CORPUS PUBLISHERS

Global Journal of Pediatrics (GJP)

Volume 1, Issue 2, 2021

Article Information

Received date : October 23, 2021

Published date: November 16, 2021

*Corresponding author

Fuyong Jiao, Children's hospital of Shaanxi Provincial People's Hospital Xi'an, Shaanxi 710001, China

Key Words

Kawasaki; Disease; Vitamin D; Immune Modulation of Coronary Artery Disease; Systemic Vasculitis; VDR; Blood Vessels; Immune Regulation; Mucocutaneous; Human Body; Pathogenesis

Research Article

Research Progress on the Effect of Vitamin D on the Pathogenesis of Kawasaki Disease and the Prediction of Coronary Artery Lesion

Fuyong Jiao[1*], Guoqian chen[2], Jing Ni[1], BH Annayev[6], Xiaohan Mei[3], Zhongdong du[4] and Liping Li[5]

[1]*Children's hospital of Shaanxi Provincial People's Hospital Xi'an, China*

[2]*Xi'an Medical College Xi'an, Shaanxi, China*

[3]*Dept of pediatrics, the First people's Hospital of Xianyang, China*

[4]*Beijing Children's hospital, Affiliated to Capital Medical University, China*

[5]*Xi'an Institute of Innovation, Yan'an University, Xi'an, China*

[6]*Hospital with the Scientific-clinical Center of Cardiology, Ashgabat city, Turkmenistan*

Abstract

Kawasaki Disease (KD), also known as mucocutaneous lymph node syndrome, is a kind of fever rash pediatric disease with systemic vasculitis as the main lesion. Its pathogenesis is not yet completely clear, the main pathological changes is systemic vasculitis, involving the small and medium-sized blood vessels of the body, especially coronary artery lesions are more obvious, can lead to coronary artery aneurysm, even serious sudden death. Because the disease can appear serious cardiovascular complications, has gradually attracted attention, in recent years, its incidence has gradually increased trend, has become one of the common pediatric acquired heart disease etiology. Vitamin D acts on the VDR in various tissues and cells of the human body. Many studies have shown that vitamin D not only participates in the traditional calcium and phosphorus metabolism, but also participates in immune regulation through a variety of mechanisms.

Introduction

Kawasaki Disease (KD), also known as mucocutaneous lymph node syndrome, is a kind of fever rash pediatric disease with systemic vasculitis as the main lesion. Its pathogenesis is not yet completely clear, the main pathological changes is systemic vasculitis, involving the small and medium-sized blood vessels of the body, especially coronary artery lesions are more obvious, can lead to coronary artery aneurysm, even serious sudden death. Because the disease can appear serious cardiovascular complications, has gradually attracted attention, in recent years, its incidence has gradually increased trend, has become one of the common pediatric acquired heart disease etiology. Vitamin D acts on the VDR in various tissues and cells of the human body. Many studies have shown that vitamin D not only participates in the traditional calcium and phosphorus metabolism, but also participates in immune regulation through a variety of mechanisms [1]. Their roles in many human diseases such as cancer, diabetes, hypertension, cardiovascular disease, autoimmune and skin diseases have also been widely studied [2]. At present, the pathogenesis of KD is not completely clear, but most of the international scholars believe that it is an autoimmune disease, and the pathogenesis by many aspects of immune inflammatory factors. In view of the role of vitamin D in the regulation of immune response, and some studies have pointed out that there is a certain correlation between the levels of vitamin d and KD, especially in children with Kawasaki disease and coronary artery damage at low levels [3,4]. Serum 25- (OH) D3 level in acute stage of Kawasaki disease has important predictive significance for the formation of CAL [5] The correlation between vitamin D and KD has attracted more and more attention in the world. In this paper, the study of vitamin D in recent years and KD in the role of the possible mechanism and vitamin D. Kawasaki disease with coronary artery disease to do a prediction.

