



Advances in Research on the Relationship Between Vitamin D and Coronary Artery Disease in Kawasaki Disease

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Abstract

Vitamin D is a fat-soluble vitamin. Many studies have shown that vitaminD not only plays an important role in calcium and phosphorus metabolism, but also participates in immune regulation, substance metabolism, cell proliferation and differentiation. In recent years, the etiology and pathogenesis of (KD) in Kawasaki disease are not clear, but many studies have found that vitaminD deficiency plays an important role in coronary artery disease in patients with KD. Vitamin D participates in KD inflammation and coronary artery damage through nuclear transcription factor- κ B (NF- κ B) and tumor necrosis factor-expressing transcription factor- α (TNF- α) activity. This review reviews the research progress on the relationship between vitaminD and coronary artery disease in patients with KD.

Keywords

Kawasaki Disease; Vitamin D; Coronary Artery Disease

Kawasaki Disease

Summary of kawasaki disease

Kawasaki Disease (KD), also known as cutaneous mucosal lymph node syndrome, is a systemic non-specific vasculitis disease of unknown causes, which mainly affects children under 5 years old. KD was first proposed by Japanese scholar Tomisaku Kawasaki in 1967. The main manifestations are persistent fever and ineffective antibiotic treatment, bilateral bulbar conjunctival membrane congestion, cleft lip, bayberry tongue, cervical lymph node enlargement, scar swelling, pleomorphic rash, flushing and scleroma of fingertip skin, and perianal membranous desquamation during convalescence [1].

Epidemiology of kawasaki disease

Epidemiological investigation shows that the incidence of KD in Northeast Asian countries such as Japan, South Korea, China and Taiwan is 10-30 times higher than that in the United States and Europe. And the incidence of KD continues to rise in Northeast Asian countries [2-5]; however, in North America [6] and Europe, the incidence of KD is stable [4]. Makino showed that the incidence of KD was increasing in Japan. The latest known figure is 308 cases per 100,000 children under 5 years old in 2014 [5], and the incidence of KD in South Korea is also increasing (194.7 cases per 100,000 children under 5 years old in 2014) [6]. According to China's regional epidemiological studies, the incidence rate of different geographic areas is different, but the overall trend is increasing [7-59]. In China, Lin Meizhi and others conducted an epidemiological survey on children in Beijing and Shanghai by means of a questionnaire. The results it in a KD epidemiological study The National Health Insurance Review and report on the incidence rate showed that the incidence of KD in children under the age of 5 was 111.6 and 71.9/10 million, respectively. Researchers in Taiwan used of KD in 2010 was 82.8/10 million (under 5 years old) [7].

Etiology of Kawasaki disease

The etiology and pathogenesis of KD are unknown. In recent years, a large number of scholars have devoted themselves to the research and exploration of the etiology of KD, but so far no breakthrough has been made.

Due to the seasonality, clinical manifestations, blood routine, biochemistry, hypersensitive CRP, ESR and other indicators of KD are similar to the manifestations of infectious diseases, some scholars believe that KD is an infectious disease. At the same time, due to the ethnic differences in the incidence of KD in children, some scholars [9] believe that the incidence of KD is related to gene polymorphism to some extent. Among them, there are many studies on gene polymorphism of Myeloperoxidase (MPO), Tumor Necrosis

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Factor (TNF), CD40, BLK, FCGR2A and HLA gene polymorphism, and susceptibility to kawasaki disease [58]. In addition to infection factors, there are also immunological factors. Matsubara [8] proposed that the pathogenesis of KD may be related to superantigen reaction; some scholars also believe that the acute reaction period of KD may be related to the immune response induced by common antigen. It is considered that KD may be an autoimmune disease, and because it can cause cardiovascular complications, more and more attention has been paid to the relationship between KD and vitamin D.

Pathological changes of coronary artery lesion in KD

The main complication of KD is the damage of coronary artery in children. Its main pathological change is non-specific inflammation of small and medium vessels in the whole body, which mainly involves coronary artery, leading to coronary artery dilatation and coronary artery aneurysm, especially in children with giant aneurysm, is easy to form intratumoral thrombus, and coronary artery stenosis or occlusion often occurs in the long term, resulting in myocardial ischemia, myocardial infarction, and even sudden death [10].

