

Research Progress of Vitamin D in Adolescent Patients with Hypertension

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Abstract. High blood pressure is a common chronic disease that affects the health of a large number of the world's population. With the development of society, the prevalence rate of adolescents is on the rise. It is estimated that 30% to 50% of people worldwide have low levels of vitamin D. Vitamin D deficiency is also more common in adolescents. In 2019, researchers used the method of meta-analysis to include 47 kinds of literature that met the requirements of blood pressure measurement at three different time points to estimate the prevalence of hypertension in children and adolescents under 19 years old worldwide. The results showed that the prevalence of hypertension in children and adolescents increased globally in the past 20 years, with the combined prevalence of hypertension (systolic blood pressure/diastolic blood pressure $\geq$ P95) being 4.0%, and the combined prevalence of prehypertension ($P90 \leq$ systolic blood pressure/diastolic blood pressure $<$ P95) was 9.67%. Although medical research has made significant progress in the prevention and treatment of hypertension, further research and exploration of new treatments are still needed.

Keywords: Adolescent hypertension, Vitamin D, antihypertensive mechanism.

1. Introduction

Vitamin D is a steroid hormone, known as the "sunshine hormone", it is a necessary nutrient for the human body, and is closely related to bone metabolism, calcium and phosphorus balance and cardiovascular disease [1-3]. Vitamin D receptor (VDR) is found in almost every nucleated cell in the body. It is a transcription factor that regulates gene expression and performs important functions in the body by binding to membrane receptors and nuclear receptors. Adolescent hypertension refers to a high blood pressure of 140/90 mm Hg during adolescence when the blood pressure is higher than normal, that is when the blood pressure is quiet. In recent years, a growing number of studies have shown a strong relationship between vitamin D deficiency and high blood pressure in adolescents. Adolescent hypertension may be related to genetics, diet, lifestyle and other factors, and vitamin D deficiency may also be an independent risk factor for adolescent hypertension. Vitamin D helps maintain calcium balance in the body and plays an important role in vascular endothelial function. Vitamin D deficiency in adolescents may lead to increased blood vessel stiffness and affect stable blood pressure. Therefore, for adolescents at risk of high blood pressure, appropriate vitamin D supplementation may help regulate blood pressure and prevent the occurrence of hypertension. Clinically, vitamin D can regulate blood pressure and prevent osteoporosis, maintain calcium balance in the human body, affect vascular endothelial function, and can also be combined with antihypertensive drugs to increase the efficacy of a variety of antihypertensive drugs.

This article aims to review the research progress of vitamin D in adolescents with hypertension. Based on the research progress in this field, it is found that there is still a large research space and application prospect. Based on its potential mechanism and clinical application prospects, this paper discusses it in an all-round way in order to provide new ideas and methods for the prevention and treatment of hypertension in adolescents.

2. Hypertension

2.1. Classification of hypertension

Essential hypertension refers to high blood pressure due to family hereditary causes, or unknown causes, usually caused by a combination of genetic and environmental factors. For example, high blood pressure in the family, smoking, alcoholism, and a diet high in salt and oil may be triggers.

Secondary hypertension means that the cause of high blood pressure can be found, and this high blood pressure is called secondary hypertension. It may be due to the presence of hyperthyroidism, hypothyroidism, glomerulonephritis, and some people may be due to adrenal occupation, renal vascular stenosis, cranial occupation, pregnancy, etc., which is called secondary hypertension.

2.2. Adolescent Hypertension

With the change of living conditions and lifestyle in modern society, hypertension has become normal in young people. Studies have shown that the level and detection rate of hypertension in adolescents and children in China have increased [4]. Teenagers' living habits, diet structure, family heredity and so on are all important influencing factors. Obesity is the main cause of adolescent hypertension, and the prevalence of hypertension in primary and secondary schools is directly related to the increase in obesity rate. Mild adolescents with high blood pressure may have no obvious symptoms for a period of time, and only a small number of individuals will experience headaches, tinnitus, and difficulty concentrating. These symptoms can be misdiagnosed or delayed because they are not obvious enough to distinguish them from other disease symptoms, or because the patient is too young to accurately express them in words.

