What relation of vitamin D levels and disease in children aged 0 to 12 years

Abstract Fat-soluble vitamin D is involved in many of the body's physiological functions. A large number of studies have shown that vitamin D deficiency is common worldwide and is particularly prevalent among children. Vitamin D deficiency affects children's bone health, leads to growth retardation, and has potential negative effects on the respiratory tract, nervous system, and autoimmune system. This article introduces diseases related to vitamin D deficiency in children aged 0 to 12 years, as well as its prevention and treatment. It aims to reduce the rate of vitamin D deficiency in children and enhance the importance of public and medical staff in timely supplementation of vitamin D and other healthy behaviors to recognize and promote the healthy growth of children.

Keywords: Children, vitamin D, growth and development , research progress

Introduction

Vitamin D is fat-soluble. In addition to participating in calcium and phosphorus metabolism and maintaining bone health, it also plays an important role in the growth, differentiation, and immune regulation of different tissue cells. Sources of vitamin D include endogenous (mainly sun exposure; 7-dehydrocholesterol stored in the basal layer of the skin is converted to vitamin D3 after ultraviolet radiation) and exogenous (vitamin D preparations and dietary supplements). Sunlight is the main source, accounting for about 90% [1].

Vitamin D is an important nutrient in the growth and development of children. At the peak of growth and development, the demand for vitamin D is relatively high. However, the Chinese people have insufficient knowledge of vitamin D and cannot provide reasonable dietary nutrition and vitamin D supplementation. At the same time, children's many schoolwork and outdoor activities are reduced, resulting in insufficient or absent vitamin D content in children, which increases the risk of disease [2]. This article provides a brief review of diseases caused by vitamin D deficiency in children 0 to 12 years and research on their treatment and prevention to

enhance the public and medical staff's knowledge of vitamin D and promote the healthy growth of children.

1. Current status of serum vitamin D levels in children

Vitamin D nutritional status has attracted much attention in China and the world. Serum 25-(OH) D3 level is the best indicator to evaluate vitamin D nutritional status and the basis for early diagnosis of vitamin D deficiency. However, the normal level of serum 25-(OH)D3 in children is still controversial. Currently, most diagnostic criteria are defined by the American Academy of Pediatrics: children's serum 25-(OH)D3 concentration >50.0 nmol/L is appropriate, 37.5 to 50.0 nmol/L is insufficient, ≤37.5 nmol/L is vitamin D deficient, and ≤12.5 nmol/L is severely deficient [3].

Relevant studies[4,5] have shown that vitamin D deficiency or insufficiency is widespread in the global population, and vitamin D deficiency is more common in Asia. Zhao Xin and colleagues conducted a survey on the status of vitamin D among children of 1 to 3 years in Wuxi in 2015; They found widespread vitamin D deficiency in infants and young children in this city, where the prevalence of vitamin D insufficiency is roughly 16.1% and the severity of vitamin D deficiency is positively correlated with age [6]. This is consistent with the trend of decreasing children's vitamin D levels with increasing age in the literature [7,8]. In recent years, lack of vitamin D in China has had large regional differences, generally related to factors such as regional living standards, latitude, and longitude. Research has shown that vitamin D deficiency affects about 10% to 40% of infants in southern China and 30% to 70% of infants in northern China[9]. This may be related to the relatively low production of vitamin D due to the lack of ultraviolet exposure due to the high northern latitudes and relatively few hours of sunlight.

2. The significance of vitamin D supplementation in children

2.1 The impact of vitamin D deficiency on bones

Vitamin D plays a key role in calcium and phosphorus metabolism. Less than 10% of calcium is absorbed. Without vitamin D, the risk of poor bone health in children is reflected in increased odds of rickets. In severe cases, bone deformities such as chicken breast, pectus excavatum, square skull, X-shaped leg, and O-shaped leg can occur. Bone density is an important indicator of bone strength. Zhang Bing

and colleagues reported in 2019 that when serum 25-(OH)D3 is insufficient or deficient, children's serum 25-(OH)D3 levels are positively correlated with bone density[10]. A study on calcium, vitamin D, and the risk of fractures showed that 93% of children's vitamin D intake was below the recommended level[11]. A study conducted by Cauley and colleagues showed that for every 25 nmol/L decrease in serum 25-(OH)D3 level, the odds of hip fracture increase. For example, if the serum 25-(OH)D3 level is less than 50 nmol/L, the odds nearly double[12]. Vitamin D insufficiency or deficiency in childhood may also affect bone health in adulthood, leading to osteoporosis.