Summary of Vitamin D

Physiological effects of vitamin D

After ultraviolet irradiation, 7-dehydrocholesterol can synthesize vitamin D, which is a steroid derivative and fat soluble vitamin. Cholecalciferol (vitamin D3) and ergocalcitol (vitamin D2), the metabolites of vitamin D, exist in plant sources and are the main sources of vitamin D in body. Cholecalciferol can also be directly obtained by diet after the skin is exposed to Ultraviolet (UV) radiation for photosynthesis. But ergocalcified alcohol can only be obtained by eating. Vitamin D, obtained from any source, is then converted into its active form 1Magne25-(OH) 2D3 by metabolism in the liver and kidneys. In hepatocytes, cholecalcitol or ergocalol is hydroxylated into 25-hydroxyvitamin D3 (25 (OH) D3), which has relatively low biological activity but mainly circulates under the action of microsomal hydroxylase. The last activation step occurred in renal tubular epithelial cells, where 25 (OH) D3 was converted into calcitriol by 1 α -hydroxylase (1mem25-(OH) 2D3) [11]. In addition to renal tubular epithelial cells, pancreatic cells, monocytes and other cells also express 1-alpha-hydroxylase, which makes the production of 1,25 - (OH) 2D3 possible outside the kidney [12]. Then, 1,25 - (OH) 2D3 was transported to the target organ and produced physiological effects by binding with vitamin D receptor. Vitamin D receptors exist in almost all tissues, especially in the colon, adrenal cortex, lungs and lymphocytes [13]. In the cardiovascular system, vitamin D receptors are found in endothelial cells and cardiomyocytes.

Therefore, vitamin D not only affects calcium and phosphorus metabolism, but also has a wide range of physiological functions. It is an essential substance to maintain human health, cell growth and development, and is closely related to a variety of diseases, including cancer, hypertension, infectious diseases and autoimmune diseases. It was also found that the active form of vitamin D, 1,25 - (OH) 2D3, has the effect of both calcium and phosphorus regulators and T / B cell proliferation inhibitors. 1,25 - (OH) 2D3 can inhibit the function of dendritic cells and macrophages, the synthesis of immunoglobulins, the transcription of IL-1, IL-2, IL-6, IL-12, TNF - α and TNF - γ [14-16]. From the point of view of immunology, it has been confirmed that the immune response is too strong and the immune tolerance is lost during vitamin D deficiency [48]. Some scholars have found that vitamin D also has a clear immunomodulatory effect, which can improve the immune balance of the body [49,50].

The effects of vitamin D on cardiovascular system

Vitamin D deficiency is associated with several serious consequences, including an increased risk of common cancers, autoimmune diseases, infectious diseases and cardiovascular disease, of which cardiovascular disease is at a higher risk, including hypertension, peripheral vascular disease, myocardial infarction,

heart failure, etc. [52]. In a cross-sectional study, Forman studied the relationship between vitamin D level and blood pressure in 184 patients with normal blood pressure. They found that compared with individuals with sufficient vitamin D content, those with vitamin D deficiency and vitamin D deficiency had higher plasma angiotension II level and renin activity. In addition, the intrinsic activity of the renin-angiotensin-aldosterone system, which is reflected in the response of the renin-angiotensin-aldosterone system to the renal plasma flow of angiotensin II, is also elevated [53]. Resnick [54] studied 51 patients with hypertension and found that there was a negative correlation between 25 (OH) 2D3 and plasma renin activity, suggesting that the decrease of plasma vitamin D level may be related to the increase of renin-angiotensin-aldosterone system activity. Some animal experiments have found that vitamin D can regulate the activity of renin-angiotensin-aldosterone system. These studies suggest that the decrease of plasma vitamin D level may be related to the increased activity of renin-angiotensin-aldosterone system.

Some studies have found that there are abnormal blood lipid levels in children with KD in acute, subacute and convalescent stages, and even abnormal blood lipid levels can persist into adulthood, and these children have a significantly increased risk of cardiovascular disease in adulthood [55,56]. Zheng [57] believed that it may be due to the decrease of serum HDL-C level, the increase of serum TC, TG, LDL-C level, the release and oxidation of low density lipoprotein particles, which further led to a large amount of LDL-C, TC influx into the intima of the vascular wall, causing damage to the vascular intima; oxidized LDL-C in turn, it attracts and stimulates macrophages to release many growth factors and pro-inflammatory mediators, thereby promoting the occurrence of inflammatory responses. Over time, high serum levels of TC and TG impair endothelial function, which in turn impairs arterial endothelium and is prone to stenosis and plaque formation, which is associated with atherosclerosis formation [56].