Adolescent hypertension is affected by both primary and secondary factors and cannot be attributed to any single factor. For adolescents with essential hypertension, genetic factors play an important role. According to research, adolescents with a family history of high blood pressure have a higher risk of developing essential hypertension. In addition, unhealthy lifestyle, such as irregular work and rest, high-salt and high-fat diet, exercise time, etc., may also be contributing factors. For adolescents with secondary hypertension, high blood pressure is due to disease. In adolescent patients, endocrine diseases, kidney diseases are important reasons.

3. Antihypertensive mechanism of vitamin D use in adolescents

3.1. Experimental Research

At present, experimental studies have confirmed that vitamin D plays a significant role in the treatment of hypertension. In the 2020 experiment, Zhang et al divided 120 patients with vitamin D deficiency and insufficiency into the observation group and the control group, 60 cases in each group. [5]. To receive antihypertensive treatment according to the Chinese Guidelines for Hypertension Prevention and Treatment, adhere to taking original antihypertensive drugs on time, do not change the type and dose of antihypertensive drugs, and guide patients to adjust their healthy life and diet. On this basis, patients in the observation group were supplemented with vitamin D and given calcitriol softgel capsule (produced by Qingdao Zhengda Haier Pharmaceutical Co., LTD.) 0.25 μ g/d in the morning for 6 months. The experimental patient was an adult, but it had certain significance for adolescents. There was no statistical significance in gender, age, TG and TC levels between vitamin D deficiency group and vitamin D deficiency group ($P>0.05$). There were significant differences in BMI, hypertension grade, high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and arterial elasticity index ($P<0.05$).

References are cited in the text just by square brackets [1]. (If square brackets are not available, slashes may be used instead, e.g. /2/.) Two or more references at a time may be put in one set of brackets [3, 4]. The references are to be numbered in the order in which they are cited in the text and are to be listed at the end of the contribution under a heading References, see our example below.

Table 1. Comparison of hypertensive patients before and after receiving vitamin D treatment [5]

	Systolic pressure (mmHg)		Diastolic blood pressure (mmHg)		TC (mmol/L)	
	pre-treatment	post-treatment	pre-treatment	post-treatment	pre-treatment	post-treatment
Control group	157.4 + / - 9.20	126.58 + / - 9.24	108.49 + / - 9.22	86.21 + / - 8.36	1.33 + / - 0.45	1.36 + / - 0.42
Observation group	159.22 + / - 10.35	121.03 + / - 10.25	110.36 + / - 8.42	82.73 + / - 8.57	1.32 + / - 0.48	1.15 + / - 0.45
T-value	0.984	3.115	1.160	2.252	0.118	2.643
p-value	0.327	0.002	0.248	0.026	0.906	0.009
	HDL-C (mmol/L)		LDL-C (mmol/L)			
	pre-treatment	post-treatment	pre-treatment	post-treatment	pre-treatment	post-treatment
Control group	4.20 + / - 0.81	4.15 + / - 0.81	1.07 + / - 0.24	1.08 + / - 0.28	2.42 + / - 0.38	2.43 + / - 0.42
Observation group	4.14 + / - 0.80	3.79 + / - 0.69	1.13 + / - 0.30	1.23 + / - 0.27	2.47 + / - 0.43	2.23 + / - 0.39
T-value	0.416	2.621	1.210	2.987	0.675	2.703
p-value	0.678	0.010	0.229	0.003	0.501	0.008
	Arterial elasticity index		BMI (kg/m ²)			
	pre-treatment	post-treatment	pre-treatment	post-treatment	pre-treatment	post-treatment
Control group	12.09 + / - 0.81	12.12 + / - 1.96	23.24 + / - 1.56	23.31 + / - 1.53		
Observation group	11.68 + / - 1.72	13.07 + / - 1.84	23.58 + / - 1.78	22.60 + / - 1.82		
T-value	1.190	2.737	1.113	2.313		
p-value	0.236	0.007	0.268	0.022		

According to the data in Table 1, systolic blood pressure, diastolic blood pressure, HDL-C, LDL-C, arterial elasticity index and BMI of patients taking vitamin D containing drugs were significantly optimized compared with the control group, and such changes indicate that taking vitamin D containing drugs has an improvement effect on hypertension.

