

Vitamin D and Cardiovascular Risk in Children

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Abstract

Objective: Vitamin D is a group of fat-soluble molecules that are structurally similar to steroids. Emerging data have led to the hypothesis that Vitamin D plays a role in the regulation of many physiological processes beyond calcium and phosphorus homeostasis. With this review, we aimed to summarize the changes in Vitamin D levels in children with cardiovascular diseases based on the literature. In addition, we also reviewed the potential mechanisms underlying cardiovascular diseases associated with Vitamin D deficiency or insufficiency.

Data Sources: The articles in English were searched from PubMed (1968–2016) and EMBASE (1991–2016), with the keywords of “Vitamin D AND cardiovascular diseases” and “Vitamin D AND children.”

Study Selection: Original articles and critical reviews about Vitamin D and cardiovascular risk in children were selected for review. Researches focused on adults were excluded.

Results: Studies have shown that several pediatric cardiovascular diseases may be associated with Vitamin D deficiency or insufficiency, including hypertension, orthostatic intolerance, and Kawasaki disease.

Conclusions: Vitamin D may play a role in the regulation of the cardiovascular system. Further investigation would hopefully disclose the usefulness of Vitamin D as a biomarker for cardiovascular diseases in children.

Key words: Cardiovascular Diseases; Children; Vitamin D

INTRODUCTION

Vitamin D is a group of fat-soluble molecules that are structurally similar to steroids. Emerging data have led to the hypothesis that Vitamin D plays a role in the regulation of many physiological processes beyond calcium and phosphorus homeostasis. The aim of this review was to summarize the changes in Vitamin D levels in children with cardiovascular diseases based on the literature. In addition, we also reviewed the potential mechanisms underlying cardiovascular diseases associated with Vitamin D deficiency or insufficiency.

METABOLISM OF VITAMIN D

Cholecalciferol (Vitamin D₃) and ergocalciferol (Vitamin D₂) are the primary sources of Vitamin D *in vivo*. Cholecalciferol is photosynthesized in response to ultraviolet (UV) irradiation of the skin and can be acquired directly by dietary intake as well. Ergocalciferol can only be acquired through food intake. Vitamin D obtained from any source is then converted to its active form 1,25(OH)₂D₃ by liver and kidney metabolism. In liver cells, cholecalciferol or ergocalciferol is

hydroxylated into 25-hydroxyvitamin D (25(OH)D₃), which has relatively low biological activity but is a major circulating form, by microsomal hydroxylase. The last activating step occurs in the renal tubular epithelial cells, where 25(OH)D₃ is converted into calcitriol (1,25(OH)₂D₃) by 1- α -hydroxylase.^[1] In addition to renal tubular epithelial cells, pancreatic cells, monocytes, and other cells also express 1- α -hydroxylase, which makes the generation of 1,25(OH)₂D₃ outside the kidney possible^[2] [Figure 1]. 1,25(OH)₂D₃ is then transported to target organs, producing physiological effects by binding to the Vitamin D receptor. Vitamin D receptor has been found in almost all tissues, especially in the colon, adrenal cortex, lungs, and lymphocytes.^[3] In the cardiovascular system, Vitamin D receptors have been found in both endothelial cells and myocardial cells.^[4,5]

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Received: 04-07-2017 **Edited by:** Yuan-Yuan Ji
How to cite this article: Xu WR, Jin HF, Du JB. Vitamin D and Cardiovascular Risk in Children. Chin Med J 2017;130:2857-62.