Metabolism and Physiological Role of Vitamin D

Vitamin D is a fat-soluble vitamin, and is also an important steroid hormone. There are more than ten known types of vitamin D. But the most important ones are vitamin D2 and vitamin D3. Vitamin D3 is transformed from 7-dehydroxy cholesterol in the epidermis and dermis of higher animals by ultraviolet radiation. VD3 is then converted by skin warming, then combined with vitamin D binding protein in plasma and transported to the liver, which is hydroxylated by 25-hydroxylase in mitochondria of liver cells. 25- (OH) D3 is transported to the kidney in blood and hydroxylated by cytochrome P450 in mitochondria of proximal tubular epithelial cells, resulting in the formation of 1,25 - (OH) 2D3,1,25-(OH) 2D3 As the most active form of vitamin D in the blood, it exerts its biological effects by specifically binding to the VDR. VDR in addition to the kidney cells, intestinal epithelial cells, thyroid cells, bone cells and other traditional cells, but also exists in macrophages, NK cells, T cells, B-cells, and other immune cells [6-8]. Vitamin D not only participates in the metabolism of calcium, phosphorus and parathyroid hormone, but also regulates the innate immune response and adaptive immunity by various mechanisms [1,9-11].

Correlation between Vitamin D and Kawasaki Disease

According to related literature, 25- (OH) D3 levels in children with KD were significantly lower than those in healthy children. It is considered that the decrease of 25- (OH) D3 level is involved in the pathological process of KD, and the children who have the obvious decrease of the level of 25 (OHD) D 3 are more likely to have coronary artery injury [12]. In addition, according to a meta-analysis [13] Concentrations of 25- (OH) D3 were inversely associated with risk of cardiovascular disease morbidity and mortality, Reduced levels of vitamin D are associated with an increased relative risk of cardiovascular disease, so the extent of the decline is likely to be related to the presence of coronary artery damage in children with KD. According to recent epidemiological data on KD in Japan [14] The incidence of KD presents a certain seasonal: higher in winter (peak in January), Summer and autumn are lower (June to July lowest), which may also be related to shorter sunshine duration and lower

vitamin D levels in winter.

