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Vitamin D and hypertension

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Abstract

Introduction: Current epidemiological studies indicate, that insufficiency of vitamin D affects 50% of the population worldwide. 1α,25$(OH)_2$D – active form of vitamin D affects tissues and organs through vitamin D receptor (VDR). Attention to the role of vitamin D deficiency in hypertension development has been continuously increased during recent decades.

The aim of the study: The purpose of this narrative systemic review was to analyse and summarize available data on role of vitamin D deficiency in hypertension development.

Material and method: Standard criteria were used to review the literature data. The search of articles in the PubMed and Google Scholar database was carried out using the following keywords: hypertension, calcitriol, vitamin D, 25-hydroxyvitamin D.

Description of the state of knowledge: Vitamin D influence blood pressure level through renin-angiotensin-aldosterone system (RAAS) and parathormone regulation. Studies conducted on animal model could explain possible mechanism of vitamin D influence on blood pressure control. However, clinical trial results are equivocal due to differences in sample size, heterogeneity of patient baseline characteristics, different vitamin D doses and study duration.

Summary: Further research is needed to confirm the role of vitamin D in hypertension development.

Key words: vitamin D, hypertension, blood pressure, cholecalciferol

Introduction

For the first time the vitamin D was discovered in the first half of 20th century. In 1922 McCollum observed that cod liver oil supplementation, which were void of vitamin A cured rickets in sick dogs. He called the factor presented in that oil vitamin D. Next, Adolf Windaus received a Nobel Prize for his study about sterols and vitamins included vitamin D. In 1931 Angew et al. discovered the structure of D2 vitamin. In 1935 Windaus et al. isolated 7-dehydrocholesterol. Vitamin D_3 structure was identified 2 years later by Windaus and Bock. During the last 100 years scientist attempted to understand the function and metabolism of vitamin D [1]. Nowadays, the fact is known, that vitamin D is truly prohormone, not the vitamin. The two major form of vitamin D are vitamin D_2 (ergocalciferol), which sources are plants and vitamin D_3 (cholecalciferol), which is synthetized in the skin. The 7-dehydrocholesterol (present in the skin) converse to vitamin D_3 –the most important form of vitamin D through ultraviolet irradiation. Vitamin D bounds with vitamin D binding protein (DBP) or albumins and is transported to the liver. There is metabolized to 25-hydroxyvitamin D_3 and next is transported to the kidney where is hydroxylated to $1\alpha,25(OH)_2D$ – principal hormonal form of vitamin D [2]. The major regulators of vitamin D metabolism are: parathyroid hormone, fibroblast growth factor (FGF23), calcium and phosphate. Active vitamin D – calcitriol effects

on the processes in most cells in human body through vitamin D receptor (VDR) [3]. The first discovered and the best known function of vitamin D is regulation of calcium absorption and homeostasis, that is connected with general musculoskeletal health. Presently, numerous studies indicate potential impact of active vitamin D low serum concentration in: cancer development, heart diseases, hypertension, diabetes, Parkinson's disease, arthritis and multiple sclerosis [4]. However, scientist observed correlation between high vitamin D_3 level and elevated risk of prostate cancer. Current epidemiological studies indicate, that insufficiency of vitamin D affects 50% of the population worldwide. About 1 billion people suffer from vitamin D deficiency [5]. Vitamin D status is examined by measurement of 25(OH)D serum levels, that's optimal concentration shall be 30-80 ng/ml [6].

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Description of knowledge

Hypertension

Normal adult blood pressure, measured in millimetres of mercury (mm Hg) consists of two numbers: systolic blood pressure, that should be below 120 mmHg and diastolic blood pressure, that should be lower than 80 mmHg. Systolic blood pressure equal to or above 140 mmHg and/or diastolic blood pressure equal or above 90 mmHg is defined as hypertension according to WHO [7]. Hypertension has become 'civilization disease' and is one of the most common cause of cardiovascular complications. It is estimated, that 40% of global population suffer from hypertension which accounts for 7.5 million deaths per year worldwide [8,9]. That is why new perspectives of hypertension therapy and prophylaxis are being sought. Epidemiological studies indicate, that blood pressure is higher among population living farther from the equator. They also show that blood pressure level changes over the year. This phenomenon may be associated with sun exposure and therefore with vitamin D synthesis. The thesis, that vitamin D affects blood pressure level is supported by the fact that hypertension risk depends on the

type skin pigmentation [10,11]. In last years the interest in role of vitamin D in hypertension prevention have grown, therefore recent data were analysed.