Access this article online

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DOI:
10.4103/0366-6999.215500

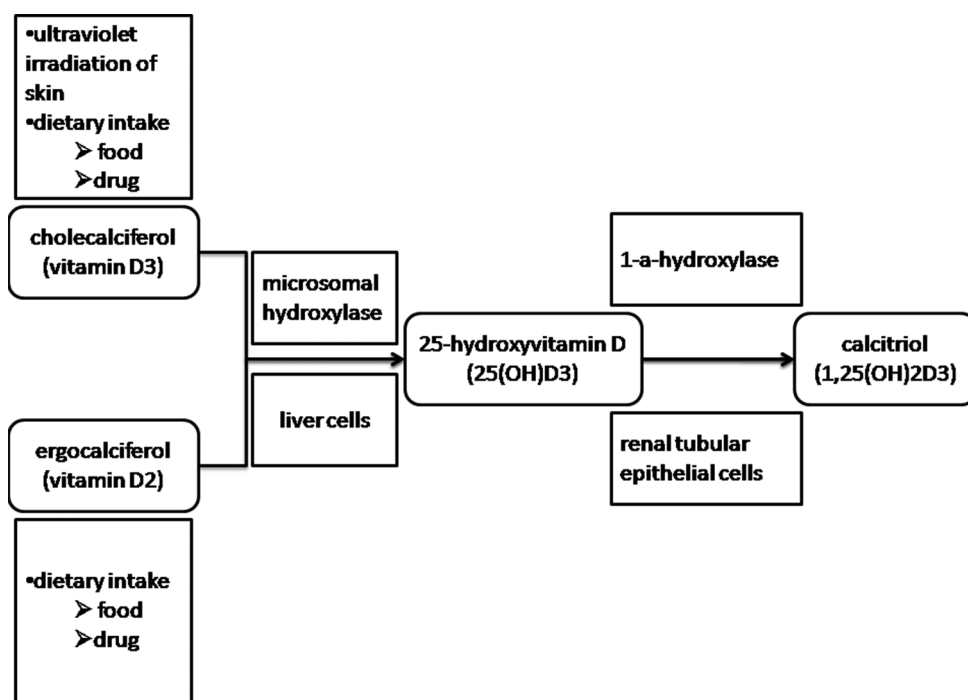


Figure 1: The metabolism of vitamin D. Cholecalciferol (Vitamin D₃) and ergocalciferol (Vitamin D₂) are the primary sources of Vitamin D *in vivo*. Cholecalciferol is photosynthesized in response to ultraviolet irradiation of the skin and can be acquired directly by dietary intake. Ergocalciferol can only be acquired through food intake. Vitamin D obtained from any source is then converted to 1,25(OH)₂D₃ by liver and kidney metabolism.

The Vitamin D receptor is a member of the steroid hormone/thyroid hormone receptor family. It is classified into two types: a membrane-bound Vitamin D receptor and a nuclear-bound Vitamin D receptor. After combining with 1,25(OH)₂D₃, the nuclear-bound Vitamin D receptor dimerizes with the retinoid X receptor, forming a joint complex. The complex then combines with specific promoter regions of target genes called Vitamin D response elements, serving as a transcription factor and regulating the expression of target genes. The process described above takes a few hours or days to work.^[6,7] 1,25(OH)₂D₃ also mediates nongenomic effects through the membrane-bound Vitamin D receptor, which occurs over a few seconds or minutes.^[7,8]

Levels of Vitamin D within the optimal range (25-hydroxyvitamin D >20 ng/ml) will maintain normal homeostasis. However, in the presence of a Vitamin D insufficiency (12–20 ng/ml 25-hydroxyvitamin D) or deficiency (25-hydroxyvitamin D ≤20 ng/ml), the physiological axis is disrupted. Children with a Vitamin D deficiency or insufficiency status have been shown to have increased cardiovascular disease susceptibility, such as hypertension, orthostatic intolerance, and Kawasaki disease, as described in detail in this review.

