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Essays

Vitamin D and hypertension

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Abstract

High blood pressure is very prevalent worldwide, as well as vitamin D deficiency. There are several observation data that support the concept that vitamin D is involved in pathogenesis of hypertension. Also some clinical date demonstrate positive effect of vitamin D therapy on hypertension. In this review epidemiological date will be presented and biological mechanism of vitamin D effect on blood pressure will be explained.

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INTRODUCTION

High blood pressure, i.e. hypertension is very prevalent worldwide. Its prevalence in Europe is about 40% of the adult population. In Croatia it is 37.5%, while in the United States it is even less – about 20% *(1)*. According to some epidemiological studies, it is estimated that more than 1 billion people worldwide could have arterial hypertension. Hypertension is a major risk factor for renal, cerebrovascular and cardiovascular disease. Therefore, it is one of the most pressing health problems in the world. Another pandemic is vitamin D insufficiency. Almost 50% of the world's population is affected by vitamin D insufficiency *(2)*. In last ten years, several observation studies have supported the concept that vitamin D is involved in the pathogenesis of arterial hypertension. In addition, there are experimental in vitro and in vivo data that support this thesis.

Almost two hundreds years ago, the relationship between rickets and a lack of exposure to sunlight was observed. At the beginning of last century the fat-soluble antirachitic substance in fish liver oil was discovered. In 1922, the treatment of rickets through exposure to UV light was introduced in clinical practice. Nine years later ergocalciferol, i.e. vitamin D, was discovered and five years after that 7-dehydrocholestreol. During the 1960s, 25-hydroxyvitamin D, 1.25 dihydroxycholecalciferol and vitamin D receptors were discovered *(2, 3)*.

There has been increased interest in vitamin D in the past decade. In addition to its well-known role in maintaining an adequate level of serum calcium, phosphorus, parathyroid hormone and normal bone metabolism, there is evidence that vitamin D has a biological effect on more than mineral metabolism *(3)*.

Vitamin D is named a »vitamin« like vitamin A or C because of its exogenous source, but without a doubt it is hormone.

In this review we will briefly discuss vitamin D metabolism, the epidemiological data on vitamin D insufficiency and hypertension, the possible biological mechanism of vitamin D deficiency and hypertension, and at the end we will discuss whether there is any potential in vi-

tamin D as antihypertensive drug. We will use the following nomenclature: vitamin D for cholecalciferol or ergocalciferol, calcidol for 25-hydroxyvitamin D, calcitriol for 1.25 dihydroxycholecalciferol, and vitamin D analogs for paricalcitol – the only one registered in our country. In rest of the world, more analogs are used, e.g. maxacalcitol, doxercalciferol.

Vitamin D metabolism

Vitamin D is a secosteroid that is made in the skin by the action of sunlight, or much less frequently, ingested through diet. During ultraviolet B radiation, 7-dehydrocholesterol (provitamin D) is converted to previtamin D, which is converted into vitamin D. Vitamin D is very rarely found in food. It can be found in fish like salmon or in fish oils. In some countries foods like milk or bread products are fortified with vitamin D, but it is not an important source of vitamin D. In the liver vitamin D is converted by the enzyme cytochrome 450 into calcidol. This conversion is under low metabolic control. Calcidol is biologically inert but it is used to determine vitamin D status because it has a long half-life, is easily measured, and there is good correlation between the level of calcidol and some diseases. Despite some controversy, vitamin D insufficiency might be defined as a calcidol level less than 25 nmol/L, deficiency between 25 to 75 nmol/L and an optimal level more than 75 nmol/L. There are many reasons for vitamin D deficiency or insufficiency: skin pigmentation, aging, obesity, lack of sun exposure, chronic disease, particularly chronic kidney disease, latitude of residence etc. *(2, 3, 4)*.

In the kidney, calcidol is metabolized by the enzyme 1α-hydroxylase (CYP27B1) to calcitriol, an active metabolite of vitamin D. The production of calcitriol is very tightly controlled by calcium and phosphorus levels, by parathyroid hormone and fibroblast growth factor 23. Another enzyme in the kidney, 24-hydroxylase (CYP24), catabolizes calcidol and calcitriol into biologically inactive calcitroic acid *(2, 3)*.