How vitamin D could affects blood pressure?

Over two decades ago the first epidemiological study about association between vitamin D and renin levels were published [12]. Since that time scientists conducted many studies about influence of cholecalciferol on blood pressure. These beneficial effects may be mentioned through several distinct mechanisms including renin-angiotensin-aldosterone system (RAAS) and parathormone regulation. Activation of RAAS plays crucial role in volume, electrolyte and blood pressure regulation. Therefore RAAS is one of relevant drug targets in hypertension treatment. To antihypertensive agent group, that block RAAS and is used widely belong: renin inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II type receptor antagonists and mineralocorticoid receptor. Several animal and human studies indicate that vitamin D seems to be RAAS inhibitor [12]. As already mentioned, active vitamin D initiates biological responses via binding to the VDR receptor, that is expressed in many tissues and organs e.g. heart, endothelium, vascular smooth muscle and T cells. VDR bonded with $1,25(OH)_2D$ may interact with retinoid X receptor (RXR) and become a transcription factor for many genes [13,14]. Renin transcription is inhibited by mechanisms including VDR activation by calcitriol. Moreover, in vitro studies have shown, that VDR activation induces nitric oxide (NO) by endothelial cells and improves the ability to angiogenesis of endothelial progenitor cells. Vitamin D deficiency could also led to secondary hyperparathyroidism (HPT), that is indirectly linked to hypertension [15].

Animal studies

Ni et al. in their study consider the influence of VDR receptor (Vitamin D Receptor), present in vascular endothelial cells on blood pressure level. They used endothelial-specific knockout of the murine VDR gene, that led to absence of endothelial VDR in mice. Afterwards, researches administered angiotensin II infusion in both : control and study group. Mice devoid of endothelial VDR were more sensitive to the hypersensitive effects of angiotensin II, that confirms role of VDR and vitamin D in hypertension and cardiovascular diseases development [16]. Andrukhova et al. come to similar conclusion during the observation mice with inactive VDR. Vasodilator nitric oxide concentration was lower in studied group, which was associated with endothelial dysfunction and changes in structure of vessels and led to hypertension [17]. Several animal studies consists of induction vitamin D deficiency and observation blood

pressure level. For example Andersen et al. observed for 3 weeks two groups of four-week-old double transgenic rats (dTGR) with excess angiotensin II production. First group received low-vitamin D diet while control group received standard chow. Diet with vitamin D depletion led to higher mean systolic pressure, increased hearth weight and creatinine concentrations. That findings indicate the impact of vitamin supplementation on blood pressure [18]. Weng et al. described similar observations in diet-induced vitamin D deficiency mice. Their systolic and diastolic blood pressure, renin level were elevated, while urinary sodium extraction was lower compare to control group. Scientists noticed also that low level of vitamin D concentration initiates foam cell formation, that could cause atherosclerosis [19].