VITAMIN D AND THE HIGH RISK OF HYPERTENSION

The data from the National Health and Nutrition Examination Surveys from 2001 to 2006 showed an inverse association between serum 25(OH)D₃ and systolic blood pressure after adjusting for age, sex, race-ethnicity, and body mass index. A total of 5281 adolescents aged from 12 to 19 years

old were included in the study. Systolic blood pressure was significantly higher in the low serum 25(OH)D₃ group (serum 25(OH)D₃ <48.1 nmol/L) than that of the middle (serum 25(OH)D₃ 48.1 to <66.2 nmol/L) and high groups (serum 25(OH)D₃ 66.2 nmol/L) (109.8 ± 0.5 vs. 108.2 ± 0.4 and 108.4 ± 0.4 mmHg, *P* = 0.01).^[9] Similarly, in a population-based study of 1,441 Peruvian adolescents aged 13–15 years old, it was found that 25(OH)D₃ deficiency (serum 25(OH)D₃ <50 nmol/L) was associated with elevated diastolic blood pressure and mean arterial pressure. In this study, diastolic blood pressure was higher in the 25(OH)D₃-deficient group than the 25(OH)D₃-sufficient group (*P* = 0.04).^[10] Pacifico *et al.* similarly concluded that with increasing serum 25(OH)D₃ levels, there was a significant decrease in median systolic and diastolic blood pressure values.^[11] Petersen *et al.* also found that each 10 nmol/L serum 25(OH)D₃ increase was associated with lower diastolic blood pressure (−0.3 mmHg, 95% confidence interval −0.6, −0.0) (*P* = 0.02), which was independent of the fat mass index.^[12]

Despite the animal experiments and epidemiological studies, a growing amount of clinical trials have suggested that Vitamin D could down-regulate the activity of the renin-angiotensin-aldosterone system, which might explain the hypertensive tendency in Vitamin D-deficient and Vitamin D-insufficient individuals. The renin-angiotensin-aldosterone system is one of the main regulatory mechanisms that maintain the homeostasis of blood pressure and electrolytes. Renin is secreted by the juxtaglomerular cells of the kidney in response to decreased renal blood flow. It converts plasma angiotensinogen to angiotensin I, which is then converted

to angiotensin II by angiotensin-converting enzyme in pulmonary vascular endothelial cells. Angiotensin II leads to the elevation of blood pressure by directly constricting the arteries, thereby stimulating the adrenal cortex to secrete aldosterone, which then increases blood volume, and by promoting the adrenal medulla as well as the sympathetic nerve endings to release catecholamine.^[13,14]

In a cross-sectional study, Forman *et al.* studied the relationship between Vitamin D levels and blood pressure in 184 normotensive individuals. Compared with individuals of adequate Vitamin D status, the Vitamin D-deficient and Vitamin D-insufficient individuals had higher plasma angiotensin II levels and renin activity. Moreover, the intrinsic activity of the renin-angiotensin-aldosterone system reflected by the renal plasma flow response to infused angiotensin II was also elevated.^[15] Resnick *et al.* studied 51 patients with essential hypertension, indicating that $1,25(\text{OH})_2\text{D}_3$ and plasma renin activity were negatively correlated.^[16] These results suggested that a decrease in the level of plasma Vitamin D might be associated with an increase in the activity of the renin-angiotensin-aldosterone system. In children, clinical trials those focused on the relationships between Vitamin D status and the renin-angiotensin-aldosterone system were limited. However, there has been a case report of an 8-month-old infant with hypocalcemia, rickets, and low $1,25(\text{OH})_2\text{D}_3$ levels who was genetically diagnosed with Vitamin D-dependent rickets Type I. The undetectable $1,25(\text{OH})_2\text{D}_3$ and elevated renin levels normalized during calcitriol therapy, which corroborates the link between Vitamin D and the renin-angiotensin-aldosterone system.^[17]

To reveal the mechanism by which Vitamin D regulates the renin-angiotensin-aldosterone system, Li *et al.* analyzed Vitamin D receptor-knockout animals. They found that the rennin gene expressed in the kidney was increased as well as the angiotensin II activity in plasma. Meanwhile, these Vitamin D receptor-knockout animals had high blood pressure, myocardial hypertrophy, and increased water intake. Interestingly, all the above processes could be reversed by angiotensin converting enzyme inhibitors. In wild-type rats, inhibition of $1,25(\text{OH})_2\text{D}_3$ synthesis led to an increase in renin expression, whereas $1,25(\text{OH})_2\text{D}_3$ supplement led to renin suppression.^[18]