Calcitriol acts by activating the vitamin D receptor (VDR), which binds together with transcription factor RXR in specific regions of DNA (VDREs, vitamin D response elements) *(5)*. Vitamin D receptors are widely distributed. In addition to tissue and organs involved in mineral and bone metabolism, VDRs are found in vascular smooth muscle, endothelium, the heart, brain, skin, pancreas, macrophages etc. Moreover, some cells like macrophages or vascular cells express 1α-hydroxylase, i.e. the possibility of converting calcidol into calcitriol. This extra renal calcitriol is not tightly controlled and the calcitriol produced in these cells have local, autocrine or paracrine effect. The distribution of VDRs and the local production of calcitriol demonstrate that vitamin D is a pluripotent hormone involved not only in calcium homeostasis and bone metabolism. Today, there is much data that vitamin D deficiency or insufficiency can cause bone disease, malignancies, metabolic and immunological diseases, and cardiovascular disease and hypertension *(2, 3, 4)*.

Vitamin D and hypertension: epidemiological data

In the last twenty years, several cross-sectional studies and only a few prospective studies have been conducted in an attempt to correlate vitamin D levels with blood pressure *(6, 7)*. One of the largest studies was the third National Health and Nutrition Examination Survey (NHANES III). It is a representative study of the non-institutionalized US population. More than 12,000 patients were included in this cross-sectional observation study between 1988 and 1994. A significant inverse correlation between blood pressure and pulse pressure and vitamin D level, i.e. calcidol was observed *(8)*. In subgroup analyses when age was included in the analysis, an inverse association between calcidol and blood pressure was discovered, but it was not statistically significant. In other analyses of NHANES III an increased prevalence of hypertension in patients with low calcidol level was observed, i.e. the prevalence of hypertension in adults in the US was 30 % higher in the lowest quartile compared to the highest quartile of calcidol level *(9)*. In two other large cross-sectional studies in Europe, the German National Interview and Examination Survey with 4,030 participants and the 1958 British Birth Cohort with more than 6,810 participants, a reduced level of calcidol was observed *(6)*. Using data from the 2003–2006 National Health and Nutrition Examination Survey a low level of calcidol and a high level of PTH were independently associated with high blood pressure. In fact, among more than 5,000 participants not taking any antihypertensive medication, systolic and diastolic blood pressure decreased linearly across quintiles of serum calcidol and increased linearly across quintiles of serum PTH. Even more similar results were observed for prehypertension (systolic blood pressure between 120–140 mmHg and diastolic 80–90 mmHg) *(10, 11)*. Recently, Burgaz A and colleagues published a meta-analysis of blood calcidol concentration and hypertension. In the analysis 18 studies were (14 cross-sectional, 4 prospective) included with a total of 78,028 participants. The pooled odds ratio of hypertension was 0.73 [95% confidence interval (CI) 0.63–0.84] for the highest versus the lowest category of blood calcidol level. In a dose response meta-analysis, the odds ratio for a 40 nmol/L increment in blood calcidol level was 0.84 (95% CI 0.78–0.9). Without a doubt the conclusion from this meta-analysis is that calcidol level is inversely associated with hypertension *(12)*.

Inverse correlation between calcidol levels and hypertension rates was confirmed also in a cross-sectional study by Bhandari SK *et al. (13)*. From more than 31000 patients aged 18 years and older, 2722 were included in analysis. The overall prevalence of hypertension was 24%. Hypertension rates were 52%, 41%, 27% and 20% in calcidol quartiles < 15 ng/mL, 15 to 29 ng/mL, 30 to 39 ng/mL ans > 40 ng/mLm, respectively ($P < 0,001$). This study demonstrates increased rates of hypertension in patients with lower levels of calcidol starting at levels < 40 ng/mL.

There are studies showing no relationship between calcidol level and hypertension. The majority of these studies were with a smaller sample size; in some hypertension was self-reported, in others studies the vitamin D level was estimated from a semi-quantitative food frequency questionnaire *(6, 7)*.

Despite these contradictory findings, it could be concluded from majority cross-sectional studies that an inverse relationship between calcidol levels and blood pressure exists.

