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Review article
Pregledni članak

VITAMIN D IN CARDIOVASCULAR AND RENAL DISEASE PREVENTION

VITAMIN D U PREVENCIJI KARDIOVASKULARNE I BUBREŽNE BOLESTI

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Summary: Cardiovascular disease is a well-known public health problem. In the last ten years nephrologists have recognized chronic kidney disease not only as a public health problem but also as one of the major cardiovascular risk factors. There are observational data that support the concept that vitamin D is involved in the pathogenesis of cardiovascular and renal disease or that at least vitamin D deficiency is a risk factor for these diseases. In this brief review epidemiological data will be presented and the biological mechanism of the vitamin D effect on cardiovascular and renal disease will be discussed.

Keywords: vitamin D, renal disease, cardiovascular disease

Kratak sadržaj: Kardiovaskularna bolest je dobro znan problem u javnom zdravstvu. U poslednjih deset godina nefrolozi su uvažili i hroničnu bolest bubrega ne samo kao problem javnog zdravlja, već i kao jedan od glavnih faktora rizika za kardiovaskularna oboljenja. Postoje podaci iz opservacionih studija koji podržavaju koncept da vitamin D učestvuje u patogenezi kardiovaskularnih i bubrežnih bolesti ili bar da nedostatak vitamina D predstavlja faktor rizika za ove bolesti. U ovom kratkom pregledu prikazaćemo epidemiološke podatke i razmotriti biološki mehanizam uticaja vitamina D na kardiovaskularnu i bubrežnu bolest.

Ključne reči: vitamin D, bubrežna bolest, kardiovaskularna bolest

Introduction

World Health Organization (WHO) has recognized chronic noncommunicable diseases, particularly cardiovascular diseases, diabetes, chronic respiratory diseases and cancer, as the most important public health problems in the developed part of the world. According to some epidemiological studies chronic noncommunicable diseases are becoming a great problem also in developing countries. Interestingly, the WHO did not include chronic kidney disease (CKD) among the most important chronic diseases despite the fact that between 5 and 10% of adult persons in the developed world suffer from chronic kidney disease (1). There are also some epidemiological data that the prevalence of CKD is of the same magnitude in developing countries. From the nephrological point of view there is no doubt that CKD is also an important chronic noncommunicable disease. On the other hand, a growing body of evidence suggests that vitamin D deficiency or insufficiency is a pandemic with more than half of the world's population currently at risk. During the past ten years several observation studies have supported the concept that vitamin D is involved in the pathogenesis of cardiovascular and renal disease. At least, there is an epidemiological connection between vitamin D disturbance, i.e. deficiency and insufficiency and the prevalence of the majority of chronic noncommunicable diseases.

In this review, we will briefly discuss the vitamin D metabolism, the epidemiological data on vitamin D insufficiency and renal and cardiovascular disease, and the possible biological mechanism, i.e. the role of vitamin D in renal and cardiovascular disease. At the end we will discuss whether vitamin D has any potential as a drug in the prevention and treatment of renal and cardiovascular disease.

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We will use the following terminology: vitamin D for cholecalciferol or ergocalciferol, calcidol for 25-hydroxycholecalciferol, calcitriol for 1,25 dihydroxycholecalciferol (2).

Vitamin D Metabolism

At the beginning of the 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. More than 40 years later, 25-hydroxyvitamin D, 1,25 dihydroxycholecalciferol and the vitamin D receptors were discovered (3–5).

There has been increasing 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 beyond mineral metabolism (4).

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. In some countries foods like milk or bread products are fortified with vitamin D, but this 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 a 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. (3–6).

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 (3, 4).

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) (8). 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 extrarenal calcitriol is not tightly controlled and the calcitriol produced in these cells has a local, autocrine or paracrine effect. The distribution of VDRs and the local production of calcitriol demonstrate that vitamin D is a pluripotent hormone involved in more than calcium homeostasis and bone metabolism. Today, there is a large amount of data suggesting that vitamin D deficiency or insufficiency is involved in the pathogenesis of bone disease, malignancies, metabolic and immunological diseases, cardiovascular disease and hypertension and progression of renal disease (3, 4).