Subsequent studies further confirmed this mechanism. When Vitamin D is insufficient or deficient, the cyclic adenosine monophosphate (c-AMP) response element binding protein combines with the c-AMP response element. The complex further recruits an auxiliary activation factor to CBP/p300 and finally leads to the activation of the renin gene promoter. When Vitamin D is sufficient, the Vitamin D receptor would bind to the ligand site of the c-AMP response element binding protein and occupy the binding site, thereby blocking their binding and activation of downstream gene promoters.^[19] To study whether the regulation of the renin-angiotensin-aldosterone system by $1,25(\text{OH})_2\text{D}_3$ was dependent on calcium-phosphorus

metabolism, Zhou *et al.* performed diet intervention on $1-\alpha$ -hydroxylase gene-knockout mice. The $1-\alpha$ -hydroxylase gene-knockout mice failed to produce active Vitamin D and therefore showed similar phenotypes as Vitamin D receptor-knockout mice, including hypocalcemia, low phosphorus levels, secondary hyperparathyroidism, growth restriction, and rickets symptoms. They found that the $1-\alpha$ -hydroxylase gene-knockout mice had an activated renin-angiotensin-aldosterone system and eventually led to high blood pressure, myocardial hypertrophy, and impaired systolic cardiac function. Dietary supplementation of calcium and phosphorus failed to correct the occurrence of high blood pressure or inhibit the activation of the renin-angiotensin-aldosterone system despite succeeding in normalizing the plasma calcium and phosphate levels. On the other hand, the supplementation of $1,25(\text{OH})_2\text{D}_3$ achieved both aims, suggesting that $1,25(\text{OH})_2\text{D}_3$ may directly inhibit the activation of the renin-angiotensin-aldosterone system.^[20] Therefore, it is possible that both Vitamin D-deficient and Vitamin D-insufficient groups have a higher risk of hypertension.

VITAMIN D AND ORTHOSTATIC INTOLERANCE IN CHILDREN

Antiel *et al.* reviewed the records of 188 adolescents with symptoms of fatigue and/or orthostatic intolerance. Of the 188 patients, 130 (69%) had excessive postural tachycardia with a heart rate change of ≥ 30 beats/min. There was a marked increase in the prevalence of hypovitaminosis D from 14% in the normal adolescent population to 30% in adolescent patients with excessive postural tachycardia.^[21,22] Shaltout and Glock identified 30 children between the ages of 10–18 years who presented with orthostatic intolerance. They found that serum $25(\text{OH})\text{D}_3$ tended to be lower in orthostatic-intolerant individuals versus nonorthostatic-intolerant individuals (18.6 ± 0.7 ng/ml, $n = 25$, vs. 22.2 ± 2.4 ng/ml, $n = 15$; $P = 0.016$). Most importantly, $25(\text{OH})\text{D}_3$ was highly and positively correlated with supine measurements of baroreflex sensitivity ($R = 0.51$, $P = 0.05$) and heart rate variability ($R = 0.44$, $P = 0.02$) in the orthostatic-intolerant group, and it was negatively correlated with sympathovagal balance, which was reflected by the low frequency to high frequency ratio (LF/HF ratio) ($R = -0.35$, $P = 0.08$).^[23]

These findings highlighted a potential role of Vitamin D in orthostatic intolerance in children and adolescents. The precise pathogenesis is not entirely clear. Studies have shown that orthostatic intolerance may be associated with several factors such as impaired cardiac autonomic tone and abnormal local vascular tension, in which Vitamin D has also been found to have a regulatory effect.

