Invited Review

Cardiovascular benefits of vitamin D

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Abstract: Vitamin D is essential for maintaining calcium and phosphate homeostasis, and vitamin D analogues have been prescribed to treat osteoporosis and hyperparathyroidism. Emerging evidence suggests that cardiovascular and chronic kidney diseases are closely associated with vitamin D deficiency resulting from either decreased sunshine exposure or inadequate intake. Vitamin D is through stimulating vitamin D receptor to form a transcriptional complex with cofactors to modulate approximately 3% gene transcription. For example, renin, matrix metalloprotease, and tumor necrosis factor-α are regulated by vitamin D. Both experimental and clinical studies support the health benefits of vitamin D in the cardiovascular system, and such benefits include protecting cardiac function, lowering blood pressure, improving endothelial function, inhibiting oxidative stress, and reducing the activity of renin-angiotensin system. This article will briefly review the cardiovascular benefits of vitamin D and its bioactive analogues and discuss the novel cellular and molecular mechanisms accounting for cardiovascular protection.

Key words: vitamin D; vitamin D receptor; renin-angiotensin system; oxidative stress; cardiovascular function

维生素D对心血管系统保护作用的研究进展

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摘　要：维生素D是机体内维持钙磷代谢稳定的重要物质，临床用于治疗骨质疏松以及甲状旁腺功能亢进。有证据显示日晒减少以及摄入不足导致的维生素D缺乏症与心血管疾病以及慢性肾脏疾病紧密相关。维生素D激活其受体，在辅助因子的作用下形成转录复合物，从而直接或间接调节机体内约3%的基因转录。肾素、肿瘤坏死因子、基质金属蛋白酶等都受其调控。基础及临床实验都已证明维生素D对心血管系统有保护作用。它可保护心脏功能、降低血压、改善血管内皮功能、抑制氧化应激、降低肾素-血管紧张素活性等。本文将就维生素D及其受体激动剂对心血管系统的保护作用以及分子机制的最新研究进展作一简单综述。

关键词：维生素D；维生素D受体；肾素-血管紧张素系统；氧化应激；心血管功能
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1 Introduction

Vitamin D, a fat soluble hormone, is the essential player to maintain calcium and phosphate homeostasis as well as bone mobilization[1, 2]. Past research on vitamin D primarily focused on its effect on bone mineralization and skeleton growth. Its discovery was resulted from a non-stop search for an efficient therapeutic for rickets. Rickets was a very common bone disease during 1600–1900s and is characterized by bone pain, attenuated bone growth, and bone weakness. Epidemiological studies reveal that the incidence of rickets is higher in people living in densely populated cities as compared to that in the rural areas, and more in cold

foggy winter than in sunny summer, implying that rickets is closely associated with limited sunlight exposure. People have nowadays been increasingly aware of the importance of sunlight exposure and outdoor activities to reduce the risk of getting rickets[3, 4].

2 Metabolism of vitamin D

Vitamin D can be obtained from both dietary intake and through the action of sunlight on the skin. Indeed, a large portion (~80%–90%) of vitamin D is synthesized by the skin under ultraviolet B (UVB) stimulation, while the remaining 10%–20% is from vitamin D-enriched fish oils, egg yolks and liver[5, 6]. Besides the initial sources of vitamin D, 25-hydroxylase and 1α-hydroxylase are needed for the conversion to the active forms, 25-hydroxyvitamin D [25(OH)D] in liver

and 1,25-dihydroxyvitamin D [1,25(OH)$_2$D] in kidney [7] (Fig. 1). This explains why the vitamin D metabolite (1,25-dihydroxyvitamin D) is clinically prescribed to patients instead of other vitamin D precursors as the liver and kidney function may have been impaired in patients. Indeed, patients with chronic kidney disease (CKD) are more prone to vitamin D deficiency[8]. CKD is accompanied by a significant decline in the ability to synthesize active forms of vitamin D in relation to the reduction of 1α-hydroxylase activity[9]. Plasma level of 25(OH)D serves as a clinical biomarker of vitamin D status in humans[10].