2.2 The effect of vitamin D on neurodevelopment

In addition to its classic role in regulating bone metabolism, vitamin D can also regulate the development and function of the nervous system. Tic disorders (TDs) are neurodevelopmental disorders that begin in childhood and adolescence. The main clinical manifestations are vocal tics or motor tics. In recent years, studies have found that TDs may be related to dopaminergic abnormalities. Vitamin D plays an important role in the normal development and function of the dopaminergic system, so TDs may be associated with vitamin D insufficiency and deficiency[13]. A case-control study by Cui Shengtao on children with TD and trace elements and vitamins showed that their serum vitamin D level was significantly lower than that of children without the disease (P<0.05)[14]. Li Honghua and colleagues showed that the serum 25-(OH)D3 level of children with TD was significantly lower than that of healthy controls and speculated that children with TD may have had low levels of vitamin D during their fetal period or after their birth. Long-term vitamin D deficiency or insufficiency induces tic symptoms [15]. Currently, there are few clinical studies on the relationship between vitamin D and TD. Autism, or autism spectrum disorder, is a widespread neurodevelopmental disorder. In the past 20 years, the prevalence of autism reported by different countries has trended upward. As early as 2008, Cannell[16] put forward the hypothesis that low vitamin D levels during the fetal period or early childhood is an important risk factor for autism. In 2017, Xu Ningan and colleagues used enzyme-linked immunosorbent assay to show that the serum 25(OH)D3 level of children with autism was significantly lower than that of healthy children. This is consistent with the research results of Dong Hanyu and colleagues[17] and confirms the above hypothesis. In addition, Dong Hanyu has said that the vitamin D level of children with autism is negatively correlated with total score on the Child Autism

Behavior Scale, indicating that the lower the vitamin D level, the higher the risk of autism and other neurological diseases.

2.3 The effect of vitamin D on the respiratory system

Vitamin D deficiency is one of the reasons that children are prone to respiratory tract infections. Studies have shown that this is closely related to the role of vitamin D as an immunomodulator in infectious diseases. Hu Yunqing and others have pointed out that compared with children with sufficient vitamin D, children a deficiency are at significantly higher risk for different types of infection, especially those of the respiratory tract[18]. Fang Caiwen and colleagues found that immunoglobulin A (IgA) levels in children with vitamin D supplementation for 3 months rose, and the number of infections within 1 year declined[19]. A meta-analysis[20] also proposed that vitamin D supplementation can prevent acute respiratory infections. Liu ZQ[21] found that vitamin D also plays an important role in maintaining the stability of mast cells. A number of studies[22-23] have suggested that vitamin D deficiency in children can significantly increase the incidence of asthma.

A meta-analysis of children and adults with asthma showed that patients with vitamin D supplementation had fewer asthma attacks, with a reduction in the average annual incidence per person from 0.44 to 0.28 [24]. Today, COVID-19 is a global pandemic, and researchers have explored the correlation between its pathological mechanism and vitamin D level. Surveys have shown that compared with countries less affected by the epidemic, vitamin D levels are generally lower in Italy, Spain, and the United Kingdom, which have had high mortality rates from COVID-19 [25]. Grant and colleagues[26] reviewed the role of vitamin D in reducing the risk of respiratory tract infection and demonstrated epidemiologic and clinical evidence that vitamin D supplementation may reduce the risk of coronavirus pneumonia. Munshi Ruhul and colleagues[27] studied the vitamin D levels of 376 patients with COVID-19 and found that their average vitamin D level was 21.9 nmol/L and that the vitamin D levels of patients with poor prognoses were significantly lower than those with good prognoses. Therefore, giving an appropriate amount of vitamin D for prevention or treatment may positively affect the development and prognosis of coronavirus pneumonia.