3.2. Maintain Calcium Balance in the Body

In addition to having a significant impact on vascular endothelial function, vitamin D helps the body maintain a calcium balance. The three organs of the kidney, gut, and bone are responsible for maintaining calcium balance and homeostasis; however, calcium regulatory factors—among which 1,25-hydroxyvitamin D is a key regulatory factor—control the fundamental mechanism [6]. A complicated calcium regulation network is formed by the interactions between factors. A fast negative feedback regulation mechanism is used to maintain blood calcium homeostasis. By stimulating the parathyroid gland's calcium-sensitive receptors, the quick drop in blood calcium can encourage the rise in PTH levels. Increased PTH works on the bone's PTH receptor, causing osteoclast activity to rise, blood to be released with calcium from the bone, and blood calcium. Simultaneously, increased PTH operates on the kidney, encouraging an increase in 1,25-hydroxyvitamin D production as well as an increase in renal tubule calcium reabsorption. In addition to increasing blood calcium through its action on intestinal vitamin D receptors, elevated 1,25-hydroxyvitamin D also acts on bone vitamin D receptors, which facilitates the release of calcium from bones into the blood and raises blood calcium levels.

The proliferation and migration of vascular endothelial cells are aided by calcium ions as signal molecules, and an increase in calcium ion concentration aids in repairing damaged vascular endothelium. The apoptosis process of vascular endothelial cells can also be influenced by calcium ions. Additionally, calcium ions are involved in the synthesis and release of nitric oxide (NO) by vascular endothelial cells. Vasodilation and vasodilation can be regulated by NO, which is an

important vasodilator. The stabilization of vascular endothelial function can be maintained by increasing the calcium ion concentration, which can promote the synthesis and release of NO.

Vitamin D deficiency can cause reduced calcium ion production, which in turn can result in vascular endothelial dysfunction, which affects blood pressure stability. Therefore, supplementing vitamin D, helps to regulate vasomotor function, which can lead to blood pressure reduction.

3.3. Activation of Renin-angiotensin-aldosterone System

Vitamin D regulates the renin-angiotensin-aldosterone system (RAAS). In vivo, renin and angiotensin II are important pressors, and vitamin D can inhibit the expression of RAAS [7]. Different experiments in animals and humans have shown that vitamin D can inhibit renin gene expression and reduce RAAS activity. First, Li et al. [8] knocked out VDR in wild-type mice and injected vitamin D at an amount of 4IU/g. After 5w of quantitative analysis, it was concluded that the renin mRNA in mice with VD knocked out was 3 times higher than that in the wild-type control group. An increase in renin leads to an increase in angiotensin II, which acts as a strong vasoconstrictor and can lead to elevated blood pressure and left ventricular hypertrophy. Later, Zhou et al. [9] found that mice lacking 1 α -hydroxylase could not produce 1,25-(OH)D. After culture for 4w, although the blood calcium and phosphorus levels were normal compared with the control group, they were found to have increased blood pressure, left ventricular hypertrophy, impaired heart function, and increased RAAS expression in cardiac and renal tissues.

The above animal experimental data show that vitamin D has a down-regulation effect on RAAS, and the effect of human vitamin D on RAAS has been studied accordingly. Dong et al. [10] administered 12h 1,25-(OH)D in vitro treatment to patients with pressure. In the study of the damaged renal artery, it was found by immunofluorescence that 1,25-(OH)D reduced the expression of angiotensin I receptor in endothelial cells, stabilized the function of endothelial cells, prevented the overproduction of peroxide, inhibited the production of renin, and reduced the activity of the RAAS system. In summary, vitamin D can inhibit plasma renin activity, reduce blood pressure, and play a cardiovascular protective role by regulating the activity of RAAS system.

