Review Article

Skeletal and Extra-Ekeletal Effects of Vitamin D Deficiency in Children

*Begum S[1], Biswash DC[2]

Abstract

Vitamin D is essential for the maintenance of calcium and phosphorus homeostasis. It has skeletal growth and extra-skeletal effects in our body. Objective of this article is to update the information on skeletal and extra-skeletal effects of vitamin D deficiency in paediatric clinical disorders. In the paediatric population, vitamin D deficiency is associated with different clinical diseases such as rickets, insulin resistance, metabolic syndrome, respiratory tract infections, asthma, and autoimmune diseases. It is associated with prematurity, obesity, malabsorption, anticonvulsant agents, extreme latitudes, low consumption, and little sun exposure. The recommendation is to prevent vitamin D deficiency and to maintain 25(OH) D serum levels >30ng/mL (>75 nmol/L).

Keywords: *Vitamin D, Vitamin-D deficiency, Extra-skeletal manifestation.*

INTRODUCTION

Vitamin D (VD) is a pro-hormone that is essential for absorption of calcium and phosphorus. Vitamin D deficiency (VDD) is associated with rickets in growing children and osteomalacia in adolescent. VD has role in skeletal health, apart from this it causes inhibition of cellular proliferation, angiogenesis and renin production, stimulating insulin production, and macrophage cathelicidin production.[1] There is high prevalence of VDD among children which is about 85% to 98%.[2]

CLASSIFICATION OF VITAMIN D DEFICIENCY

Optimum level of 25(OH) D is >30ng/ml (>75nmol/L) and hypercalcaemia is associated if the level is >150ng/mL (> 374nmol/L).[3]

Table I: Classification of VDD [3]

Vitamin D status	ng/mL	nmol/L
Severe deficient	<5	<12.5
Deficient	<20	<50
Insufficient	20-30	50-75
Sufficient	>30	>75
Risk of Toxicity	100	250
Intoxication	>150	>374

Table II: Etiology of vitamin D Deficiency[4]

Decreased VD synthesis	Skin pigmentation, physical agents blocking ultraviolet ray exposure, clothing, latitude, season, air pollution, cloud cover, altitude, sedentary lifestyle and winter season
Decreased intake of VD	Strict vegetarian, high phytates diet
Age and physiology related	Prematurity, elderly, obese
Decreased maternal VD stores	Exclusive breast feeding
Mal-absorption	Celiac disease, pancreatic insufficiency, biliary obstruction
Decreased synthesis	Chronic liver disease
Increased degradation of 25 (OH) D	Drugs: rifampicin, isoniazid, anticonvulsants, glucocorticoids.

1. *Prof. Dr. Suraiya Begum, Professor and Chairman, Department of Paediatrics, Head of the Paediatric Endocrinology Division, Bangabandhu Sheikh Mujib Medical University (BSMMU), E-mail: suraiyadr07@yahoo.com, Phone: 01715131535
2. Dr. Dhiraj Chandra Biswash, Assistant Registrar, 300 bed hospital, Kanpur, Narayanganj

*For Correcpondence

VD levels are low in breast milk which is 22IU/L (15 -80IU/L) in vitamin D sufficient mother.[5] VDD is associated with cardiovascular disease, hypertension, autoimmune diseases, and cancer.[6,7,8,9] The reasons of VDD in this subcontinent could be low dietary VD intake, high fiber and phytate intake, reduced exposure of skin to sun light because of cultural and traditional habits or pollution.[10,11,12] Individuals with darker skin require a

longer time in the sunlight than those with lighter skin to produce the same amount of VD.[13] Sunscreens reduces the ability of the skin to produce vitamin D by over 95% to 98%.[14] Vitamin contents of food vary depending on cooking methods, fried fish loses 50% of VD.[4]

VD has effect related to: 1) Nuclear and cytosolic characteristics of VD receptor (VDR) and the enzyme that metabolizes VD in multiple tissues e.g., adipose tissue, muscle, and pancreas. 2) Regulation of more than 200 genes. 3) The risk associated with VDD, and the presence of multiple diseases.[15,16,17] Over 30 different types of tissues have been identified as having cells with a VDR.[18] Neonate has 60--70% of maternal VD levels. In case of maternal deficiency, the neonate's low reserves of VD can cause hypo-calcemic symptoms in the first six months of infant.[19]