2.4 Impact of vitamin D on the immune system

In addition to regulating calcium and phosphorus, vitamin D also has a wide

range of effects on the immune system. It is considered a new neuroendocrine-immunomodulatory hormone, and its importance in immune regulation is slowly becoming clear[28]. The vast majority of cells related to immune function contain vitamin D receptors (VDRs) such as mononuclear macrophages and activated T cells and B lymphocytes. In 2017, Gan Yingyan [29] and other scholars pointed out that children with autoimmune encephalitis (AIE) generally have insufficient or absent vitamin D levels and showed that a decline in vitamin D levels triggers AIE, which may be related to vitamin D. By combining with VDR in the AIE-prone brain area (cerebral limbic system), vitamin D plays a role in immune regulation and other functions. Systemic lupus erythematosus (SLE) is a T lymphocyte-dependent, immune complex-mediated autoimmune disease involving multiple systems. After studying children with SLE, researchers found that their vitamin D levels were lower than in healthy people[30]. After daily vitamin D supplementation for SLE patients for 12 consecutive months, SLE improved significantly more than that in the control group. The researchers pointed out that vitamin D supplementation should be given more attention during the active period of the disease[31].

Recent studies have shown that vitamin D levels are associated with Kawasaki disease, especially with coronary artery damage. Zhang Xiaoying and others[32] reported that the serum 25-(OH)D3 level of children with coronary artery damage was lower than that of children with no coronary artery damage and of the control group, suggesting that vitamin D deficiency may increase the risk of coronary artery damage in children with Kawasaki disease. This is consistent with the study by Zhang Yuanda and colleagues[33], who reported that children with Kawasaki disease have decrease 25-(OH)D3 levels and that the more obvious the decrease, the greater the possibility of coronary artery damage.

3. Prevention and treatment of vitamin D deficiency

Pregnant and lactating women usually take part in fewer outdoor activities, spent insufficient time in the sun, and have large changes in hormone levels and metabolism. They are prone to vitamin D deficiency, which directly affects the health of the fetus and newborn. A study on vitamin D guidelines in China and abroad suggests that [34]. All vitamin D guidelines surveyed recommend that pregnant and lactating women take vitamin D supplements to maintain an appropriate 25-(OH)D3 level. The Italian

consensus in 2018[35] recommended that all pregnant and breastfeeding women start taking 600 IU/d of vitamin D starting in the beginning of pregnancy. China recommends that pregnant women take 800 IU/d of vitamin D supplements daily during the perinatal period for them and their babies.

The prevention and treatment of vitamin D deficiency in childhood is based on adequate sunshine and dietary and vitamin D supplementation. However, excessive sun exposure can negatively affect children's health. Studies have shown that the younger the sun exposure, the greater the risk of skin cancer. The American Academy of Pediatrics recommends that babies 6 months or younger should avoid direct exposure to ultraviolet rays. Children need sunscreen and protective clothing outdoors. If the 25-(OH)D3 level cannot be reached through outdoor activities and dietary supplementation, vitamin D preparations are needed. The 2015 Recommendations for Prevention and Treatment of Vitamin D Deficiency and Vitamin D Deficiency Rickets [36] said that infants should receive at least 400 to 800 IU/d of vitamin D as soon as possible after birth and that high-risk groups (eg, premature infants, low birth-weight infants, twins) should receive 800 to 1000 IU/d of vitamin D.

After continuous vitamin D supplementation for 3 months, the guidelines changed to recommend 400 to 80 0IU/d. The Global Consensus Recommendation for Nutritional Rickets Control (2016)[37] recommended supplementation with at least 400 IU/d vitamin D for infants and at least 600 IU/d for children older than 12 months. At the same time, Holick and colleagues[38] said that vitamin D should be given in a small dose once a day (400 IU/d for infants 0 to 1 year and 600 IU/d for those older than 1 year). They added that high-dose vitamin D supplementation three times a year (0 to 6 months, 1000 IU/d; 6 months to 1 year, 1500 IU/d; 1 to 3 years, 2500 IU/d; 4 to 8 years, 3000 IU/d; and 8 years and older, 4000 IU/d) can maintain the serum concentration of 25-(OH)D3 in the normal range. Although there are differences in vitamin D supplementation in China and abroad, children 0 to 12 years can take 400 IU/d of vitamin D.

Conclusion

In summary, vitamin D deficiency can have a profound impact on the healthy growth of children. To meet the vitamin D requirements of children, in addition to adequate sunshine and a healthy diet, reasonable vitamin D supplementation is essential. Both UNICEF and the World Health Organization mentioned in their child development goals that the most direct and effective way to promote early childhood

development is the nurturing of health[39,40]. Therefore, in the process of children's growth, supplementation of vitamin D should be paid great attention and the 25-(OH)D3 level in children monitored regularly to reduce the incidence of vitamin D insufficiency or deficiency.