Effect of vitamin D on KD

The effect of vitamin D on immune regulation

The pathogenesis of KD is still unclear, vitamin D deficiency may affect the immune regulation function and inflammatory response of children with KD, and participate in the occurrence and development of KD and Coronary Artery Injury (CAL). At present, most scholars believe that the level of vitamin D is closely related to the occurrence and development of KD, and that low level of vitamin D is a risk factor for KD [22]. It is found that the disorder of immune regulation may be one of the main mechanisms of Kawasaki disease, among which, some scholars have found that the abnormal activation of T cells in children with KD is the key to vascular injury [17].

T lymphocytes develop from lymphoid stem cells in thymus bone marrow. Mature T cells settle in the peripheral immune organs and exert their immune function through lymphatic vessels, blood circulation and tissue fluid blood circulation and lymphatic transport circulation. T cells are small lymphocytes. Apoptosis occurs after 24 hours of culture in vitro, and death and cleavage occurs 72 hours later. Therefore, it is necessary to add PHA, concanavalin A (ConA) or CD3 monoclonal antibodies to T cells in vitro culture to stimulate cell proliferation and avoid apoptosis [18,19]. PHA is the most widely used stimulator to stimulate human lymphocyte mitosis, and the resulting lymphocyte proliferation belongs to non-specific transformation. Although T cells have different recognition processes for specific and non-specific antigens, the process of inducing division and proliferation is the same.

The abnormal activity of T cells may be the initial link of immune system activation and eventually lead to vascular immune injury, and then lead to waterfall effect of various cytokines in the body, and finally lead to systemic inflammatory response mediated by inflammatory factors [33]. Qi Xiaoli [21] used T cell separation column to isolate T cells with purity up to 90%. Before isolation, peripheral blood mononuclear cells were stimulated and cultured with PHA. It is found that 1,25-(OH)2D3 receptor vitamin D receptor (VDR) was

expressed in T cell nucleus, and the expression of VDR Vitamin D Receptor (VDR) in T cells of children with KD was significantly higher than that in children with infectious fever and normal children, which may be closely related to abnormal activation of T cells in children with KD. Apoptotic T cells in the peripheral blood of children with KD can not initiate normal apoptotic procedures, continue to proliferate and differentiate, eventually leading to the increase and abnormal activation of T cells, leading to immune imbalance. 1,25-(OH)2D3 can inhibit T cell overproliferation by regulating part of the signal transduction pathway. Suzuki and his colleague [20] found that the markers of T cell activation in the acute phase of KD increased, while the markers of T cell activation in the acute phase of refractory KD increased more significantly. T cell activation may play an important role in the development of KD vasculitis itself and CAL.

Wang Juanli conducted a case-control study and found that the serum 25-(OH)D3 level in the CAL group was significantly higher than that in the non-coronary artery injury (NCAL) group, and CD4/CD8 in the CAL group was significantly higher than that in the NCAL group. It was further confirmed that 25-(OH)D3 participated in the KD inflammatory response and the occurrence of coronary artery damage, which may be related to its influence on the distribution of T cell subsets [23].

The effect of vitamin D on coronary artery endothelial cells

Vitamin D receptors and 25OH D are expressed in several cells of the vascular wall, such as endothelial cells and vascular smooth muscle cells, by enzymes necessary to activate 1,25(OH)2D or inactivate 24R-hydroxylated metabolites [44]. They locally produce a potent vasodilator, Nitric Oxide (NO), by stimulating endothelium-induced NO synthase [45]. Meanwhile, 1,25(OH)2D reduces the production of vasoconstrictors by inhibiting COX-1 [46]. 1,25(OH)2D also reduces the production of superoxide in the vascular wall by inhibiting p22(Phox) and NADPH oxidase subunits, thereby reducing the production of H2O2 [47]. Uberti and colleagues found that 1,25(OH)2D could inhibit endothelial cell apoptosis in vitro by inhibiting oxidative stress and mitochondrial release of cytochrome C.

It has been found that vitamin D can regulate immune function and inhibit inflammatory reaction, which is closely related to autoimmune diseases [31], and plays an important role in the pathogenesis of cardiovascular system diseases [32]. In early studies, Some scholars have demonstrated that nuclear transcription factor- κ B (NF- κ B) is a transcription factor- α (TNF- α) activity that regulates the expression of pro-inflammatory cytokines and tumor necrosis factor plays an important role in the pathogenic process of KD [24-28].