Mechanism of Vitamin D in Kawasaki Disease

At present, the pathogenesis of Kawasaki disease is not completely clear. The possible mechanisms include genetic susceptibility, infection, autoimmune and perinatal exposure [15,16]. Vitamin D may be involved in the regulation of the pathogenesis of Kawasaki disease in the following aspects, of which immune disorders and inflammatory reactions are the most important mechanisms. According to research, [11,17,18], the biological function of most 1,25 (OH) 2D3 is strong and related to the presence of vitamin D receptors (V DR) in almost all immune nuclei (including T cells, dendritic cells, mononuclear cells and macrophages, activated B cells). The specific combination is mediated. CD4+T cells are one of the targets of vitamin D action, which can be divided into Th1 cells, which secrete interleukin (IL)-2, tumor cell necrosis factor (TNF) beta, interferon (IFN) gamma, thus mediating cell immunity, and Th2 cells mainly secrete I L-6, IL-4, IL-5, IL-10, mediated humoral immunity, both of which are inhibitory T cells. Studies have shown that when VD3 is lacking, Th1 cell activity increases, Th2 cell and regulatory T cell activity weakens, inducing Th1 dominant immune response. VD3 can also bind to the VD reaction element (VDRE) in the IFN-γ promoter area through the VDR complex to directly inhibit the expression of IFN-γ. In addition, vitamin D can inhibit mononuclear. Platelet activation occurred in the acute stage of Kawasaki disease, showing an increase in platelet-derived particle levels and platelet CD41 levels, resulting in the formation of coronary artery thrombosis [22,23]. Vitamin D receptors exist on platelets, so platelet function is affected by vitamin D. When the VD level is within a certain range, with the increase of vitamin D levels, the averages of MPV, P-LCR and PWD gradually decrease [24]. This shows that VD has the effect of inhibiting platelet activation, lipid factor release and inflammation. Vitamin D can reduce the expression of plasminogen activator I, tissue factors and thrombo regulatory proteins. Its lack of adverse effects on hemostasis and thrombosis have been confirmed in vitro and animal experiments [25]. In addition, research shows that platelet activating factor in children with Kawasaki disease (PAF) content is significantly higher than that in healthy children, and the PAF content in the acute coronary artery injury group is higher than that in the non-injury group [26]. At the same time, the haploid type of platelet endothelial cell adhesion molecule 1 Leu-Ser-Arg may also be related to increased platelet count and the subsequent risk of chronic coronary artery lesions. . In the process of type I hypersensitivity reaction, IgE level is related to related inflammatory cytokines. The release of these inflammatory factors will also cause platelet activation, accelerate platelet release, and allow many immature large-volume tissues to enter local hematoma, which leads to an increase in MPV levels and thus expressing more Membrane protein molecules accelerate platelet activation, activate platelets or release a large number of bioactive substances, and participate in inflammatory reactions [24]. Therefore, vitamin D deficiency can increase platelet activation and promote inflammatory response through the above-mentioned mechanisms. Endothelial dysfunction is also an important pathogenesis of Kawasaki disease. In mouse experiments using the Kawasaki disease model, it shows [27,28], the number of bone marrow endothelial progenitor cells in the Kawasaki disease mouse model has decreased significantly, and various functions and biological activities are seriously damaged. In the determination of an independent factor in the determination of elevated serum plasminogen activator inhibitor 1 (PAI-1EPC) in children with Kawasaki disease, active vitamin D can improve the activity of endothelin convertase-1 and its mRNA and related proteins by specifically binding vitamin D receptors expressed by endothelial cells. Da, promote endothelin-1 (ET-1) [31], suggesting that vitamin D can promote EPC synthesis. Therefore, vitamin D can improve endothelial cell disorders through the above mechanisms and thus reduce a series of effects caused by endothelial cell disorders in Kawasaki disease. Some of the children with Kawasaki disease are significantly related to infection, and the pathogens of Kawasaki disease are not only related to bacteria and viruses, but may also be related to the increased activity of certain related enzymes of microorganisms such as chlamydia, ricketrus, mycoplasma and mites [32]. Recent studies have shown that bacterial superantigens are related to the etiology of KD. Among them, exogenous antigens are the antigens that cause Kawasaki disease, mainly toxic shock syndrome toxins, Streptococcus A-induced thermal exotoxin A-C, Staphylococcus aureus enterotoxin A-C, suggesting that Kawasaki disease is genetically susceptible [33], caused by physical infection with pathogens. According to the results of Liu Zhiyuan and others [34], when the body lacks 25-(OH) vitamin D3, it causes the body's immune function to decline or even infection. This is mainly because 25-(OH) vitamin D3 can induce the expression of antibacterial peptides that resist bacterial and viral infections by binding to vitamin D receptors on the monocyte membrane, thus playing an immune role. At the same time, it can promote the differentiation of mononuclear cells into phagocytosis cells and enhance the body's resistance. In addition, 25-(OH) vitamin D3 can regulate the differentiation of antigen presentation cells, the proliferation of lymphocytes and the secretion of cytokines [35]. When the body is attacked by pathogenic microorganisms, 25-(OH) vitamin D3 can accelerate the secretion of anti-inflammatory cytokines and devour pathogens to protect the body from infection. Because Kawasaki disease has obvious differences between races and regions, genetic factors may also play an important role in the pathogenesis of KD. At present, the most extensive research related to KD includes inositol 1,4,5-triphosphate 3 kinase (ITPKC), cystatase 3 (CASP3), B lymphocyte kinase (BLK), CD40, Fc fragments of HLA, TGF-β, and IgG [15], these factors Various pathways can be used to participate in the activation of immune cells such as T cells, B cells and dendritic cells, thus participating in maintaining the corresponding pro-inflammatory and anti-inflammatory balance [20]. Sun Ting [36] and others analyzed DNA methylation chips and gene expression chips by integrating bioinformatics, and found that most of the methylation genes related to Kawasaki disease were in a low methylation state, mainly participating in resonance reactions, inherent immune responses, coagulation and chemokine signaling pathways, and appropriate vitamin D supplementation. It can improve its whole genome methylation level [37], and research on vitamin D and epigenomes also shows that immune-related genes are usually significantly increased by vitamin D, while genes involved in cell metabolism are less sensitive to nuclear hormones. It can be seen that vitamin D can be raised in humans at a certain level. The epigenetics of Kawasaki disease affects the pathogenesis and return of Kawasaki disease. Therefore, when vitamin D is deficient, the release of inflammatory factors can be promoted through the above-mentioned mechanisms, thus damaging vascular endothelial cells, increasing vascular permeability and inducing the occurrence of vasculitis.

