005-1436
14. Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of Vitamin D Deficiency Among Healthy Adolescents. *Arch Pediatr Adolesc Med*. 2004;158(6):531.

doi:10.1001/archpedi.158.6.531
15. Lehtonen-Veromaa MK, Möttönen TT, Nuotio IO, Irjala KM, Leino AE, Viikari JS. Vitamin D and attainment of peak bone mass among peripubertal Finnish girls: a 3-y prospective study. *Am J Clin Nutr*. 2002;76(6):1446-1453. doi:10.1093/ajcn/76.6.1446
16. Greer FR. 25-Hydroxyvitamin D: functional outcomes in infants and young children. *Am J Clin Nutr*. 2008;88(2):529S-533S. doi:10.1093/ajcn/88.2.529S
17. Vieth R. Why the minimum desirable serum 25-hydroxyvitamin D level should be 75 nmol/L (30 ng/ml). *Best Pract Res Clin Endocrinol Metab*. 2011;25(4):681-691. doi:10.1016/j.beem.2011.06.009
18. Prentice A, Goldberg GR, Schoenmakers I. Vitamin D across the lifecycle: physiology and biomarkers. *Am J Clin Nutr*. 2008;88(2):500S-506S. doi:10.1093/ajcn/88.2.500S
19. Clemens TL, Henderson SL, Adams JS, Holick MF. INCREASED SKIN PIGMENT REDUCES THE CAPACITY OF SKIN TO SYNTHESISE VITAMIN D3. *Lancet*. 1982;319(8263):74-76. doi:10.1016/S0140-6736(82)90214-8
20. Öhlund I, Silfverdal S-A, Hernell O, Lind T. Serum 25-Hydroxyvitamin D Levels in Preschool-Age Children in Northern Sweden Are Inadequate After Summer and Diminish Further During Winter. *J Pediatr Gastroenterol Nutr*. 2013;56(5):551-555. doi:10.1097/MPG.0b013e3182838e5b
21. Glatt DU, McSorley E, Pourshahidi LK, et al. Vitamin D Status and Health Outcomes in School Children in Northern Ireland: Year One Results from the D-VinCHI Study. *Nutrients*. 2022;14(4):804. doi:10.3390/nu14040804
22. Amrein K, Scherkl M, Hoffmann M, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. *Eur J Clin Nutr*. 2020;74(11):1498-1513. doi:10.1038/s41430-020-0558-y
23. Yao P, Bennett D, Mafham M, et al. Vitamin D and Calcium for the Prevention of Fracture. *JAMA Netw Open*. 2019;2(12):e1917789. doi:10.1001/jamanetworkopen.2019.17789
24. Kong SH, Jang HN, Kim JH, Kim SW, Shin CS. Effect of Vitamin D Supplementation on Risk of Fractures and Falls According to Dosage and Interval: A Meta-Analysis. *Endocrinol Metab*. 2022;37(2):344-358. doi:10.3803/EnM.2021.1374
25. LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults. *N Engl J Med*. 2022;387(4):299-309. doi:10.1056/NEJMoa2202106
26. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med*. 2009;6(7):e1000097. doi:10.1371/journal.pmed.1000097
27. Ward LM, Gaboury I, Ladhani M, MD SZ. Vitamin D–deficiency rickets among children in Canada. *Can Med Assoc or its Licens*. 2007;177(5):8.
28. Gallo S, Comeau K, Vanstone C, et al. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: A randomized trial. *Jama*. 2013;309(17):1785-1792. doi:10.1001/jama.2013.3404
29. Anderson LN, Heong SW, Chen Y, et al. Vitamin D and Fracture Risk in Early Childhood: A Case-Control Study. *Am J Epidemiol*. 2017;185(12):1255-1262. doi:10.1093/aje/kww204
30. El-Sakka A, Penon C, Hegazy A, Elbatrawy S, Gobashy A, Moreira A. Evaluating Bone Health in Egyptian Children with Forearm Fractures: A Case Control Study. *Int J Pediatr*. 2016;2016:1-6. doi:10.1155/2016/7297092
31. Ponnapakkam T, Bradford E, Gensure R. A treatment trial of vitamin d supplementation in breast-fed infants: Universal supplementation is not necessary for rickets preventio in southern louisiana. *Clin Pediatr (Phila)*. 2010;49(11):1053-1060. doi:10.1177/0009922810376320
32. Uush T. Prevalence of classic signs and symptoms of rickets and vitamin D deficiency in Mongolian children and women. *J Steroid Biochem Mol Biol*. 2013;136(1):207-210. doi:10.1016/j.jsbmb.2012.10.014
33. Mondal K, Seth A, Marwaha RK, et al. A randomized controlled trial on safety and efficacy of single intramuscular versus staggered oral dose of 600 000IU Vitamin D in treatment of nutritional rickets. *J Trop Pediatr*. 2014;60(3):203-210. doi:10.1093/tropej/fmt105
34. Gyll J, Ridell K, Öhlund I, Karlsland Åkeson P, Johansson I, Lif Holgerson P. Vitamin D status and dental caries in healthy Swedish children. *Nutr J*. 2018;17(1):11. doi:10.1186/s12937-018-0318-1
35. Vitamin OA, Childhood E, Original C, et al. Impact of vitamin D on development of early childhood caries. *Pak Armed Forces Med J*. 2017;67(25):429-433.
36. Wheeler BJ, Dickson NP, Houghton LA, Ward