Vitamin D and regulation of the cardiovascular autonomic tone

The autonomic nervous systems (the sympathetic nervous system and the parasympathetic nervous system) interact to ensure homeostasis and to control a series of spontaneous

physiological processes, including digestion, respiration, and cardiovascular function. The disturbance of the cardiovascular autonomic system gives rise to a series of diseases.

Postural tachycardia syndrome, a common cause of orthostatic intolerance in children and adolescents, is one of them. It is known that the production of active Vitamin D metabolites requires a hydroxylation process by the kidneys. In chronic kidney disease patients, the prevalence of Vitamin D deficiency is obviously higher than that of the general population due to the dysfunctional renal tissue.^[24] Simultaneously, patients with chronic kidney disease have a high incidence of impaired cardiac autonomic tone. In a survey by Chan *et al.*, the heart rate variability indices of 239 adult hemodialysis patients showed characteristics of sympathetic overactivity and vagal withdrawal.^[25] Similar statistics in children are still limited, as only one study on the heart rate variability of children with chronic kidney disease the heart rate variability of children with chronic kidney disease has been published to date. Their findings are also similar to those in adults,^[26] therefore leading to the hypothesis that Vitamin D may be associated with the cardiac autonomic tone.

Krause found that after whole-body UV radiation, the median of the RR-interval time and the mean of the standard deviation of the RR-intervals increased by 20% and 25%, respectively, and were accompanied by the elevation of serum 1,25(OH)₂D₃ to its maximum level.^[27] These findings implied that UV exposure could improve the cardioprotective vagal activity through elevating the Vitamin D status.

In healthy controls, there have also been increasing investigations that implicate an interaction between Vitamin D and the cardiovascular autonomic system. Mann *et al.* found that there was a significant association between low serum 25(OH)D₃ levels and decreased baseline cardiac autonomic activity in healthy controls. They also found that low serum 1,25(OH)₂D₃ levels were associated with unfavorable cardiac autonomic activity in response to the acute angiotensin II stressor.^[28] This phenomenon may explain the elevated cardiovascular disease risk in the Vitamin D-deficient population.^[29,30] However, the small sample size included in the trial reduced the generalizability of their conclusion. In a cross-sectional study, Tak *et al.*^[31] enrolled 176 healthy volunteers, and analyzed the serum 25(OH)D₃ levels and heart rate variability indices. Eventually, they found that lower 25(OH)D₃ levels were associated with lower heart rate variability, which was consistent with the results from Mann *et al.*^[32] Canpolat *et al.* also found that cardiac autonomic functions were impaired in patients with Vitamin D deficiency despite the absence of overt cardiac involvement and symptoms.^[33]

Furthermore, Mann *et al.* found that Vitamin D supplementation (10,000 IU cholecalciferol) could improve the cardiac autonomic nervous system balance, especially the vagal activity in response to an external stressor in healthy humans.^[32]

Vitamin D and vascular endothelial function

London *et al.* measured brachial artery distensibility, flow-mediated vasodilation, serum 25(OH)D₃ levels, and serum 1,25(OH)₂D₃ levels in 52 patients on hemodialysis. Independent of age and systolic blood pressure, they observed positive correlations between the two metabolites of Vitamin D and brachial artery distensibility as well as flow-mediated vasodilation. The results suggested that low 25(OH)D₃ and 1,25(OH)₂D₃ status might be associated with endothelial dysfunction in patients on hemodialysis.^[34] Then, in a subsequent study that comprehensively assessed vascular function in a community-based asymptomatic population, Al Mheid *et al.* discovered a positive correlation between serum 25(OH)D₃ levels and flow-mediated vasodilation.^[35] Nitric oxide, an endogenous gaseous signal molecule that has been accepted as a vasodilatation factor, could reflect vascular endothelial cell function. A significant correlation between flow-mediated vasodilation and the activity of nitric oxide synthase, the key enzyme in the production of nitric oxide, has been demonstrated.^[36] Andrukhova *et al.* found that both 3- and 9-month-old Vitamin D receptor-knockout mice showed decreased aortic expression of nitric oxide synthase 3. Moreover, the above process was regulated by the direct effect of Vitamin D on the Vitamin D receptors of endothelial cells and vascular smooth muscle cells.^[4] Therefore, it might be possible that 1,25(OH)₂D₃ stimulates the transcription of nitric oxide synthase 3 through the nuclear-bound Vitamin D receptor pathway and increases the production of nitric oxide, which, in turn, acts on the vascular smooth muscle cells to control vascular tone.^[37]