Prediction of Vitamin D on Kawasaki Disease Coronary Artery Disease

According to studies such as Zhang Yuanda [1], the level of 25-(OH) D3 in children with K D is significantly lower than that of healthy children. Considering that the decline in the level of 25-(OH) D3 is involved in the pathological process of KD. Most studies believe that children with a significant decline in 25-(OH) D3 levels are more likely to have coronary artery damage [38,39]. It can be seen that the degree of decline in 25-(OH) D3 levels may be related to whether children with KD have coronary artery damage. Therefore, serum 25-(OH) D3 levels in the acute stage of Kawasaki disease are of great predictive significance for CAL formation. However, the average low vitamin D water level of all Kawasaki patients decreased. Some studies have shown [12] that the serum 25-(OH) D3 levels of children with Kawasaki disease combined with CAL was significantly higher than that of non-CAL groups, and the acute 25-(OH) D3 levels increased and CAL occurred. There is a correlation. The diagnostic fold point is 64ng /mL or 65ng /mL, which may cause coronary artery hyper calcification, stimulate increased expression of cytochromes CYP27B1, resulting in an increase in blood 25-(OH) D3 levels [40], and due to inflammation It should be violent, leading to an increase in the number of receptors, resulting in an increase in the level of 25-(OH) D3 [41]. However, whether the vitamin D level is increased or decreased, the above studies have pointed out that serum 25-(OH) vitamin D3 levels in the acute stage are of great predictive significance for the formation of Kawasaki disease combined with CAL.

Conclusion

Vitamin D is closely related to children's Kawasaki disease due to its many effects of immune regulation and anti-inflammatory. Vitamin D deficiency may affect the return of Kawasaki disease and is closely related to Kawasaki disease complicated by coronary damage. However, some children with Kawasaki disease also show elevated vitamin D, which may be related to severe inflammatory reactions, excessive coronary artery calcification, and stimulating increased expression of cytochromes CYP27B1. Because the pathogenesis of Kawasaki disease and vitamin D are mostly adjuvant treatments in the prevention of coronary artery damage of Kawasaki disease, some large-scale clinical trials are still needed for further exploration and confirmation.

References

1. Hanel Andrea, Carlberg Carsten (2019) Vitamin D and evolution: Pharmacologic implications. Biochem Pharmacol 173: 113595.
2. Umar Meenakshi, Sastry Konduru S, Chouchane Aouatef I (2018) Role of Vitamin D Beyond the Skeletal Function: A Review of the Molecular and Clinical Studies. Int J Mol Sci 19.
3. Zhang Xiaoying, Li Chaoxiong, OU Zhongai, Lin Nana, Zheng Xiaoyan (2019) Serum 25-hydroxyvitamin D levels in children with Kawasaki disease and its clinical significance. Chinese journal of contemporary medicine 26(05): 98-104.

