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Vitamin D deficiency and arterial hypertension: what is in common?

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Abstract

This review includes the results of the original prospective studies and meta-analyses focusing on the relationship between vitamin D deficiency and arterial hypertension (HTN). We discuss potential mechanisms of HTN development in vitamin D deficiency subjects and the associations between high blood pressure and VDR gene polymorphisms. The vitamin D treatment impact on blood pressure was demonstrated. The data provided could widen the knowledge related to different pathogenetic mechanisms of HTN and would be of interest to different specialists.

Key words: vitamin D deficiency, 25(OH)D, arterial hypertension

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Дефицит витамина D и артериальная гипертензия: что общего?

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Резюме

Настоящий обзор посвящен оценке современных представлений о взаимосвязях между дефицитом витамина D и артериальной гипертензией (АГ) и включает в себя результаты оригинальных отечественных и зарубежных исследований, проспективных наблюдений, а также данных метаанализов. В работе представлены возможные механизмы развития кардиоваскулярной патологии в условиях дефицита витамина D и носительства различных полиморфизмов гена рецептора витамина D. Отдельно проанализированы данные о влиянии терапии препаратами витамина D на уровень артериального давления и риск развития АГ. Информация, представленная в данном обзоре, позволит расширить представление о патогенетических механизмах развития АГ и будет интересна специалистам широкого профиля.

Ключевые слова: дефицит витамина D, 25(OH)D, артериальная гипертензия

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Recently, vitamin D deficiency could be considered as a non-classic risk factor for different health disturbances, including hypertension. Hence, the association between the serum 25-hydroxyvitamin D (25(OH)D) level and blood pressure (BP) was published by different recearches S. Pilz et al. [1], and results of the prospective studies showed increased hypertension risk in subjects with vitamin D deficiency [2–4]. Besides, "Health Professional Follow Up Study" showed that men with vitamin D deficiency had a hypertension risk 3.03 times (95 % CI: 0.94–9.76), and women 1.42 times (95 % CI: 0.79–2.56), higher than the general population [2]. Similar data had been obtained also during the "Nurse's Health Study" where a baseline serum 25(OH)D level lower than 30 ng/ml (75 nmol/l) was found to be connected with increased hypertension risk by 1.47 times (95 % CI: 1.10–1.97) [3] and A. G. Pittas et al. showed an increased hypertension risk by 1.76 times (95 % CI: 1.27–2.44) in subjects with low serum 25(OH)D levels [4]. However, other investigators could not reveal reliable differences

in the analysis of 10-year risk of hypertension in subjects with various vitamin D status [5]. Similar results were received also at the survey of residents of Norway, whose initial serum 25(OH)D level was not connected with blood pressure [6].

The associations between the vitamin D status and cardiovascular diseases, in particular hypertension, can be explained with several pathways. It is known that vitamin D receptors are presented in cardiomyocytes, vascular smooth muscle cells and the endothelium [7–11]. Researches in vitro revealed that 1.25-dihydroxyvitamin D (1.25(OH)2D) suppress the renin gene expression, regulates growth and proliferation of the vascular smooth muscle cells and cardiomyocytes, and also slows the release of cytokines from lymphocytes [12–14].

It is known that the renin-angiotensin-aldosterone system (RAAS) plays an important role in the regulation of blood pressure and electrolytic homeostasis, and the increase of its activity is the key link of hypertension pathogenesis [15–17]. The relationship between vitamin D status and blood pressure as well as plasma renin activity has been debated in many studies. The first data about existence of inverse relationship between 1.25-dihydroxyvitamin D and the RAAS in hypertensive subjects were published more than 20 years ago [18]. Several studies confirming negative regulation of the renin gene by calcitriol have been published by the group of Li et al., who showed that renin expression and plasma angiotensin II production were increased several-fold in vitamin D receptor-null (VDR-null) mice, leading to hypertension, cardiac hypertrophy, and increased water intake. In wild-type mice, inhibition of 1.25(OH)2D synthesis also led to an increase in renin expression, whereas 1.25-dihydroxyvitamin D injection led to renin suppression [14, 19]. In another study they demonstrated that suppression of renin expression by 1.25-dihydroxyvitamin D in vivo is independent of parathyroid hormone (PTH) and calcium [20, 21]. It is worth mentioning that the interlink between hemodynamic parameters and serum 25(OH)D was shown also in some clinical trials [18, 22], while other works could not identify such patterns [23].

It should be noticed that both vitamin D deficiency and high PTH level can exert negative impact on the cardiovascular system. Previous studies showed positive correlations between PTH level and vascular remodeling parameters, as well as cardiomyocytes hypertrophy [24, 25]. Besides, some investigators managed to find PTH pro-inflammatory properties such as affecting the release of cytokines in vascular smooth muscle cells [8, 26]. However, such works are single and their results are very ambiguous.