LM, Taylor BJ. Incidence and characteristics of Vitamin D deficiency rickets in New Zealand children: A New Zealand Paediatric Surveillance Unit study. *Aust N Z J Public Health*. 2015;39(4):380-383. doi:10.1111/1753-6405.12390

37. Hill TR, Aspray TJ. The role of vitamin D in maintaining bone health in older people. *Ther Adv Musculoskelet Dis*. 2017;9(4):89-95. doi:10.1177/1759720X17692502
38. Laird E, Ward M, McSorley E, Strain JJ, Wallace J. Vitamin D and Bone Health; Potential Mechanisms. *Nutrients*. 2010;2(7):693-724. doi:10.3390/nu2070693
39. Sunyecz J. The use of calcium and vitamin D in the management of osteoporosis. *Ther Clin Risk Manag*. 2008;Volume 4:827-836. doi:10.2147/TCRM.S3552
40. Schoenau E, Neu CM, Beck B, Manz F, Rauch F. Bone Mineral Content per Muscle Cross-Sectional Area as an Index of the Functional Muscle-Bone Unit. *J Bone Miner Res*. 2002;17(6):1095-1101. doi:10.1359/jbmr.2002.17.6.1095
41. Arabi A, Tamim H, Nabulsi M, et al. Sex differences in the effect of body-composition variables on bone mass in healthy children and adolescents. *Am J Clin Nutr*. 2004;80(5):1428-1435. doi:10.1093/ajcn/80.5.1428
42. Ross AC, Taylor CL, Yaktine AL, Valle HB Del. *DIETARY REFERENCE INTAKES (Calcium, Vitamin D)*. National Academy Press; 2011. https://www.ncbi.nlm.nih.gov/books/NBK56070/pdf/Bookshelf_NBK56070.pdf
43. Vogiatzi MG, Jacobson-Dickman E, DeBoer MD. Vitamin D Supplementation and Risk of Toxicity in Pediatrics: A Review of Current Literature. *J Clin Endocrinol Metab*. 2014;99(4):1132-1141. doi:10.1210/jc.2013-3655
44. Brustad N, Yousef S, Stokholm J, Bønnelykke K, Bisgaard H, Chawes BL. Safety of High-Dose Vitamin D Supplementation Among Children Aged 0 to 6 Years. *JAMA Netw Open*. 2022;5(4):e227410. doi:10.1001/jamanetworkopen.2022.7410
45. MARKESTAD T, HALVORSEN S, HALVORSEN KS, AKSNES L, AARSKOG D. Plasma Concentrations of Vitamin D Metabolites before and during Treatment of Vitamin D Deficiency Rickets in Children. *Acta Paediatr*. 1984;73(2):225-231. doi:10.1111/j.1651-2227.1984.tb09933.x
46. Holick MF. Resurrection of vitamin D deficiency and rickets. *J Clin Invest*. 2006;116(8):2062-2072. doi:10.1172/JCI29449
47. Ganmaa D, Holick MF, Rich-Edwards JW, et al. Vitamin D deficiency in reproductive age Mongolian women: A cross sectional study. *J Steroid Biochem Mol Biol*. 2014;139:1-6. doi:10.1016/j.jsbmb.2013.09.011
48. Uush T. Prevalence of classic signs and symptoms of rickets and vitamin D deficiency in Mongolian children and women. *J Steroid Biochem Mol Biol*. 2013;136:207-210. doi:10.1016/j.jsbmb.2012.10.014
49. Salek M, Hashemipour M, Aminorroaya A, et al. Vitamin D Deficiency among Pregnant Women and Their Newborns in Isfahan, Iran. *Exp Clin Endocrinol Diabetes*. 2008;116(06):352-356. doi:10.1055/s-2008-1042403
50. Bassir M, Laborie S, Lapillonne A, Claris O, Chappuis MC, Salle BL. Vitamin D deficiency in Iranian mothers and their neonates: a pilot study. *Acta Paediatr*. 2001;90(5):577-579. http://www.ncbi.nlm.nih.gov/pubmed/11430721
51. Kazemi A, Sharifi F, Jafari N, Mousavinasab N. High Prevalence of Vitamin D Deficiency among Pregnant Women and their Newborns in an Iranian Population. *J Women's Heal*. 2009;18(6):835-839. doi:10.1089/jwh.2008.0954
52. STRAND MA, PERRY J, JIN M, et al. Diagnosis of rickets and reassessment of prevalence among rural children in northern China. *Pediatr Int*. 2007;49(2):202-209. doi:10.1111/j.1442-200X.2007.02343.x
53. Lawson DE, Cole TJ, Salem SI, et al. Etiology of rickets in Egyptian children. *Hum Nutr Clin Nutr*. 1987;41(3):199-208. http://www.ncbi.nlm.nih.gov/pubmed/3610666
54. Sachan A, Gupta R, Das V, Agarwal A, Awasthi PK, Bhatia V. High prevalence of vitamin D deficiency among pregnant women and their newborns in northern India. *Am J Clin Nutr*. 2005;81(5):1060-1064. doi:10.1093/ajcn/81.5.1060
55. Ozkan B, Doneray H, Karacan M, et al. Prevalence of vitamin D deficiency rickets in the eastern part of Turkey. *Eur J Pediatr*. 2009;168(1):95-100. doi:10.1007/s00431-008-0821-z
56. Zuberi LM, Habib A, Haque N, Jabbar A. Vitamin D Deficiency in ambulatory patients. *J Pak Med Assoc*. 2008;58(9):482-484. http://www.ncbi.nlm.nih.gov/pubmed/18846794