4. An Xinjiang, Fu Mingyu,Tian Jing (2016) Significance of serum 25-hydroxyvitamin D and interleukin-6 levels in immunoglobulin treatment of Kawasaki disease in children. Exp Ther Med 12: 1476-1480.

5. Zhang Yuan-da, DONG Qing-wei, BI Bin-bin, MA Lei, QI Rui-fang, et al. (2018) Significance of endogenous hydrogen sulfide and 25-hydroxyvitamin D3 levels in children with Kawasaki disease. Image research & medical applications 2(15): 184-186.

6. Arnson Y, Amital H, Shoenfeld Y (2007) Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis 66 (9): 1137-1142.

7. Mok CC (2013) Vitamin D and systemic lupus erythematosus: an update. Expert Rev Clin Immunol 9 (5): 453-463.

8. Bhalla AK, Amento EP, Clemens TL, Holick MF, Krane SM (1983) 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 57 (6): 1308-1310.

9. Azrielant S, Shoenfeld Y (2017) Vitamin D and the Immune System. Isr Med Assoc J 19(8): 510-511.

10. Li Yan Chun,Chen Yunzi, Liu Weicheng (2014) MicroRNA-mediated mechanism of vitamin D regulation of innate immune response. J Steroid Biochem Mol Biol 81-86.

11. Goischke Hans-Klaus (2019) Vitamin D Supplementation as Add-on Therapy in Multiple Sclerosis-Balance between Benefit and Risk?: A Commentary on Vitamin D Supplementation in Central Nervous System Demyelinating Disease-Enough Is Enough. Int J Mol Sci 20(6): 1513.

12. Chen XH, LUO XM, MA XH, Weng JJ, Wu H, et al. (2019) Prediction value of 25-hydroxyvitamin D-3 in coronary artery disease of Kawasaki disease. Chinese maternal and child health research 30(05): 558-561.

13. Gholami Fatemeh, Moradi Ghobad, Zareei Bushra (2019) The association between circulating 25-hydroxyvitamin D and cardiovascular diseases: a meta-analysis of prospective cohort studies. BMC Cardiovasc Disord 19: 248.

14. Makino Nobuko, Nakamura Yosikazu, Yashiro Mayumi (2019) Nationwide epidemiologic survey of Kawasaki disease in Japan. Pediatr Int 61: 397-403.

15. Shreya Agarwal, Devendra K Agrawal (2017) Kawasaki Disease: Etio pathogenesis and Novel Treatment Strategies. Expert Review of Clinical Immunology 10.

16. Guo H M, Han Y Y (2015) Research progress in etiology and pathogenesis of Kawasaki disease. Medical heald Above 21(23): 4260-4263.

17. Hewison Martin (2010) Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am 39: 365-379.

18. Cantorna Margherita T, Snyder Lindsay, Lin Yang-Ding (2015) Vitamin D and 1, 25(OH) 2D regulation of T cells. Nutrients 7: 3011-3021.

19. Shen Ying, Li Ye, Bai Jie (2016) Research progress of vitamin D_3 and systemic lupus erythematosus. Chinese Journal of Geriatric Science 36(04): 1009-1011.

20. Carlberg Carsten (2019) Vitamin D Signaling in the Context of Innate Immunity: Focus on Human Monocytes. Front Immunol 10: 2211.

21. Konijeti Gauree Gupta, Arora Pankaj, Boylan Matthew R (2016) Vitamin D Supplementation Modulates T Cell-Mediated Immunity in Humans: Results from a Randomized Control Trial. J Clin Endocrinol Metab 101: 533-538.

22. Yahata T, Suzuki C, Yoshioka A (2014) Platelet activation dynamics evaluated using platelet-derived microparticles in Kawasaki disease. Circ J 78(1): 188-193.

23. Laurito M, Stazi A, Delogu AB (2014) Endothelial and platelet function in children with previous Kawasaki disease. Angiology 65(8): 716-722.