References

[1] Jiang Meihua, Lai Shanrong, Lin Shaokai, et al. Study on serum vitamin D levels and influencing factors of pregnant women[J]. Chinese Journal of Nutrition, 2019, 41(06): 544-549.

[2] Zhu Z, Zhan J, Shao J, et al.High prevalence of vitamin D deficiency among children aged1month to16years in Hangzhou, China. Bmc Public Health, 2012, 12:126.

[3] Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations[J]. Pediatrics, 2008, 122(2): 398-417. DOI:10.1542/ peds. 2007-1894.

[4] Hou Shuning. Analysis of influencing factors of vitamin D levels in preschool children [J]. International Journal of Laboratory Medicine, 2016, 37(6): 756-757.

[5] van Schoor NM, Lips P. Worldwide vitamin Dstatus[J]. Best Pract Res Clin Endocrinol Metab, 2011, 25(4): 671-680.

[6] Zhao X, Xiao J, Liao X. Vitamin D Status among Young Children Aged 1-3 Years: A Cross-Sectional Study in Wuxi, China[J]. Plos one,2015,10(10): e0141595.

[7] Gao Tieying, Yu Guoying, Hao Shuhong, et al. Comparative analysis of serum vitamin D levels in children of different ages and its relationship with bone alkaline phosphatase[J]. Pediatrics of Integrated Traditional Chinese and Western Medicine, 2014, 6(1): 8-9.

[8] Wang Wei, Yang Lifang, Dong Li, et al. A study on the correlation between age, sex and season and the vitamin D status of children aged 0～12 years in Xi'an [J]. Chengdu Medical College Journal, 2018, 13(01): 32-36.

[9] Wu Guangchi. How far is vitamin D deficiency from us? [J]. Chinese Journal of Maternal and Child Health, 2014, 5(03): 72-75.

[10] Zhang Bin, Wang Bing, Pan Xiaogui, et al. The relationship between vitamin D nutritional status and bone mineral density in children aged 0～7 years[J]. China Maternal and Child Health Care, 2019, 34(24): 5670-5672.

[11] Hassan A Alshamrani, Hana Alloub, Derek Burke, et al. Vitamin D intake, calcium intake and physical activity among children with wrist and ankle injuries and

the association with fracture risk. Nutrition and Health, 2019, 25(2): 113-118.
[12] Cauley JA, Lacroix AZ, Wu L, et al. Serum 25-hydroxy vitamin D concentrations and risk for hip fractures[J]. Ann Intern Med,2008,149: 242~250.
[13] Zhang Chenghui, Zhao Yunjing. Research progress of vitamin D and childhood neuropsychiatric diseases[J]. International Journal of Pediatrics, 2017, 01: 47-51.
[14] Cui Shengtao. Study on the correlation between tics in children and trace elements and vitamin A/D/E [D]. Jilin: Changchun University of Traditional Chinese Medicine, 2017.
[15] Li Honghua, Wang Bing, Shan Ling, et al.. Detection of serum 25-hydroxyvitamin D levels in children with tic disorder[J]. Chinese Journal of Contemporary Pediatrics, 2017, 19(11): 1165-1168.
[16] Cannell. Autism and Vitamin D[J]. Med Hypotheses,2008,70:750-759.
[17] Dong Hanyu, Wang Bing, Li Honghua. A study on the correlation between vitamin D levels and core symptoms of autism in children with autism spectrum disorder[J]. Chinese Journal of Pediatrics, 2017, 55 (12).
[18] Hu Yunqing, Xue Jinlian, Li Qingyun, et al.. Serum 25-hydroxyvitamin D3 levels and clinical significance of respiratory tract infections in preschool children[J]. Shanxi Medical Journal, 2018, 47(04): 454-455.
[19] Fang Caiwen, Zou Xufeng, Xu Xiaojuan, et al.. Risk factors of recurrent respiratory infections in preschool children and their correlation with vitamin D[J]. Chinese Journal of Child Health Care, 2019, 27(06): 673-676 .
[20] Tang Huiya, Ge Xuhua, Li Zhuo, Zet al.. The relationship between serum vitamin D levels in infants and young children and the severity of bronchiolitis and their effects on alveolar epithelial cell function [J]. Journal of Nanjing Medical University (Natural Science Edition)), 2019, 39(03):387-392.
[21] Liu ZQ, Li XX, Qiu SQ, et al. Vitamin D contributes to mast cell stabilization[J],Allergy,2017,72(8):1184-1192.
[22] Elysia M. Hollams, Shu Mei Teo, Merci Kusel, et al. Vitamin D over the first decade and susceptibility to childhood allergy and asthma. Journal of Allergy and Clinical Immunology, 2017,139(2):472-481e9.
[23] Wolsk Helene M, Chawes Bo L, Litonjua Augusto A, et al. Prenatal vitamin D supplementation reduces risk of asthma/recurrent wheeze in early childhood: A combined analysis of two randomized controlled trials..PLoS ONE, 2017, 12(10):e0186657.