In countries where foods are not fortified, available option is to intake of fatty fish, which provides 5-13μg of VD/three ounces of fish, egg yolk contains 0.5 μg of VD and three ounces of beef liver contains 0.3μg of VD. It would be difficult to obtain the necessary 25μg of VD through these sources.[20] When fortified foods are not available and exposure to sunlight is limited, supplementation is the only measure for attaining adequate VD status.[21]

MANIFESTATIONS OF VITAMIN D DEFICIENCY

Musculo-skeletal manifestation: VDD is associated with nutritional rickets and osteomalacia which is characterized by bone deformations, hypocalcemic seizures, tetany, severe bone pain, muscle weakness and short stature.[22] At infancy and adolescent there are increased growth velocity, the increased demand for calcium, and the children may present with hypocalcemia even before radiologic signs of rickets are observed.[23] Severe vitamin VDD is associated with cardiomyopathy related to hypocalcemia.[24]

Obesity: VD sequestration occurs in adipose tissue because of its lipid-soluble nature.[25] The active form of VD regulates gene transcription in adipogenesis, inflammation, and insulin resistance in the adipose tissue.[26] In muscle and pancreas, 1,25(OH)2D may improve insulin sensitivity, controlling insulin secretion in pancreatic beta cells and increasing insulin receptor expression in peripheral tissues.[4] Higher circulating 25(OH)D3 level was associated with low body fat, and lower number of metabolic disturbances.[27]

Insulin Resistance: There is reverse association between vitamin D and insulin resistance and VD supplementation reduces the risk for type 1 diabetes.[28]

Metabolic syndrome: Low VD levels in adolescents were strongly associated with metabolic syndrome, regardless of adiposity.[29] There is reduction in low density lipoproteins cholesterol (LDL-C) following VD supplementation.[30] There is increased risk of hypertension with VDD.[31]

Intestinal malabsorption syndromes: VDD in malabsorption syndromes due to reduced absorption of lipid soluble vitamins, and hyperparathyroidism secondary to hypocalcemia. This leads to a greater 25(OH) D conversion into 1,25 (OH)2D and lower 25(OH)D levels.[32] The prevalence of VDD in Cystic fibrosis is 95%.[33]

Anticonvulsant agents: Prevalence of VDD is 50% in children with epilepsy receiving anticonvulsant agents such as phenytoin, phenobarbital, and carbamazepine. These drugs inducing the activity of cytochrome- P450-hydroxylase enzymes, thus leading to an accelerated VD catabolism.[34]

Respiratory tract infections: There is increased risk for wheezing in children of women who had VDD during pregnancy.[35] Cord blood VDD is associated with respiratory syncytial virus bronchiolitis.[36] VD reduces the risk for influenza and achieve an adequate vaccine response because it activates T cells.[37] There is an association between VDD and asthma severity and significant reduction of asthma exacerbation with VD supplementation.[38]

Cardiovascular diseases: Low VD are associated with secondary elevation of parathyroid hormone, increased arterial resistance, and endothelial dysfunction leading to hypertension.[39] VD acts as a cardiovascular and renal protective factor by suppressing the renin-angiotensin-aldosterone system, which inhibits vascular calcification and plaque formation, and has anti-inflammatory and immunomodulatory actions.[40]

Diabetes mellitus: VD supplementation was associated with significant reduction in the progression of diabetes and higher reversal to normoglycemia. It acts on

pancreatic β-cells by binding VDR to produce insulin synthesis and on the muscle and fat cells to reduce insulin resistance.[41]

Muscle Strength: VDD causes muscle weakness and repeated fall. Infants and children with severe VDD and rickets may present with delayed motor development, muscle hypotonia, and weakness.[42]

Immune Effects: VD binds to VDR on various cells and modulate activation and deactivation of the innate and adaptive responses. VD modulates B-lymphocyte and T-lymphocyte function.[43] VDD is associated with autoimmune diseases such as type 1 diabetes and multiple sclerosis.[44,45] Protective effects of VD supplementation have been demonstrated against rheumatoid arthritis and inflammatory bowel disease.[46,47] VD supplementation showed a positive impact on autoimmunity by significantly reducing the fall in thyroid peroxidase antibody in autoimmune thyroiditis.[48]