24. Jiang Linlin, Yang Jianmin, Wang Huan, Tian Xianmin, Chen Li, et al. (2017) Study on the relationship between mean platelet volume, vitamin D and immunoglobulin E levels in children. International Journal of Laboratory Medicine 38(21): 3001-3003.

25. Yu Lin, Chen Mingqun, XU Min (2018) Effect of serum PAI-1 level on vascular endothelial cell viability in children with Kawasaki disease complicated with coronary artery injury. Hebei medical 24(11): 1761-1765.

26. Wang Yang ji, SHI Wei-qun, WANG Qian, WANG Yan, Lu Jin-quan (2018) Changes and significance of platelet reactive protein-1 and platelet activating factor in kawasaki disease. Journal of Jiangsu University Medical Science 28(4): 313-319.

27. Wang HF (2015) Study on the role of endothelial progenitor cell Notch4 signaling pathway in coronary artery injury and repair in kawasaki disease model. Zhejiang University 22(03): 202-206.

28. Liu J F, Du Z D, Chen Z (2012) Status of endothelial progenitor cells in kawasaki disease model mice. Chinese Medical Journal 92(22): 1560-1564.

29. Abdi-Ali Ahmed, Nicholl David D M, Hemmelgarn Brenda R (2014) 25-Hydroxyvitamin D status, arterial stiffness and the renin-angiotensin system in healthy humans. Clin Exp Hypertens 36: 386-391.

30. Andrukhova Olena, Slavic Svetlana, Zeitz Ute (2014) Vitamin D is a regulator of endothelial nitric oxide synthase and arterial stiffness in mice. Mol Endocrinol 28: 53-64.

31. Martínez-Miguel P, Valdivielso JM, Medrano-Andrés D (2014) The active form of vitamin D, calcitriol, induces a complex dual upregulation of endothelin and nitric oxide in cultured endothelial cells. Am J Physiol Endocrinol Metab 307(12): E1085-E1096.

32. Nakamura Akihiro, Ikeda Kazuyuki, Hamaoka Kenji (2017) Aetiological Significance of Infectious Stimuli in Kawasaki Disease. Front Pediatr 7: 244.

33. Xiao Rong, Wang Guodong, Chang Xin (2019) Research progress on etiology and pathogenesis of kawasaki disease in children. World Latest Medical Information Abstract 19(63): 90-92.

34. Liu ZHIyuan (2018) Analysis of serum 25-hydroxyvitamin D level and its influencing factors in patients with severe pneumonia. Journal of Acute and Critical Medicine 24(05): 428-430.

35. Bikle Daniel D (2018) Vitamin D and the immune system: role in protection against bacterial infection. Curr Opin. Nephrol Hypertens 17: 348-352.

36. Sun Ting, Zhang Lianhong, Wen Fangfang (2019) Kawasaki disease related methylation gene and its role. Guangxi Medical Journal 41(02): 216-220.

37. Zhu H, Bhagatwala J, Huang Y (2016) Race/ethnicity-specific association of vitamin D and global DNA methylation: cross_sectional and interventional findings. PLoS One 11(4): e0152849.

38. An X, JFu MY, Tian J (2016) Significance of serum 25-hydroxyvitamin D3 and interleukin-6 levels in immunoglobulin treatment of Kawasaki disease in children. Exp Ther Med 12(3): 1476-1480.

39. Matsubara T, Ichiyama T, Furukawa S (2005) Immunological profile of peripheral blood lymphocytes and monocytes/macrophages in Kawasaki disease. Clin Exp Immunol 141: 381.

40. Chen Y LWang J L, Li W Q (2014) Prediction of the risk of coronary arterial lesions in Kawasaki disease by serum 25-hydroxyvitamin D3. Eur J Pediatr 173(11): 1467-1471.

41. Stagi S, Rigante D, Lepri G (2016) Severe vitamin D deficiency in patients with Kawasaki disease: a potential rolein the risk to develop heart vascular abnormalities. Clin Rheumatol 35(7): 1865-1872.