Nowadays, not only the role of vitamin D status, but also a contribution of a VDR gene polymorphism to the development of pathological states is actively being studied [27–29]. Essential hypertension is an example of a complex, multifactorial and polygenic disease where different metabolic pathways are involved and some gene variants, including VDR gene polymorphisms, could be factors producing the hypertensive phenotype Evidence studies showed endothelium VDR in regulating endothelial function and blood pressure. More than that, VDR gene polymorphisms (BsmI, ApaI and FokI) can be associated with a left ventricle hypertrophy, atherosclerosis and hypertension [30–33].

Some researches demonstrate the existence of interrelation between a BsmI genotype and level BP in healthy men and women. Hence, carriers of VDR gene b allele have their BP higher than B allele carriers [34]. N. Swapna et al. showed similar data [35]. At the same time, a research in residents of Korea showed opposite results [36]. Interestingly, a negative correlation was observed between 25(OH)D levels and BP in the FokI non-FF (Ff/ff, n=35) group compared with the FF one (n=39) [37].

These results were confirmed by a large case-control study investigating the relationship between the VDR FokI polymorphism and BP in 280 hypertensive patients and 200 healthy subjects. The risk for hypertension in FF homozygotes was found to be 2.2 times greater than in Ff carriers and 2.2 times greater than ff carriers. However, significant difference between Ff and ff genotypes was not revealed [37]. Recently, a prospective study that included 695 normotensive men in USA showed that hypertension incidence was 1.25 times higher in Bb and BB BsmI polymorphism carriers in comparison with bb homozygotes during 15.3-year follow-up and 1.32 times higher in ff FokI polymorphism carriers than FF and ff genotype subjects [38].

Besides, some VDR polymorphisms could be associated with decreased expression of NO-synthetase and NO bioavailability leading to endothelial

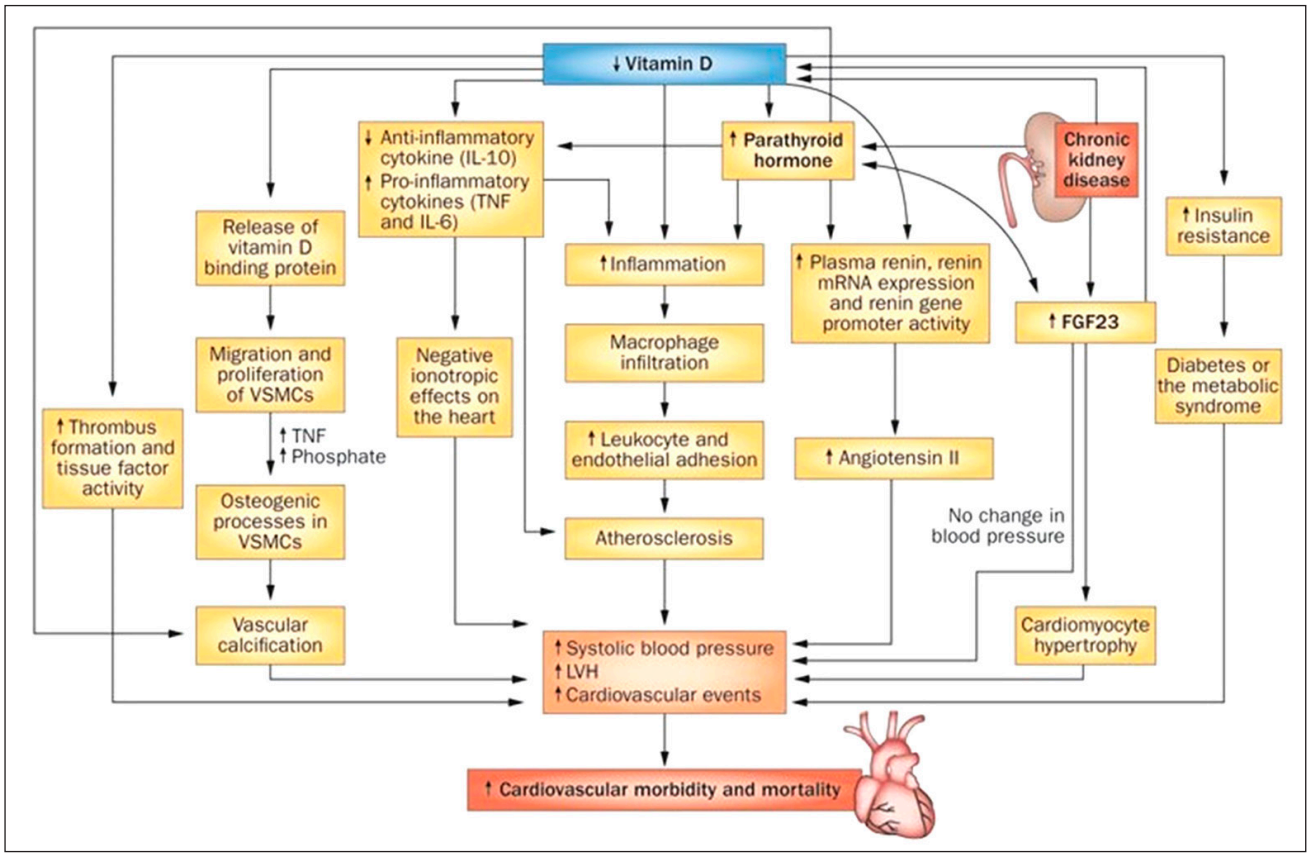
dysfunction, increase in vascular resistance, aortic remodeling, systolic and diastolic dysfunction regardless of the RAAS activity [39].