The optimal concentration of vitamin D is vital to health, especially in bone mobilization and the homeostasis of calcium associated with parathyroid hormone levels. Optimal serum vitamin D level about 75 nmol/L (30 ng/mL) was once defined as the minimal concentra-
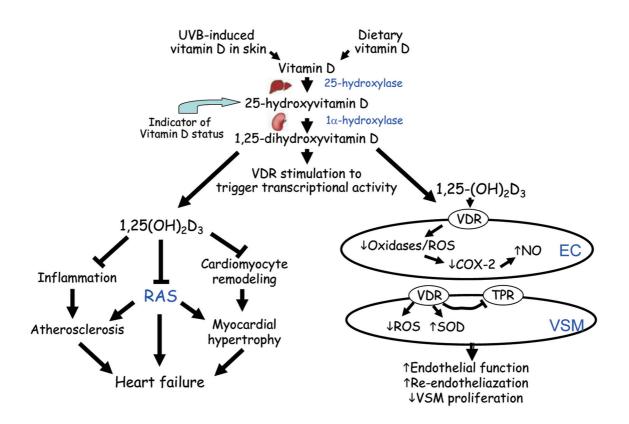

Fig. 1. Vitamin D produced from sunlight or obtained from diets, is converted into 25-hydroxyvitamin D in liver and 1,25-dihydroxyvitamin D [1,25-(OH)$_2$D] in kidney. The latter binds to vitamin D receptor (VDR) to regulate gene transcription. The 1,25-dihydroxyvitamin D$_3$ [1,25-(OH)$_2$D$_3$], a potent endogenous suppressor of the renin-angiotensin system (RAS) by directly inhibiting renin gene transcription, it retards the development of atherosclerosis and myocardial hypertrophy, thus improving cardiac function in heart failure. On the other hand, 1,25-(OH)$_2$D$_3$ is anti-inflammatory in blood vessels by inhibiting the over-expressed oxidases and associated reactive oxygen species (ROS) over-generation and inhibiting the expression of another pro-inflammatory enzyme, cyclooxygenase-2 (COX-2) in endothelial cells (EC) and reducing the expression of thromboxane prostanoid receptor (TPR) in vascular smooth muscle cells (VSM), resulting in the improved endothelial function and reduced VSM proliferation and inflammation.

tion of 25(OH)D needed to prevent against the increase of parathyroid hormone. Nowadays, the vitamin D status can be classified into (1) severe deficiency at ≤ 25 nmol/L (10 ng/mL), (2) deficiency at 25–50 nmol/L (10–20 ng/mL), (3) insufficiency at 50–75 nmol/L (20– 30 ng/mL), (4) sufficiency at ≥ 75 nmol/L (30 ng/mL), and (5) toxicity at ≥ 375 nmol/L (150 ng/mL)[11]. Vitamin D deficiency is more common in blacks and people with darker skin as the cholecalciferol production is limited by a great amount of melanin in their skin. In fact, vitamin D deficiency is a global problem partly due to decreased outdoors activities[12, 13]. Vitamin D deficiency can lead to elevated circulating levels of parathyroid hormone; the latter has negative impact on bone metabolism and cardiovascular function. By contrast, over-consumption of vitamin D supplements may cause calcification in which excessive calcium is deposited in the vascular wall, kidneys and lungs[14].

3 Clinical applications of vitamin D

Vitamin D is recommended as a daily dosage of 400 international units (IU) for an average adult, while a higher daily dosage of ≤ 800 IU for pregnant women and children. Vitamin D is generally prescribed for improving bone health, alleviation of rickets and osteoporosis, and treatment of secondary hyperparathyroidism[15, 16]. For aged women at postmenopausal stage, vitamin D is also medicated to prevent osteoporosis as a result of decreased estrogen production.

4 Vitamin D deficiency

The decreased exposure to sunlight due to outdoors inactivity can lead to vitamin D deficiency, a condition that is linked to bone dysfunction and the impaired cardiovascular function. Exiting evidence suggests an inverse association between the plasma level of vitamin D and dysfunction of the cardiovascular system[17–19]. Epidemiological studies show that the lack of vitamin D is implicated in the development of cancer, hypertension and multiple sclerosis[20, 21]. A National Health and Nutrition Examination Survey (NHANES) on the general population between 2001 and 2004 reveals that about 71% population have their plasma level of 25(OH)D above 75 nmol/L, 23% population with between 25–75 nmol/L, and 6% population with below 25 nmol/L. In patients with CKD, the relative proportion of individuals with 25(OH)D level below 25 nmol/L

is increasing with the progression of CKD.