Infectious Disorders: VD supplementation modulates T-cell function in human immunodeficiency virus (HIV) infected patients, and a useful adjunct to antiretroviral therapy.[49] VDD was associated with increased susceptibility of sepsis.[50] Systematic review was indicated that low vitamin D status might be associated with an increased risk of COVID-19 infection.[51]

Cancer: The biologically active form of VD can modulate gene expression, inhibit the cellular proliferation, induction of differentiation, and apoptosis ultimately inhibiting the cell growth of cancer. An increased incidence of VDD was observed in children suffering from cancer as compared to the control.[52] VD supplementations reduced total cancer mortality.[53]

Sleep and Pain: VD plays an important role in sleep and pain. Supplementation of VD with chronic pain improved the pain score, sleep latency, sleep duration and body pain.[54]

Skin: Keratinocytes express the VDR, and when these cells are exposed to VD, their growth is inhibited and they are stimulated to differentiate. This has led to the use of topical VD analog to treat psoriasis.[55]

Psychiatric Conditions: VDD has been linked to an increased incidence of schizophrenia, bipolar disorder and depression.[56,57] Maintaining VD sufficiency in utero and during early life is important for VD receptor transcriptional activity in the brain, brain development and maintenance of mental function later in life.[58]

Other effects: In VDD, menarche is started 9 months earlier.[59] It was found that the BMI, body fat, and testosterone were higher in polycystic ovarian syndrome with VDD. VD supplementation has provided improvement of hyperinsulinism, fertility and hyperandrogenism in PCOS.[60]

Table III: Screening of vitamin D deficiency [3]

i.	Dark skinned infants who live at higher altitude and infants born to VDD mothers
ii.	Nonspecific symptoms like poor growth, gross motor developmental delay
iii.	Suspected rickets, osteoporosis
iv.	Chronic kidney disease
v.	Hepatic failure
vi.	Malabsorption syndromes: Cystic fibrosis, Inflammatory bowel disease
vii.	Hyperparathyroidism
viii.	Medications: Anticonvulsants, Glucocorticoids, AIDS medications, Ketoconazole
ix.	Obese children and adults
x.	Granuloma forming disorders: Sarcoidosis, Tuberculosis, Histoplasmosis
xi.	Children with non-traumatic fall

TREATMENT

As per the Endocrine Society Clinical Practice Guideline, infants require 400IU/d, children ≥1 year require 600IU/d, adults between 19–70 years require 600IU/d, and elders ≥70 years of age require at least 800IU/d of VD to maximize bone health and muscle function.[4]

VD therapy is necessary for infants and children who manifest clinical features of hypocalcemia due to VDD or rickets and when VD levels are in the deficient range even if asymptomatic. [4]

Table IV: Prevention and treatment of VDD Indian Academy of Pediatrics guideline.[61]

Age	Prevention	Treatment	Treatment with large dose (oral route preferred)
Premature baby	400IU/day	1000IU/day	NA
Neonates	400IU/day	2000IU/day	NA
1-12 months	400IU/day	2000IU/day	60,000IU weekly (> 3 months of age)
1-18 years	600IU/Day	3000-6000 IU/day	60000IU weekly
At risk groups	400-1000IU/day	As per age group	As per age group

Treatment should be continued for a minimum of 3 months, after that daily maintenance doses to be given.

Table V: Recommendations for VD supplementation in different diseases in the pediatric age group

Diseases	Recommendation
Obesity	1200-2000IU/day[62]
Insulin resistance	4000IU/day for 6 months to obese children and adolescents with VDD[63]
Type 1 diabetes	2000IU/day[64]
Cystic fibrosis	Children <1 year old: 400-800IU/day; if VDD: 800IU to 2000IU/day Children 1-10 years old: 800-1000IU/day; if VDD up to 4000IU/day[65]
Celiac disease	400-600IU/day[66]
Asthma	500-1200IU/day[67]
Neurological diseases	800-1000IU/day[68]

Lactating women given 4000IU of vitamin D3 per day were able to transfer enough vitamin D3 into their milk to satisfy an infant's requirement.[69]

The following recommendations have been made to prevent VDD in the pediatric population:[70]

- Adequate sun exposure to the face, hands or legs (at least 3 times a week for 15 minutes).In extreme latitudes and during the winter, ensure an adequate consumption of food sources.
- For infants, administer VD3 at 400 IU/day until 1 year old –due to the low VD content in breast milk.
- Prevent overweight and obesity.
- Assess VD status who are at risk for deficiency and administer according to recommendations.