Human clinical studies

An increasing number of studies suggest that vitamin D could play a role in diseases associated with aging such as hypertension. However, the findings from different clinical trials are incoherent. The table below present findings of described studies. Older adults are at risk for lower levels of vitamin D as a result of decreased skin synthesis and supplementation with diet. Bricio-Barrios et al. observed decreased systolic and diastolic blood pressure in group consisting of older adults and supplemented calcitriol for 6 weeks compared with placebo group [20]. Also McGreevy et al. noticed the positive influence on systemic arterial stiffness measured by augmentation index (AI) in patients with vitamin D deficiency, supplemented 100,000 IU vitamin D [21]. Alpsoy and co-workers measured vitamin D levels in patients with white coat hypertension (WCHT) and compared with sustained hypertension (SHT) and normotension (NT) patients. White coat hypertension is a condition in which the blood pressure level is elevated, resulted by patient's feeling of anxiety in a medical environment. They reported lower vitamin D levels in sustained hypertensive patients, then in WCHT and NT groups. This study suggests that vitamin D deficiency may be related to hypertension [22]. In contrast to previous studies, Borgi et al. did not observed any improvement in endothelial function after vitamin D supplementation, once a week (50,000 units) for 8 weeks in nonhypertensive, nondiabetic overweight, or obese individuals with vitamin D deficiency [23]. Also McMullan et al. did not confirm the hypothesis, that vitamin D influences RAS activity. They measured RAS activity by measuring plasma flow response to captopril in high sodium balance among the group of overweight individuals without hypertension, treated for 8 weeks with ergocalciferol or placebo [24]. In other study, high dose oral vitamin D supplementation for 2 months did not reduce blood pressure in patients with resistant hypertension [25]. The same author conducted the study

in which older patients with isolated systolic hypertension received 100,000 UI oral vitamin D every 3 months for 1 year but supplementation did not improve orthostatic hypertension [26].

Table 1. Findings from clinical studies of Vitamin D and hypertension risk

References (First author and year of publication)	**N** SG (study group) PL (placebo group)	**Method**	**Findings**
McMullan et al. 2017 [24]	84 total overweight individuals without hypertension SG=43 PL=41	SG: 50,000 U/week for 8 weeks Renal angiotensin system activity was measured using renal plasma flow (RPF) response to capropril in high sodium balance.	Ergocalciferol supplementation had no effect on blood pressure, plasma renin activity and angiotensin II
Borgi et al. 2017 [23]	Group of nonhypertensive, nondiabetic overweight or obese individuals with vitamin D deficiency SG=43 PL=45	50,000 IU/week for 8 weeks Endothelial-dependent vasodilation (EDV) was measured by brachial artery ultrasound	No improvement in endothelial function after vitamin D supplementation
Alpsoy et al. 2016 [22]	42 patients with white coat hypertension (WCHT) 59 sustained hypertension pateints (SHT) NT –normotensive group	Plasma vitamin D levels were meausered using electrochemiluminescence immunoassay method.	SHT patients have lower vitamin levels than white coat hypertensive and normotensive individuals.
Bricio- Barrios et al. 2016 [20]	SG= 22 PL= 23	1000 IU of cholecalciferol /day for 6 weeks	Calcitriol group: decrease od systolic blood pressure (20.25 mmHg) and diastolic blood pressure (7mmHg) compared to placebo group.
McGreevy et al. 2015 [21]	119 subjects with vitamin D deficient (<50nmom/L)	SG1: 50,000 IU i.m. vitamin D3 SG2: 100,000 IU i.m. vitamin D3 Median pulse wave velocity and augmentation index were measured	Significant decrease in augmentation index was seen in the group received 100,000 IU vitamin D. In this group also median pulse wave velocity decreased.
Witham et al. 2014 [25]	Total 68 individuals with hypertension resistant SG= 34 PL=34	100,000 IU oral vitamin D supplementation every 2 months for 6 months. BP and Left ventricular mass was measured	Vitamin D supplementation did not reduce blood pressure or left ventricular mass
Witham et al. 2014 [26]	Total 75 patients with isolated systolic hypertension	100,000 UI oral vitamin D every 3 months for 1 year. Office supine and standing BP were measured every 3 months	1 year high-dose vitamin D3 supplementation did not improve orthostatic hypertension in older patients with isolated systolic hypertension

Summary

Attention to the role of vitamin D deficiency in hypertension development has been continuously increased during recent decades. Epidemiological and animal studies strongly support hypothesis, that vitamin D deficiency may be related to hypertension. Moreover, studies conducted on animal model could explain possible mechanism of vitamin D influence on blood

pressure control. Nevertheless, presented double-blind randomized controlled trials show incoherent results. Differences in sample size, heterogeneity of patient baseline characteristics, different vitamin D doses and study duration could contribute to disparities between results. Further research is needed to confirm the role of vitamin D in hypertension development.

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