Biological links between vitamin D and blood pressure

The renin-angiotensin-aldosterone system (RAAS) is a main regulator of blood pressure and plays a critical role in the regulation of volume and electrolyte homeostasis. Increased activation of RAAS is associated with hypertension. It is well known that renin is produced in juxtaglomerular cells of the kidney and that it stimulates angiotensin II and aldosterone production. Their increased production elevates blood pressure by vasoconstriction and water retention. Experimental evidence shows that calcitriol inhibits renin synthesis in the kidney. In a very good study Li et al. demonstrated that vitamin D, i.e. calcitriol, is a potent inhibitor of renin synthesis *(14)*. They showed that renin expression and plasma angiotensin II production is increased in VDR receptor-null mice, leading to hypertension, cardiac hypertrophy and increased water intake. In wild mice, i.e. mice with intact VDR receptors, the inhibition of calcitriol synthesis also led to increase in renin expression, whereas calcitriol injection led to renin suppression. Kong et al. have demonstrated that this action of calcitriol on juxtaglomerular cells, i.e. inhibition of renin expression, is independent of calcium and PTH *(15)*. Moreover, Zhou et al. in a few experimental studies have demonstrated that defect in the 1α-hydroxylase gene, i.e. local production of calcitriol in some cells led to hypertension, left ventricular hypertrophy and systolic dysfunction *(16)*. Tomaschitz A et al. evaluated the concentration of plasma renin, angiotensin 2 and calcidol and calcitriol in a large cohort of patients (LURIC study) *(17)*. In 3,296 subjects a steady increase of plasma renin concentration across a declining concentration of calcidol or calcitriol was observed. They concluded that in humans a lower level of calcidol or calcitriol is related to the upregulation of RAAS.

Obviously, there are enough results showing negative relationship between calcidol or calcitriol levels and RAAS activity.

There are also other mechanisms involved in the relationship between blood pressure and vitamin D. Secondary hyperparathyroidism, commonly seen in vitamin D deficiency, could be the reason for hypertension. The mechanism is not completely clear, but it is a well known association that high PTH levels affect vascular smooth muscle cells and increase vascular stiffness and promotes atherosclerosis. This is very often seen in patients with chronic kidney disease *(6)*.

Another mechanism is the effect of vitamin D on cell of the vessel. These cells express the VDR and 1α-hydroxylase activity. Vitamin D deficiency is associated with endothelial dysfunction and could promote increased and accelerated atherosclerosis and systolic hypertension *(7)*.

Finally, vitamin D deficiency is connected with obesity, metabolic syndrome and insulin resistance. All of these are related to hypertension *(7)*.

Vitamin D as antihypertensive drug

Unfortunately, at this time not enough studies have been conducted to investigate the effect of calcidol of calcitriol as an antihypertensive agent. In a small trial Pfeiffer et al. demonstrated greater systolic blood pressure reduction in the vitamin D plus calcium group versus only the calcium group ($p=0.02$) *(18)*. Calcitriol as a single i.v. dose significantly decreased systolic and diastolic pressure 2h after administration in a small group of dialysis patients. Such changes were not observed in patients with essential hypertension or healthy volunteers *(6)*. In a pilot feasibility study Judd E. *et al.* have demonstrated that blood pressure could be reduced with calcitriol *(19)*. Nine hypertensive subjects were randomized to receive standard antihypertensive therapy in addition to placebo, vitamin D or calcitriol. Only seven subjects completed the study. Subjects on calcitriol therapy had a significant decrease in systolic blood pressure compared to a placebo. Interestingly, one week after discontinuation of calcitriol therapy, systolic blood pressure returned to pre-treatment levels.

These studies are by no means very promising but for our every day clinical practice we need more date before about vitamin D as antihypertensive agent.

CONCLUSION

Clinical and epidemiological studies support a possible relationship between vitamin D and hypertension. There are some plausible biological mechanisms. Treatment of patients with hypertension is still a challenge for physicians *(20)*. Patients with hypertension and vitamin D deficiency could benefit from vitamin D supplementation or calcitriol treatment, particularly patients with chronic kidney disease *(21)*. Undoubtedly, we need more large prospective studies.

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