Calcium supplementation: In VDD, 50-75mg/kg calcium supplementation are important for avoiding subsequent hypocalcaemia from an increase bone mineralization as PTH levels normalize due to hungry bone syndrome. The maximal dose of elemental calcium that should be taken at a time is 500mg.[71]

CONCLUSIONS

VDD is associated with different clinical diseases such as bone alterations, insulin resistance, metabolic syndrome, respiratory tract infections, asthma, and autoimmune diseases. It is associated with prematurity, obesity, malabsorption, use of anticonvulsant agents, and lifestyle characteristics, such as clothing, extreme latitudes, low consumption, and little sun exposure. Inadequate vitamin D levels may be responsible for the progression of cardiovascular disorders, diabetes mellitus, autoimmune disorders, sleep disturbance and pain to a considerable extent. Therefore, awareness is needed to combat the increasing prevalence of VDD through all age groups. Screening and treatment strategies are required for VDD. Adequate intake of VD through supplementation is essential for daily requirement as VDD has impact on various comorbidities.

Undiagnosed VDD is not uncommon. It is very difficult to obtain that much vitamin D3 on a daily basis from dietary sources. Thus, sensible sun exposure and the use of supplements are needed to fulfill the body's VD requirement.

CONFLICT OF INTEREST: The authors declare that there is no conflict of interest.

REFERENCES

1. Hilger J, Friedel A, Herr R, Rausch T, Roos F, Wahl DA, et al. A systematic review of vitamin D status in populations worldwide. Br J Nut. 2014; 111:23-45.
2. Garg MK, Marwaha RK, Khadgawat R, Ramot R, Obroi AK, Mehan N, et al. Efficacy of Vitamin D loading doses on serum 25-hydroxy Vitamin D levels in school going adolescents: An open label non-randomized prospective trial. J Pediatr Endocrinol Metab. 2013; 26:515–23.
3. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An Endocrine Society clinical practice guideline. J Clin Endocrin Metab. 2011; 96:1911-30.
4. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M. Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management. Review of current knowledge and Recommendations. Pediatrics. 2008; 122; 398-417.
5. Leerbeck E, Sondergard H. The total amount of VD in human milk and cow`s milk. Br.J.Nutr. 1980; 44(1):7-12.
6. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in The Third Health and Nutrition Examination Survey. Atherosclerosis. 2008; 205(1):255-60.
7. Wang TJ, Pencina MJ, Booth SL, Jacques PF, Ingelsson E, Lanier K, et al. Vitamin D deficiency and risk of cardiovascular disease. Circulation. 2008; 117:503-11.
8. Cantorna MT. Vitamin D and its role in immunology: multiple sclerosis and inflammatory bowel disease. Prog Biophys Mol Biol 2006; 92(1):60-4.
9. Garland CF, Garland FC, Gorham ED, Lipkin M, Newmark H. The role of vitamin D in cancer prevention. Am J Public Health 2006; 96(2):252-61.
10. Khadilkar AV. Vitamin D deficiency in Indian Adolescents. Indian Paediatr. 2010; 47:756-7.
11. Ekbote VH, Khadilkar AV, Mughal MZ, Hanumante N, Sanwalka N, Khadilkar VV, et al. Sunlight exposure and development of rickets in Indian toddlers. Indian J Pediatr. 2010; 77:61-5.
12. Agarwal KS, Mughal MZ, Upadhyay P, Berry JL, Mawer EB, Puliyel JM et al. The impact of atmospheric pollution on vitamin D statusof infants and toddlers in Delhi, India. Arch Dis Child 2002; 87:111-3.
13. Dawson-Hughes B. Racial/ethnic considerations in making recommendations for vitamin D for adult and elderly men and women. Am J Clin Nutr. 2004; 80:176S176S.
14. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune disease, cancers, and cardiovascular disease. Am J Clin Nutr 2004a; 80:1678-88.
15. Maestro B, Molero S, Bajo S, et al. Transcriptional activation of the human insulin receptor gene by 1,25-dihydroxyvitamin D(3).Cell Biochem Funct. 2002; 20(3):22.
16. Carlberg C, Molnár F. Vitamin D receptor signaling and its therapeutic implications: Genome-wide and structural view. Can J Physiol Pharmacol. 2015; 93(5):311-8.
17. Autier P, Boniol M, Pizot C, Mullie P. Vitamin D status and ill health: a systematic review. Lancet Diabetes Endocrinol, 2014; 2(1):76-89.
18. Norman AW. Mini review: Vitamin D receptor: new assignments for an already busy receptor. Endocrinology, 2006; 147(12):5542-8.
19. Balasubramanian S, Ganesh R. Vitamin D deficiency in exclusively breast fed infants. Indian J Med Res. 2008; 127:250-5.
20. U.S. Department of Agriculture/Agricultural Research Service (USDA/ARS). 2005. USDA National Nutrient Database for Standard Reference, Release 18. USDA/ARS, Washington D.C.
21. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. J Nutr. 2005; 135:310-6.