Local researches in the field are seldom and do not reflect the actual relationship between vitamin D status, the carriage of VDR gene polymorphisms and hypertension risk. Of note, we previously published the follow-up results of 657 female residents of St.-Petersburg and showed high prevalence of vitamin D deficiency in the surveyed population [40]. We did not find significant difference between BP and RAAS activity in vitamin D deficient and sufficient women. Hypertension risk in women with vitamin D deficiency was 1.01 [95%CI: 0.44–2.30] and did not differ from women with normal vitamin D status. Though positive relations have been revealed between the PTH levels and aldosteron/plasma renin activity (A/PRA) ratio (r = 0.25, p = 0.008) in normotensive women, while in hypertensive women no associations have been found. Taking into account the fact that women with hypertension were older than those with normal BP, RAAS parameters were analyzed according to age. The negative correlation was revealed between plasma renin and serum 25(OH)D in the 40–50 age group women (n = 89). Besides, a negative correlation was revealed between serum 25(OH)D level and aldosterone as well as plasma renin activity in abdominal obese women. Thus, obesity might be the link between vitamin D deficiency and hypertension. It seemed that hypertension risks and BP levels did not associate with VDR polymorphisms (ApaI, TaqI, BsmI and FokI) in the study population [41]. Of note many investigators report a high prevalence of vitamin D deficiency in the studied population, and this could have an effect on the analysis of the presence or absence of the relationships between VDR polymorphisms and blood pressure.

The role of vitamin D deficiency in cardiovascular diseases pathogenesis is presented in figure 1 [42].

Taking into account the association between vitamin D deficiency and hypertension, recently several trials with vitamin D therapy in hypertensive patients were initiated. So, Pfeifer, et al. pub-

Figure 1. Potential relationship between vitamin D deficiency and cardiovascular diseases [42]



Note: LVH — left ventricular hypertrophy; IL — interleikin; TNF — tumor nesrosis factor; FGF-23 — fibroblast growth factor-23; VSMCs — vascular smooth muscle cells.

lished their study results and showed that women over 70 years who took vitamin D therapy in a dose up to 800 IU per day with calcium carbonate had significant decrease in systolic BP [35]. Also, intake of 100.000 or 200.000 IU of vitamin D had no benefical antihypertensive effect in interventional and control healthy group with normal baseline serum 25(OH)D level and blood pressure [44]. Data analysis of patients with hypertension receiving vitamin D therapy showed large variation in daily doses of the used drugs (from 400 to 8571 IU) and in the treatment duration (from 1 to 7 years) [6.45–49]. Meta-analysis was published by Witham, et al. showed that vitamin D intake in hypertensive patients led to significant decrease of diastolic BP (–3.1 mm Hg) but did not seem to affect the systolic BP (–3.6 mm Hg) [50]. And though high doses vitamin D intake is safe it seems to have no additional advantages over standard doses when it comes to hypertension [47]. Vitamin D therapy in combination with calcium for 7 years was associated with a reduced risk of developing hypertension in white people, but was followed by risk augmentation in the Afro-Americans [49].

At the same time, some researchers demonstrated the absence of anti-hypertensive effect from single large vitamin D dose [51], as well as the absence of hypertension risk reduction in 36282 women included in the Women's Health Initiative Study receiving 400 IU of vitamin D and calcium [49]. Some experts demonstrated that absence of vitamin D antihypertensive effect is not dose-dependant [52]. According to results of Styrian Vitamin D Hypertension Trial, treatment of 200 hypertensive patients with 2800 IU of vitamin D per day or placebo, not only did not have any impact on the BP levels, but neither did it affect the risk of cardiovascular diseases [53].

Thus, despite the potential associations between serum 25(OH)D level and BP level, the results of different trials shows that vitamin D therapy influence on BP are rather neutral, than positive. However, vitamin D deficiency can be considered as an additional non-classical risk factor for cardiovascular diseases and its correction, taking into account cost, safety and, perhaps, efficiency of therapy, can be considered as a component of an integrated approach in the prevention and the treatment of hypertension.

Conflict of interest
The authors declare no conflict of interest.

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