VITAMIN D AND KAWASAKI DISEASE

Kawasaki disease is characterized by acute systemic vasculitis and is the most common cause of acquired cardiovascular disease in children in developed countries. It results in coronary artery abnormalities in up to 25% of children if left untreated.^[38] The etiology and pathogenesis of Kawasaki disease are not fully clear, although much progress has been made in recent years. It has been hypothesized that the initiation of vasculitis might be associated with various inflammatory cytokines as well as the activation of endothelial cells and vascular smooth muscle cells.^[39,40]

Stagi *et al.* compared the serum 25(OH)D₃ levels of 79 children with Kawasaki disease with 234 healthy controls. By echocardiography, 4 of the children with Kawasaki disease were confirmed to have developed coronary artery aneurysms. Finally, they found that Kawasaki disease patients had severely reduced serum 25(OH)D₃ levels compared with healthy sex-/age-matched controls (9.17 ± 4.94 vs. 23.3 ± 10.6 ng/ml, $P < 0.0001$), especially within the subgroup of patients who had developed coronary artery aneurysms (4.92 ± 1.36 vs. 9.41 ± 4.95 ng/ml, $P < 0.0001$). In addition, by evaluating the correlation among 25(OH)D₃, age at diagnosis, sex, and other general or laboratory data, they noted that 25(OH)D₃ levels were negatively correlated with coronary artery aneurysms ($\beta = -0.38$, $P = 0.013$).^[41]

However, there have been inconsistent results. Chen *et al.* analyzed the serum 25(OH)₂D₃ levels of 35 children with Kawasaki disease in the acute phase and 30 healthy children, showing that serum 25(OH)₂D₃ levels were significantly increased in children with Kawasaki disease who also had coronary arterial lesions.^[42]

The correlations between Vitamin D and Kawasaki disease might be partly explained by the recent findings that 1,25(OH)₂D₃ exhibits anti-inflammatory effects. Suzuki *et al.* found that the pretreatment with 1,25(OH)₂D₃ significantly inhibited tumor necrosis factor- α (TNF- α)-induced nuclear factor κ B activation and TNF- α -induced expression of E-selectin in human coronary artery endothelial cells.^[43] Similarly, pretreatment with 1,25(OH)₂D₃ significantly inhibited the expression of TNF- α -induced adhesion molecules (vascular cellular adhesion molecule-1 and interleukin-8) in human coronary artery endothelial cells.^[44] In addition, it was demonstrated that Vitamin D could down-regulate the expression of adhesion molecules to prevent vascular smooth muscle cell proliferation and macrophage activation. However, some studies reported that low Vitamin D concentrations might not be a causal factor rather than the result of inflammation.^[45,46]

EXPECTATION

Further studies are required to explore the precise role of Vitamin D in the diagnosis, treatment and prognosis of cardiovascular diseases in children. At present, there are still some problems to be solved, such as the cutoff value that would definitely lead to morbidity and the boundary value that indicates a need for intervention. There also have not been reports regarding whether supplementation of Vitamin D could reduce the cardiovascular risk in children, such as lowering blood pressure, improving orthostatic intolerance, and attenuating coronary artery aneurysms in children with Kawasaki disease. In addition, further investigation would hopefully disclose the usefulness of Vitamin D as a biomarker for cardiovascular diseases in children.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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