22. Bhattoa HP, Konstantynowicz J, Laszcz N, Wojcik M, Pludowski P. Vitamin D: musculoskeletal health. Rev Endocr Metab Disord. 2017; 18(3):363–71.

23. Ladhani S, Srinivasan L, Buchanan C, Allgrove J. Presentation of vitamin D deficiency. Arch Dis Child. 2004; 89(8):781–4.

24. Uysal S, Kalayci AG, Baysal K. Cardiac functions in children with vitamin D deficiency rickets. Pediatr Cardiol. 1999; 20(4): 283–6.

25. Brinkmann K, Le Roy C, Iñiguez G, Borzutzky A. Deficiencia severa de vitamina D en niños de Punta Arenas, Chile: influencia de estado nutricional en la respuesta a suplementación. Rev Chil Pediatr. 2015; 86(3):182-8.

26. Ding C, Wilding JPH, Bing C. 1,25-dihydroxyvitamin D3 protects against macrophage-induced activation of NFκB and MAPK signalling and chemokine release in human adipocytes. PLoS One. 2013; 8(4):e61707.

27. Beydoun MA, Boueiz A, Shroff MR, Beydoun HA, Wang Y, Zonderman AB. Associations among 25-hydroxyvitamin D, diet quality, and metabolic disturbance differ by adiposity in adults in the United States. J Clin Endocrinol Metab. 2010; 95: 3814-27.

28. Liu C, Lu M, Xia X, Wang J, Wan Y, He L, Li M. Correlation of serum vitamin D level with type 1 diabetes mellitus in children: a metaanalysis. Nutr Hosp. 2015; 32(4):1591-4.

29. Reis JP, von Mühlen D, Miller ER, 3rd, Michos ED, Appel LJ. Vitamin D status and cardiometabolic risk factors in the United States adolescent population. Pediatrics. 2009; 24(3):e371-9.

30. Hirschler V, Molinari C, Maccallini G, Sanchez M, Gonzalez C, On Behalf Of San Antonio de Los Cobres Study Group Collaborators Graciela Colque, et al. Status of Dyslipidemia in Vitamin D Supplemented Argentinean Indigenous Children Versus A Non-supplemented Mixed Population Group. Cardiovasc Hematol Agents Med Chem. 2015; 13(2):129-36.

31. Forman JP, Curhan GC, Taylor EM. Plasma 25-hydroxyvitamin D levels and risk of hypertension among young women. Hypertension. 2008; 52:828-32

32. Margulies SL, Kurian D, Elliott MS, Han Z. Vitamin Ddeficiency in patients with intestinal malabsorption syndromes--think in and outside the gut. J Dig Dis. 2015; 16(11):617-33.

33. Norton L, Page S, Sheehan M, Mazurak V, Brunet-Wood K, Larsen B. Prevalence of inadequate vitamin D status and associated factors in children with cystic fibrosis. Nutr Clin Pract. 2015; 30(1):111-6.

34. Le Roy OC, Rebollo GM, Moraga FM, Diaz X, Castillo-Duran C. Nutrición del Niño con Enfermedades Neurológicas Prevalentes. Rev Chil Pediatr. 2010; 81(2):103-13.