[24] Martineau AR, Cates CJ, Urashima M, et al. Vitamin D for the management of asthma[J].Cochrane Database Syst Rev,2016,9(9):CD011511.
[25] Vitamin D deficiency may have a strong correlation with the mortality rate of new coronary pneumonia [N]. Science and Technology Daily. 2020.05.13 (02th Edition: International News).
[26] Grant WB, Lahore H, McDonnell SL, et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths [J].Nurtients,2020,12:998-1017.
[27] Munshi Ruhul, Hussein Mohammad H, Toraih Eman A, et al. Vitamin D insufficiency as a potential culprit in critical COVID-19 patients[J].Medical Virology,2021, 93(2):733-740.
[28] Chen Yanmei, Zhou Jichang. Research progress on the mechanism of vitamin D on the immune system[J]. Chinese Journal of Nutrition, 2020, 42(03): 301-307.
[29] Gan Yingyan, Mai Jianning, Wu Wenlin. The correlation between childhood autoimmune encephalitis and serum 25-hydroxyvitamin D[J]. Hainan Medicine, 2018, 29(11): 1583-1585.
[30] Tian-Biao Zhou, Zong-Pei Jiang, Zhi-Jun Lin, et al. Association of vitamin D receptor gene polymorphism with the risk of systemic lupus erythematosus. Journal of Receptors and Signal Transduction, 2015, 35(1): 8-14.
[31] Li Jinpu, Wei Dandan, Li Xiaofeng, Wen Hongyan. The role of vitamin D in autoimmune diseases [J]. Chinese General Practice, 2015, 18(18): 2184-2187.
[32] Zhang Xiaoying, Li Chaoxiong, Ou Zhongai, et al. The changes and clinical significance of serum 25-hydroxyvitamin D levels in children with Kawasaki disease [J]. China Contemporary Medicine, 2019, 26(05): 98-100+ 104.
[33] Zhang Yuanda, Li Rongmin, Ji Chaoyu. Changes and significance of 25-hydroxyvitamin D3 levels in children with Kawasaki disease [J]. Chinese Journal of Contemporary Pediatrics, 2016, 18(03): 211-214.
[34] Li Weiguo, Li Yuning, Zhang Xiumin, et al. AGREE□ Evaluation of 9 Children and Adolescent Vitamin D Clinical Practice Guidelines and Consensus and Differences in Recommendations[J]. Chinese Journal of Evidence-Based Pediatrics, 2012, 7(05): 372-379
[35] Giuseppe Saggese, Francesco Vierucci, Flavia Prodam, et al. Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians.

Italian Journal of Pediatrics, 2018, 44(1):51.
[36] Yang Shufen, Wu Guangchi. Recommendations for the prevention and treatment of vitamin D deficiency and vitamin D deficiency rickets[J]. Chinese Journal of Child Health Care, 2015, 23(07): 781-782.
[37] Munns CF, Shaw N, Kiely M, et al. Global Consensus Recommendations onPrevention and Management of Nutritional Rickets[J]. J Clin Endocrinol Metab, 2016, 101(2): 394-415.
[38] Holick MF,Binkley NC,Bischoff-Ferrari HA,et al.Evaluation treatment and prevention of Vitamin D deficiency:an Endocrine Society clinical practice guideline[J].J Clin Endocrinol Metab ,2011,96(7):1911- 1930.
[39] Bhutta.ZA.Nurturing case:promoting early childhood development[J].Lancet,2017,389(10064):91-102.
[40] UNICEF.Integrating Early Childhood Development(ECD) activities into nutrition programmes in emergencies[J]. World Health Organization, 2013.