5 General function of vitamin D

The effect of vitamin D is mediated by vitamin D receptor (VDR) which belongs to the nuclear receptor superfamily. Upon activation, vitamin D binds to VDR to form a heterodimer complex with the retinoid X receptor (RXR)[22]. The VDR-RXR complex then binds to specific DNA sequences termed vitamin D responsive elements, which are sequences located in the promoter regions of vitamin D target genes. The gene-modulating activity of vitamin D is also conferred through its interaction with transcription factors, such as nuclear factor (NF)-AT and NF-κB[23, 24]. Vitamin D directly or indirectly modulates about 3% gene transcription of the whole body, and these genes include renin, insulin, and cytokines such as interleukin-6 and tumor necrosis factor-α. Owing to the universal expression of VDR, vitamin D exerts its actions on the musculoskeletal, gastrointestinal, prostate, renal, endocrine, and cardiovascular systems[2, 25].

6 Benefits of vitamin D in the cardiovascular system

Weishaar *et al*. was the first to investigate the relationship between vitamin D and cardiovascular health using a rat model fed a diet without vitamin D[26–28]. These early studies showed that the vitamin D-deficient rats had an elevated blood pressure and greater contractile activity of both cardiac and vascular smooth muscle as compared with the control rats, and these observations formed an important basis for subsequent research on the health benefits of vitamin D in the cardiovascular system. Both experimental and clinical evidence points to a close link between vitamin D status and cardiovascular health. It is hypothesized that people with vitamin D deficiency are more susceptible to and have higher risk of developing cardiovascular diseases such as cardiac hypertrophy, hypertension, and myocardial infarction. In fact, a number of clinical studies have shown that people living at high latitudes or with darker skin are more prone to develop hypertension and suffer higher cardiovascular mortality[29–32].

Cardiovascular disease is generally associated with elevated activity of the renin-angiotensin system (RAS). The RAS expressed in the kidney maintains the homeostatic balance between water and electrolyte and

thus plays a positive role in the regulation of blood volume and pressure. Vitamin D is an endogenous suppressor of the RAS[18, 33]. Through blocking the activity of the cyclic AMP response element in the renin gene promoter vitamin D can directly inhibit renin expression[34]. Such inhibitory effect of vitamin D on the renin transcription has been demonstrated both *in vivo* and *in vitro*[35]. The expression of cardiac and renal renin is found to be increased in VDR knockout mice and 1α-hydroxylase knockout mice as compared to wild type mice[33, 36], and the elevated renin may help to increase blood pressure in these knockout mice. Chronic vitamin D supplementation, along with captopril (angiotensin-converting enzyme inhibitor) or losartan (angiotensin receptor blocker), lowers blood pressure in the 1α-hydroxylase-deficient mice[37].

6.1 Vitamin D and cardiac protection

The RAS is expressed at higher levels in the heart and kidney of spontaneously hypertensive rats (SHR)[38]. Cardiac hypertrophy of SHR is associated with the elevated expression and activity of the RAS[39]. Vitamin D deficiency or VDR knockout mice exhibit cardiac hypertrophy[40, 41]. Co-treatment of paricalcitriol and enalapril ameliorates cardiac oxidative injury in uremic rats[42]. Hypertrophy of left ventricular myocytes and the augmented levels of atrial natriuretic peptide are reported in VDR deficient mice, and these abnormalities are reversed by captopril treatment[36]. Notably, vitamin D is negatively related to the incidence of congestive heart failure[32], suggesting a housekeeping role of vitamin D in cardiac health. Reduced levels of vitamin D increase the renin expression and angiotensin II production, thus contributing to cardiac hypertrophy[33, 43]. In addition, vitamin D deficiency also participates in the pathogenesis of congestive heart failure in which the levels of inflammatory cytokines such as C-reactive protein and interleulin-10 are elevated[44]. Rahman *et al.* reported that cardiac collagen deposition is increased in VDR knockout mice, accompanied by the increased activity of matrix metalloprotease (MMP)-2 and MMP-9 and decreased activity of tissue inhibitor of metalloprotease. Vitamin D-deficient diet can also promote collagen deposition in the extracellular space of the myocardium and vitamin D is therefore hypothesized to regulate the expression of MMP transcriptionally[45].

In vitro studies using primary culture of neonatal rat cardiomyocytes show that vitamin D attenuates the proliferation of ventricular myocytes and prevents the transcription of genes relating to endothelin-induced myocyte proliferation and hypertrophy such as c-myc, proliferating cell nuclear antigen and atrial natriuretic peptide[40]. It is probable that vitamin D may modulate the growth of myocytes directly independent of the RAS (Fig. 1).