35. Camargo CA Jr, Rifas-Shiman SL, Litonjua AA, Rich-Edwards JW, Weiss ST, Gold DR, et al. Maternal intake of vitamin D during pregnancy and risk of recurrent wheeze in children at 3 y of age. Am J Clin Nutr. 2007; 85:788-95.

36. Belderbos ME, Houben ML, Wilbrink B, Lentjes B, Bleomen Em, Kimpen Jl, et al. Cord blood vitamin D deficiency is associated with respiratory syncytial virus bronchiolitis. Pediatrics. 2011; 127(6):e1513-20.

37. Rashima M, Segawa T, Okazaki M, Kurihara M, Wada Y, Ida H. Randomized trial of vitamin D supplementation to prevent seasonal influenza A in schoolchildren. Am J Clin Nutr. 2010; 91(5):1255-60.

38. Kerley CP, Hutchinson K, Cormican L, Faul J, Greally P, Coghlan D, et al. Vitamin D3 for uncontrolled childhood asthma: A pilot study. Pediatr Allergy Immunol. 2016; 27(4):404-12.

39. Ullah MI, Uwaifo GI, Nicholas WC, Coch CA. Does Vitamin D Deficiency Cause Hypertension? Current Evidence from Clinical Studies and Potential Mechanisms. Int J Endocrinol 2010; 579-640.

40. Li YC, Qiao G, Uskokovic M, Xiang W, Zheng W, Kong J. Vitamin D: a negative endocrine regulator of the renin–angiotensin system and blood pressure. J Steroid Biochem Mol Biol. 2004; 89:387–92.

41. Hollick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest.2006;116:2062-2072

42. Thomson RL, Spedding S, Buckley JD. Vitamin D in the aetiology and management of polycystic ovary syndrome. Clin Endocrinol (Oxf). 2012; 77:343-50.

43. Bhalla AK, Amento EP, Clemens TL, Holick MF, Krane SM. Specific high-affinity receptors for 1,25-dihydroxyvitamin D3 in human peripheral

blood mononuclear cells: presence in monocytes and induction in T lymphocytes following activation. J Clin Endocrinol Metab. 1983; 57(6):1308 –10.

44. Staples JA, Ponsonby AL, Lim LL, McMichael AJ. Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: latitude, regional ultraviolet radiation, and disease prevalence. Environ Health Perspect. 2003; 111(4):518 –23.

45. McMichael AJ, Hall AJ. Does immunosuppressive ultraviolet radiation explain the latitude gradient for multiple sclerosis? Epidemiology. 1997; 8(6):642– 5.

46. Kostoglou-Athanassiou I, Athanassiou P, Lyraki A, Antoniadis C. Vitamin D and rheumatoid arthritis. Ther Adv Endocrinol Metab. 2012; 3:181-7.

47. Cantorna MT, Munsick C, Bemiss C, Mahon BD. 1,25- Dihydroxycholecalciferol prevents and ameliorates symptoms of experimental murine inflammatory bowel disease. J Nutr. 2000; 130(11):2648 –52.

48. Chaudhary S, Dutta D, Kumar M, Saha S, Mondal SA, Kumar A, et al. Vitamin D supplementation reduces thyroid peroxidase antibody levels in patients with autoimmune thyroid disease: an open-labeled randomized controlled trial. Indian J Endocrinol Metab 2016; 20:391-8.

49. Lachmann R, Bevan MA, Kim S, Patel N, Hawrylowicz C, Vyakarnam A, et al. A comparative phase 1 clinical trial to identify anti-infective mechanisms of vitamin D in people with HIV infection. AIDS 2015; 29:1127-35.

50. Upala S, Sanguankeo A, Permpalung N. Significant association between vitamin D deficiency and sepsis: a systematic review and meta-analysis. BMC Anesthesiol. 2015; 4:15-84.

51. Liu N, Sun J, Wang X, Zhang T, Zhao M, Li H. Low vitamin D deficiency is associated with coronavirus disease 2019 outcomes: a systematic review and meta-analysis. international Journal of Infectious Diseases 2021; 104:58-54.

52. Mohan R, Mohan G, Scott JX, Rajendran A, Paramasivam V, Ravindran M. Vitamin D insufficiency among children with cancer in India. Indian J Med Paediatr Oncol.2016; 37(1):14-9.