Vitamin D and Renal Disease

The kidney is the major site of synthesis of calcitriol, the natural activator of VDR, and has an important function in mineral homeostasis (6, 8). Many studies showed a high prevalence of vitamin D deficiency or insufficiency in CKD patients. Recent experimental, observational and clinical studies have shown that dysregulation of vitamin D metabolism in CKD contributes not only to mineral metabolism disturbance but also to progression of renal disease and a high incidence of cardiovascular disease. There are several mechanisms for vitamin D deficiency in CKD, particularly in proteinuric renal disease (diabetic nephropathy and many glomerulopathies). The first one is the degree of proteinuria. Calcidol is bound to vitamin D binding protein. Due to similar molecular weight as albumin, it is filtered at glomeruli and lost into the urine. The second mechanism is impaired reabsorption of calcidol by megalin-mediated endocytotic activity. The third mechanism is elevated activity of the catabolic enzyme CYP24A1, involved in calcidol and calcitriol degradation. At the same time, the activity of enzyme CYP27B1 (1α-hydroxylase) is very reduced i.e. there is reduced conversion of calcidol to calcitriol. The fourth mechanism is increased activity of fibroblast growth factor 23, a major phosphatonin that suppresses calcitriol production (6, 8).

Vitamin D deficiency in CKD patients is associated with increased all-cause and cardiovascular mortality. For example, data from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States revealed a correlation between low serum calcidol and the risk of all-cause mortality in the general population and in patients with CKD not yet on dialysis (9). Data from Germany, i.e. the Ludwigshafen Risk and Cardiovascular (LURIC) Health Study confirmed that vitamin D deficiency is associated with all-cause and cardiovascular mortality in CKD patients (10). There is a lot of data indicating that

vitamin D deficiency is associated with renal disease progression. Albuminuria is a major risk factor for renal disease progression. The abovementioned NHANES III study revealed a correlation between low levels of vitamin D and increased prevalence of albuminuria (9).

Today, we have enough experimental and clinical data showing that vitamin D could have antiproteinuric, i.e. renoprotective activity. The renoprotective activity of vitamin D could be mediated by the activation of VDR and through several mechanisms. First, by suppression of the renin-angiotensin system (RAS). This intrarenal system is a major mediator of renal damage. Li et al. (11) demonstrated that vitamin D, i.e. calcitriol, is a potent inhibitor of renin synthesis. They showed that renin expression and plasma angiotensin II production are increased in VDR receptor-null mice. 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, i.e. vitamin D is a negative regulator of the RAS. The second mechanism is by suppression of NF-κB factor, an important factor involved in inflammation, proliferation and fibrogenesis. Vitamin D could be involved in the regulation of Wnt/β-catenin, an important factor in podocyte injury (12). Also, there are experimental data that vitamin D may regulate genes in the synthesis of the proteins involved in the formation of the slit diaphragm in the glomerulus. Several clinical studies have demonstrated the vitamin D renoprotective activity, particularly antiproteinuric activity. Alborzi P. et al. (13) have conducted a small pilot double-blind, placebo controlled trial to evaluate the effect of paricalcitol (vitamin D analog) on markers that are linked to the progression of CKD. In patients treated with paricalcitol significant reduction of albuminuria was observed. Similar results were obtained in CKD patients with proteinuria greater than 400 mg/24 h (14). In 31 patients treated with 1 mg paricalcitol significant reduction of proteinuria was observed in comparison with a placebo group. In a large randomized placebo controlled study, the VITAL study, involving 281 patients with type 2 diabetes and albuminuria and already on renin-angiotensin inhibitor therapy, significant reduction of albuminuria was seen in patients treated with 2 μg of paricalcitol. The reduction of albuminuria was recorded also in patients who were on 1 μg of paricalcitol, but this was not as significant. No incidence of hypercalcemia or any other adverse events was a very important observation (15). These and other clinical studies confirmed the antiproteinuric effect of vitamin D.