3.4. Anti-inflammatory

Vitamin D also has anti-inflammatory effects, which can inhibit the production and release of inflammatory mediators, thereby reducing the damage of vascular endothelial cells and protecting vascular function. Vitamin D can stimulate the production of nitric oxide (NO)- by endothelial cells, prevent the occurrence of oxidative stress, prevent the apoptosis of endothelial cells, reduce oxidative stress and platelet aggregation, improve the function of endothelial cells by down-regulating the production of NF- κ B and PTH, inhibit pro-inflammatory factors and increase the secretion of anti-inflammatory cytokines [11].

Vitamin D can also promote the innate immune system's production of anti-inflammatory cytokines, which have an effect on viral and bacterial infections. Vitamin D also plays an important role in acquired immunity and is a regulator of acquired immunity [12]. 1,25 (OH)D can reduce the production of pro-inflammatory Th1 cytokines, such as tumor necrosis factor (TNF) and interferon (IFN) and inhibit helper T lymphocyte type 1 (Th1) mediated responses [13]. Vitamin D can also promote the production of cytokines by helper T lymphocytes type 2 (Th2), which helps to supplement the indirect inhibition of Th1 cells mediated by multiple cell types [14].

Schleithoff et al. [15] randomly selected 123 patients who were randomly given vitamin D3/d+500mg Ca/d [D (+) group] or placebo +500mg Ca/d [D (-) group] for 9 months, and statistically significant therapeutic effects were obtained. To observe the serum concentration of vitamin D (P = 0.001), the TNF alpha (P = 0.006) and IL - 10 (P = 0.042). In group D (+), vitamin D concentration was increased by 26.8 μ g/L, and anti-inflammatory cytokine IL-10 was significantly increased. In the D (-) group, the pro-inflammatory cytokine TNF- α increased, but remained unchanged in the D (+) group. The anti-inflammatory effect of vitamin D is reflected in many aspects, not limited to a single impact.

4. Conclusion

In summary, vitamin D has an important effect on adolescent hypertension. This paper discusses the causes of hypertension in adolescents and the mechanism of vitamin D in reducing blood pressure. Vitamin D deficiency, as an independent factor affecting adolescent hypertension, affects the probability of adolescent hypertension, and its content in the body needs to maintain a normal level, which is crucial to human health. The antihypertensive mechanisms of vitamin D can be broadly divided into three categories: maintenance of calcium balance, RAAS, and anti-inflammatory. They both cooperate and work together to make vitamin D have a blood pressure lowering effect.

According to research, people with insufficient vitamin D are more likely to develop high blood pressure, and supplementing with vitamin D to normal levels can help reduce the risk of high blood pressure. Vitamin D can also work with folic acid to intervene in high blood pressure, taking high blood pressure medications at the same time vitamin D and folic acid supplementation, therapy can significantly reduce blood pressure levels. The combination of high risk factors of hypertension, drug targeted genotype detection, vitamin D blood concentration and folic acid as a set of diagnosis and treatment plan is conducive to the treatment of hypertension, and it is also convenient to deal with individual differences and formulate individual medication plans for patients. Drugs containing vitamin D are also used in clinical treatment, such as calcitriol soft gel capsules (produced by Qingdao Zhengda Haier Pharmaceutical Co., LTD.), which have achieved good results in clinical practice.

Adolescent vitamin D deficiency is a global problem, in order to prevent this problem from living habits, dietary habits and other changes, vitamin D supplementation is to prevent hypertension, the importance of vitamin D cannot be ignored. The views analyzed in this paper hope to provide reference for future research.

In the field of adolescent hypertension, experimental data and clinical reports are relatively lacking, so drugs specifically for adolescent hypertension can also be seen. This aspect is an important part of future research. There are not many research experiments and clinical reports specifically on adolescent hypertension cited in this paper. It is hoped that future research can make up for this gap.

Research in the field of adolescent hypertension and vitamin D, the relationship between the two needs to be further explored, I believe that in the future, there will be more studies to prove the role of vitamin D in adolescent hypertension. These studies will also provide new ideas for the prevention and treatment of hypertension.

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