53. Keum N, Giovannucci E. Vitamin D supplements and cancer incidence and mortality: a meta-analysis. Br J Cancer. 2014; 111:976-80. .

54. Huang W, Shah S, Long Q, Crankshaw AK, Tangpricha V. Improvement of pain, sleep, and quality of life in chronic pain patients with vitamin D supplementation. Clin J Pain. 2013; 29:341–7.

55. Smith EL, Pincus SH, Donovan L, Holick MF. A novel approach for the evaluation and treatment of psoriasis: oral or topical use of 1,25-dihydroxyvitamin D3 can be a safe and effective therapy for psoriasis. J Am Acad Dermatol. 1988; 19(3):516 –28.

56. McGrath J, Saari K, Hakko H, Jokelainen J, Jones P, Järvelin MR. Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. Schizophr Res. 2004; 67(2–3):237–45.

57. Hare EH, Price JS. Mental disorder and season of birth: comparison of psychoses with neurosis. Br J Psychiatry. 1969; 115(522):533–40.

58. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. Trends Endocrinol Metab. 2002; 13(3):100 –5.

59. Villamor E, Marin C, Mora-Plazas M, Baylin A. Vitamin D deficiency and age at menarche: a prospective study. Am J Clin Nutr, 2011; 94(4): 1020-5.

60. Shah P. Polycustic ovarian Syndrome and its Association with Vitamin D. Ann. Med Medical Res. 2018; 1:1008.

61. Khadilkar A, Khadilkar V, Chinnappa J, Rathi N, Khadgawat R, Balasubramanian S, et al. Indian Academy of Pediatrics 'Guideline for Vitamin D and Calcium in Children' Committee. Prevention and Treatment of Vitamin D and Calcium Deficiency in Children and Adolescents: Indian Academy of Pediatrics (IAP) Guidelines. Indian Pediatr. 2017; 54:567-73.

62. Płudowski P, Karczmarewicz E, Bayer M, Carter G, Chlebna-Sokół D, Czech-Kowalska J, et al. Practical guidelines for the supplementation of vitamin D and the treatment of deficits in Central Europe-recommended vitamin D intakes in the general population and groups at risk of vitamin D deficiency. Endokrynol Pol. 2013; 64(4):319-27.

63. Belenchia AM, Tosh AK, Hillman LS, Peterson CA. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. Am J Clin Nutr. 2013; 97(4):774-81.

64. Caruso R, Pallone F, Stasi E, Romeo S, Monteleone G. Appropriate nutrient supplementation in celiac disease. Ann Med. 2013; 45(8): 522-31.

65. Tangpricha V, Kelly A, Stephenson A, Maguiness K, Enders J, Robinson KA, et al. An update on the screening, diagnosis, management, and treatment of vitamin D deficiency in individuals with cystic fibrosis: evidence-based recommendations from the Cystic Fibrosis Foundation. J Clin Endocrinol Metab. 2012; 97(4):1082-93.

66. Capriles VD, Martini LA, Arêas JAG. Metabolic osteopathy in celiac disease: importance of a gluten-free diet. Nutr Rev. 2009; 67(10):599-606.

67. Tachimoto H, Mezawa H, Segawa T, Akiyama N, Ida H, Urashima M. Improved control of childhood asthma with low-dose, short-term vitamin D supplementation: a randomized, double-blind, placebocontrolled trial. Allergy 2016; 71(7):1001-9.

68. Le Roy OC, Rebollo GM, Moraga FM, ximenadíaz SM, CASTILLO-DURÁN C. Nutrición del Niño con Enfermedades Neurológicas Prevalentes. Rev Chil Pediatr. 2010; 81(2):103-13.

69. Hollis BW, Wagner CL. Vitamin D requirements during lactation: high-dose maternal supplementation as therapy to prevent hypovitaminosis D for both the mother and the nursing infant. Am J Clin Nutr. 2004; 80(6):1752S-1758S.

70. Cediel G, Pacheco-Acosta J, Castillo-Durán C. Vitamin D deficiency in pediatric clinical practice. Arch Argent Pediatr. 2018; 116(1): e75-e81.

71. Balasubramanian S, Dhanalakshmi K, Amperayani S. Vitamin D deficiency in childhood—A review of current guidelines on diagnosis and management. Indian Pediatr. 2013; 50:669-75.