Vitamin D and Cardiovascular Disease

More than thirty years ago, the hypothesis that the increased CVD incidence in winter may be a consequence of vitamin D deficiency or insufficiency was postulated. This hypothesis together with the discovery of the VDR in the rat heart stimulated research of vitamin D and cardiovascular disease (16).

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 cardiovascular disease (16–18). 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 self-reported angina, myocardial infarction, heart failure, blood pressure and vitamin D level, i.e. calcidol was observed (19). More recently, combined data from the NHANES III and the NHANES 2001–2006 (more than 270,000 participants) showed that lower vitamin D levels are associated with increased heart rate and blood pressure; in other words, low vitamin D status may increase cardiac work. It is well known that high blood pressure is the most important cardiac risk factor (20). Several studies have reported an inverse association between vitamin D level and high blood pressure. In the NHANES 2001–2006 study 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 120–140 mmHg and diastolic 80–90 mmHg) (21). Recently, Burgaz et al. (22) published a meta-analysis of blood calcidol concentration and hypertension. In the analysis 18 studies (14 cross-sectional, 4 prospective) were 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 (22).

Biological Links between Vitamin D and Cardiovascular Disease

Vitamin D may exert various direct effects on heart and blood vessels through VDR activation or by locally produced calcitriol with autocrine and paracrine function. Very briefly, there are a lot of experimental studies suggesting that vitamin D downregulates the genes involved in myocardial hypertrophy (12, 23). Also, the effect of vitamin D on the heart could be by regulation of cardiac extracellular matrix

turnover or by modulation of heart contractility. Probably the most important activity is the suppression of RAS. The effect of vitamin D on blood vessels could be protection against atherosclerosis, endothelial dysfunction and calcification (23, 24). From the clinical point of view, vitamin D could have an effect on various cardiovascular risk factors: suppression of PTH, reduction of inflammation, prevention of diabetes mellitus, beneficial effect on dyslipidemia and on the progression of CKD, an important cardiovascular risk factor. Probably the most important effect of vitamin D in terms of cardiovascular protection is the well-known negative relationship between calcidol or calcitriol levels and RAAS activity, i.e. the inhibition of this system (23).

Vitamin D as a Cardiovascular and Antihypertensive Drug

Unfortunately, at this time not enough studies have been conducted to investigate the effect of calcidol or calcitriol as a cardioantihypertensive agent (25). In a small trial Pfeiffer et al. (27) demonstrated greater systolic blood pressure reduction in the vitamin D plus calcium group versus only the calcium group ($p=0.02$). Calcitriol as a single i.v. dose significantly decreased systolic and diastolic pressure 2 h after administration in a small group of dialysis patients. Such changes were not observed in patients with essential hypertension or healthy volunteers (26, 27). In a pilot feasibility study Judd SE et al. (28) have demonstrated that blood pressure could be reduced with calcitriol. 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 the placebo. Interestingly, one week after the discontinuation of calcitriol therapy, the systolic blood pressure returned to pretreatment levels.

Table I Vitamin D and renal and cardiovascular disease: strength of evidence.

Disease	Experimental	Observational	Interventional
Hypertension	+++	++	+
ISHD	+	+++	0
PVD	+	++	0
CHD	++	++	0
Dyslipidemia	++	++	0
Renal disease	+++	+++	+

ISHD, ischemic heart disease; PVD, peripheral vascular disease; CHD, congestive heart disease.
0, absence of evidence; +, limited evidence of association; ++, moderate evidence of association; +++, strong evidence of association.

Unfortunately, at this moment there are no data regarding the therapeutic efficacy of vitamin D and its analogs as primary or complementary therapy in cardiovascular disease.

Conclusion

Clinical and epidemiological studies support a possible relationship between vitamin D and renal and cardiovascular disease (*Table I*). There are some plausible biological mechanisms. Treatment of patients with renal and cardiovascular disease is still a challenge for physicians (24). Patients with hypertension, cardiovascular, renal disease and vitamin D deficiency could benefit from vitamin D supplementation or calcitriol treatment, particularly patients with chronic kidney disease (23). Undoubtedly, we need more large prospective studies.

Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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