6.2 Vitamin D and blood pressure

Existing evidence shows that vitamin D levels are negatively correlated with blood pressure. Mice with VDR knockout or vitamin D deficiency are hypertensive[36]. Supplementation with active vitamin D normalizes the elevated blood pressure in nephrectomized and hypertensive rats[46, 47]. Hypertensive patients undergoing 3-month UVB radiation therapy had elevated circulating vitamin D levels with reduced systolic and diastolic blood pressure[48, 49]. These observations are also supported by a number of epidemiologic studies[50–52].

In addition to a direct effect on the RAS, the antihypertensive benefit of vitamin D is probably also indirectly associated with its impact on the regulation on calcium and parathyroid hormone. Vitamin D deficiency can result in low levels of calcium as vitamin D is needed to enhance intestinal calcium absorption and renal calcium re-absorption. Vitamin D also stimulates osteoclasts to release calcium. Low levels of calcium stimulate the secretion of parathyroid hormone via a negative feedback mechanism in order to maintain normal plasma calcium. The elevated parathyroid hormone can increase blood pressure as infusion of parathyroid hormone to normotensive subjects was found to induce hypertension[53]. A recent clinical study show there is a high prevalence of hypovitaminosis D in elder population and that serum 25(OH)-D_3 levels are inversely correlated with blood pressure[54]. Almirall *et al.* suggest taking measures to prevent hypovitaminosis D in older people not only for protecting the skeletal system but also for promoting cardiovascular health[54].

6.3 Vitamin D and endothelial function

Normal endothelial function is attained by the balance between the production of endothelium-derived relaxing and contracting factors (EDRF and EDCF)[55]. Endothelial dysfunction occurs when such balance is disturbed by reduced EDRF production or/and enhanced EDCF release. Although vitamin D supplementation has been demonstrated to improve endothelial function in diabetic patients[56], there are limited mechanistic

studies regarding how calcitriol protects vascular function. VDR activation reduces thrombosis and sustains plaque stability in atherosclerotic lesions. Whilst plaque vulnerability is closely related to inflammatory states, VDR stimulation through modulating immune response may attenuate macrophage activation[57]. Wu-Wong observed that VDR activation can negatively regulate smooth muscle cell proliferation and differentiation under inflammation during the development of hypertension[57] (Fig. 1).

We were the first to provide evidence that calcitriol, an active form of vitamin D is vasoprotective in blood vessels from hypertensive patients. By acting on VDR, calcitriol rescues the impaired renovascular dysfunction in hypertension through favorable alteration of the expression and activity of several key proteins involved in redox signaling[58]. Calcitriol treatment normalizes the ROS over-production, the over-expression of angiotenin type 1 receptor, NADPH oxidase subunits [NOX-2, NOX-4, and p67^{phox}] and under-expression of super-oxide dismutase-1 in renal arteries from human and rats[58]. These novel findings suggest that calcitriol is effective to preserve endothelial function in hypertension.

Diabetic patients have higher levels of advanced glycation end products (AGEs) which cause endothelial dysfunction. AGEs decrease the mRNA expression of endothelial nitric oxide synthase in human umbilical vein endothelial cells. Calcitriol, one of active forms of vitamin D inhibits the harmful effect of AGEs by reducing the NF-κB-P65 DNA binding activity[59].

Cardiovascular risks increase in postmenopausal women. While vitamin D is supplemented for osteoporosis, it is not known whether it protects renal arterial function during estrogen deficiency. Our recent study demonstrates that long-term calcitriol treatment reverses the impairment of endothelium-dependent relaxation in renal arteries of estrogen-deficient rats and this benefit is accompanied by reduction in the increased expression and activity of both cyclooxygenase-2 (COX-2) and thromboxane-prostanoid receptor (TPR) in isolated intralobal renal arteries and primary aortic endothelial cells from ovariectomized rats. Calcitriol restores endothelial function through downregulating both signaling proteins during estrogen deficiency[60]. The potential benefits of calcitriol or other active vitamin D analogues in postmenopausal women need further clinical investigation and verification.

7 Summary and perspective

Sufficient vitamin D levels are essential for maintaining normal cardiovascular homeostasis. Active analogues of vitamin D protect cardiovascular function through several newly elucidated cellular mechanisms including inhibition of (1) the RAS, (2) associated NADPH oxidases, (3) ROS over-production, (4) cardiac hypertrophy, (5) COX-2 up-regulation, (6) TPR up-regulation, and (7) vascular smooth muscle cell proliferation. Since excessive exposure to sunlight may increase the risk of skin cancer, dietary vitamin D supplementation is therefore recommended to individuals in health and disease.

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