High-level expression of intercellular adhesion molecule-1 (ICAM-1, CD54) and vascular cell adhesion molecule-1 (VCAM-1, CD106) in vascular endothelial cells in the acute phase of Kawasaki disease may be induced by NF- κ B activation Systemic vasculitis caused by TNF- β [29]. It is reported that 1,25-(OH) 2D3 can be used to treat inflammatory diseases, including Behcet's disease, inflammatory bowel disease, multiple sclerosis, experimental sepsis, and inflammatory polyarthritis [30].

In addition, arterial endothelial cells are known to be activated in acute KD because of elevated levels of soluble forms of various adhesion molecules in peripheral blood [29,30]. It has also been found that the production of TNF- α in macrophages and the activation of NF- γ B, and the expression of intercellular adhesion molecule-1 (ICAM-1,CD54) and vascular cell adhesion molecule-1 (VCAM-1,CD106) in human umbilical vein endothelial cells induced by TNF- α are inhibited by 1,25-(OH) 2D3 [33-38]. Therefore, the reduction of vitamin D content in the body makes the coronary arteries of KD patients more vulnerable to injury, which provides a basis for the use of vitamin D in the treatment of coronary endothelial injury in KD patients.

In addition, vitamin D can alleviate vascular calcification and reduce the risk of CAL by regulating calcium ions. Some animal experiments have found that VDR knockout mice have elevated blood pressure and cardiac hypertrophy, suggesting that vitamin D binds to VDR, stimulate calcium pump (Ca2+ATPase) activity and calcium absorption in coronary artery, cardiomyocytes and vascular smooth muscle cells, reduce vascular wall calcification and reduce cardiovascular risk. It was found that coronary artery calcification was inversely proportional to serum 25-(OH) D3 level [39]. It can be seen that vitamin D can regulate Ca2+, improve vascular disease and play a role in cardiovascular protection. In conclusion, vitamin D can improve vascular endothelial function and coronary inflammatory response of KD children through multiple mechanisms, which can prevent the occurrence of cal to some extent.

The predictive effect of vitamin D on coronary lesions in children with KD

Stagi [40] compared the levels of 25-(OH) D3 in 79 children with KD and normal children. The results showed that the level of serum 25-(OH) D3 in children with KD was significantly lower than that in normal children ($P < 0.0001$), especially in patients with coronary artery abnormality ($P < 0.0001$). It was also found that the level of 25-(OH) D3 was negatively correlated with erythrocyte sedimentation rate and CRP ($P < 0.0001$). It is suggested that the level of low serum 25-(OH) D3 may play an important role in the occurrence and development of vasculitis and coronary artery complications in children with KD.

According to Zhang Yuanda [41], the level of 25-(OH) D3 in children with KD was significantly lower than that in healthy children. Considering the decrease of 25-(OH) D3 level, it was involved in the pathological process of KD. Most studies believe that children with a significant decrease in 25-(OH) D3 level are more likely to have coronary artery injury, so the extent of the decrease in 25-(OH) D3 level may be related to whether KD children have coronary artery injury. Therefore, the level of serum 25-(OH) D3 in the acute stage of KD plays an important role in predicting the formation of CAL. On the contrary, it was also found that the serum 25-(OH) D3 level in Kawasaki disease patients with cal was significantly higher than that in NCAL group and healthy children group [22,23-51], the diagnostic break point is 64ng/ml [51] or 65ng/ml [22], which may be related to the excessive calcification of coronary artery, the increase of CYP27B1 expression, and the increase of blood 25-(OH) D3 level [22], and the increase of 25-(OH) D3 level due to the intense inflammatory reaction, resulting in the increase of receptor number [40].

Conclusion

KD is a acute febrile rash disease with systemic vasculitis as the main lesion. Clinical manifestations are not simultaneous, and it is difficult to differentiate from other diseases. Laboratory examination is also lack of specificity. In recent years, the incidence rate of KD is getting higher and higher, which has attracted clinicians' high attention. At present, KD has become the most common cause of childhood acquired heart disease in Japan, Europe and North America. As KD will be complicated with multiple system and organ damage, including CAL is the most common, severe coronary artery aneurysm can occur, resulting in myocardial ischemia infarction and even life-threatening [42]. At this stage, the standard treatment for patients with KD is intravenous Infusion of Gamma Globulin (IVIG) combined with high-dose aspirin. The study found that early intervention in patients with KD can reduce the incidence of coronary artery injury to 3.0% to 5.0%, and the mortality rate to 0.2%. The incidence of CAL in children without timely intervention is 15.0% to 25.0% [43], so early prediction of coronary artery injury is of great significance for children with KD.

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