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Review

Vitamin D in Cardiovascular Disease

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Abstract. *Cardiovascular disease is the prevalent cause of morbidity and mortality in the world, affecting many millions of individuals every year. Atherosclerosis, a chronic inflammatory condition that involves different cell types, several cytokines and adhesion molecules, is the underlying cause of cardiovascular disease. Vitamin D is known to control skeletal patho/physiology, regulating calcium and phosphorus and bone remodeling along with other calcium-regulating hormones. However, several active metabolites of vitamin D can exert both direct action, mainly via vitamin D_3 receptor trans-activation and indirect actions on several other tissues by an endocrine, autocrine and paracrine manners. With regard to cardiovascular disease, vitamin D deficiency has been associated with activation of the pro-inflammatory mechanism, promoting atherogenesis. There are several large-scale clinical studies, as well as meta-analyses that support this finding. However, it is still unclear whether the plasma 25-hydroxyvitamin D level can be used as a biomarker for future cardiovascular disease. Herein we review the studies reporting a causative role for vitamin D in cardiovascular disease.*

Over the past few years, spectacular progress has been made in the fields of drug and biomarker discovery, as well as in understanding of the pathophysiological mechanisms of several diseases (*e.g.* cardiovascular and neurodegenerative diseases, and cancer). Interestingly, a growing body of research is now focusing on prevention, rather than the treatment of disease. Thus, the discovery of new biomarkers, especially for early stages of a disease, has become of particular interest in the context of early identification of disease that can lead to improved therapeutic efficacy and greater overall survival.

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Cardiovascular Disease and Atherosclerosis

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide. It is defined as a set of diseases and conditions that usually manifest as heart attacks and strokes. It was considered to be a disease of the Western world, but recent evidence points to the fact that populations of emerging and even low-income countries also suffer from it. In 2015, the World Health Organization (WHO) estimated that CVD accounted for more than 17.7 million deaths, representing a total 31% of global deaths (1).

The main condition underlying CVD is atherosclerosis. Atherosclerosis is nowadays not considered to be a lipid storage disease, but can be better termed as low-grade inflammation of the vascular wall. It is characterized by the deposition of lipids and the subsequent accumulation of T-cells and macrophages as a result of endothelial injury response (2). In these process, reactive oxygen species play a pivotal role as they can cause oxidation of lipids such as low-density lipoprotein (LDL) and polyunsaturated fatty acids that are deposited in the vascular wall, directly damage cellular components, and further promote inflammation by activating several pro-atherogenic transcriptional factors (3). Over the course of time, atherosclerotic lesions are formed, which through the action of several cytokines can rupture and lead to occlusion of the vascular lumen. Depending on the area of rupture, these can manifest as acute myocardial infractions or stroke or acute ischaemia of any nearby organ (4).

Over the last few years, our understanding of atherosclerotic processes has vastly improved; however, there are still many mechanisms that have not been fully elucidated. It is evident that prevention and early detection of atherosclerotic plaques still remains a high priority. Towards this end, many biomarkers have been developed, with many being used in everyday clinical practice. Often these biomarkers have significant advantages and disadvantages and numerous clinical studies have been conducted in order to verify their use in clinical practice (5). Most biomarkers are cardiac muscle-related, but there is an increasing interest in novel biomarkers that can allow detection of CVD well before damage to cardiac muscle occurs (6).

Vitamin D Biosynthesis and VDR Signaling

Vitamin D is a group of secosteroids mainly responsible for enhancing the intestinal absorption of calcium and phosphate. The most important compounds in this group are vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol). Cholecalciferol and ergocalciferol can be ingested from the diet as well as from various supplements (7). The human body is also capable of synthesizing vitamin D, specifically cholecalciferol, in the skin from cholesterol when sun exposure is adequate. Although vitamin D is commonly called a vitamin, it is not actually an essential dietary vitamin in the strict sense as it can be synthesized in adequate amounts by most mammals exposed to sunlight. By definition, only substances that cannot be synthesized sufficiently by a living organism and can only be obtained through its diet can be classified as essential vitamins. Similarly to other compounds commonly called vitamins, vitamin D was discovered in an effort to find the dietary substance lacking in individuals in with rickets, the childhood form of osteomalacia (8). Similarly to other vitamins, in many parts of the world, vitamin D is added to staple foods, such as milk, to avoid disease due to its deficiency.

Synthesis from exposure to sunlight, as well as intake from the diet, generally contributes to the maintenance of adequate vitamin D concentrations in serum. Evidence indicates the synthesis of vitamin D from sun exposure is regulated by a negative feedback loop that prevents toxicity, but no recommendations have been issue on suggested exposure to sunlight for optimal vitamin D synthesis, due to uncertainty about the cancer risk from sunlight (9). The Dietary Reference Intake for vitamin D assumes no synthesis occurs and that all vitamin D intake is from food, although in practice such an occurrence is very rare (10). In the liver, cholecalciferol (vitamin D_3) is converted to 25-hydroxycholecalciferol, or 25-hydroxyvitamin D_3, ($25(OH)D_3$) (11). Ergocalciferol (vitamin D_2) is converted in the liver to 25-hydroxyergocalciferol, also known as 25-hydroxyvitamin D_2 ($25(OH)D_2$). These are the two specific vitamin D metabolites that are measured in serum/plasma to determine a person's vitamin D status (12). Part of calcidiol is converted by the kidneys to calcitriol, the biologically active form of vitamin D (4). Calcitriol circulates as a hormone in the blood, regulating the concentration of calcium and phosphate in the bloodstream and promoting healthy growth and remodeling of bone. Calcitriol also affects neuromuscular and immune function (13). A plasma concentration above 50 nmol/l is the target level for dietary intake recommendations of vitamin D in several Western countries, using data of studies of optimal and suboptimal skeletal health (14).

Vitamin D_3 is often considered a hormone rather than a vitamin because of the fact that the active vitamin D metabolite exerts its action through the vitamin D receptor (VDR) in cells. The VDR is an intracellular hormone receptor that specifically binds the biologically active form of vitamin D_3, calcitriol. It subsequently interacts with specific response elements and induces response of various genes with a plethora of physiological effects (15). VDR is almost ubiquitously expressed in the nucleus of most cells. Circulating calcitriol diffuses through the cell membrane and nuclear membrane and binds to the VDR, causing a conformational change in the receptor, leading to its heterodimerization with retinoic acid X-receptor (RXR). It can also form a heterodimer with other members of the steroid receptor gene family (16). This trans-activation of VDR results in the expression or repression of several other genes. It has been estimated that calcitriol regulates more than 200 genes, directly or indirectly, thereby influencing a wide variety of physiological processes (15). Interestingly, VDR–DNA binding can help facilitate the targeting of genes that can be further modified by calcitriol. However, there are many cases where the changes in gene expression are not mediated directly by the VDR but through many different co-regulatory elements (17). These complexes usually contain one VDR regulatory component and have significant enzymatic activity (16).

Vitamin D and Cardiovascular Physiology

Several cells and tissues of the cardiovascular system abundantly express either calcitriol or VDR. These include cardiomyocytes, and vascular and endothelial cells (18). VDR activation in endothelial cells can regulate their development through modulation of elements in the vascular endothelial growth factor (*VEGF*) promoter (19). Furthermore, higher VDR expression has been observed in stressed endothelial cells (20) and increased concentrations of calcitriol have been shown to decrease cytokine and adhesion molecule expression (21).

In cardiomyocytes, calcitriol was found to regulated cell maturity and differentiation (22). In addition, animal models lacking VDR expression demonstrated increased ventricular mass and higher levels of matrix metalloproteases (MMPs) and

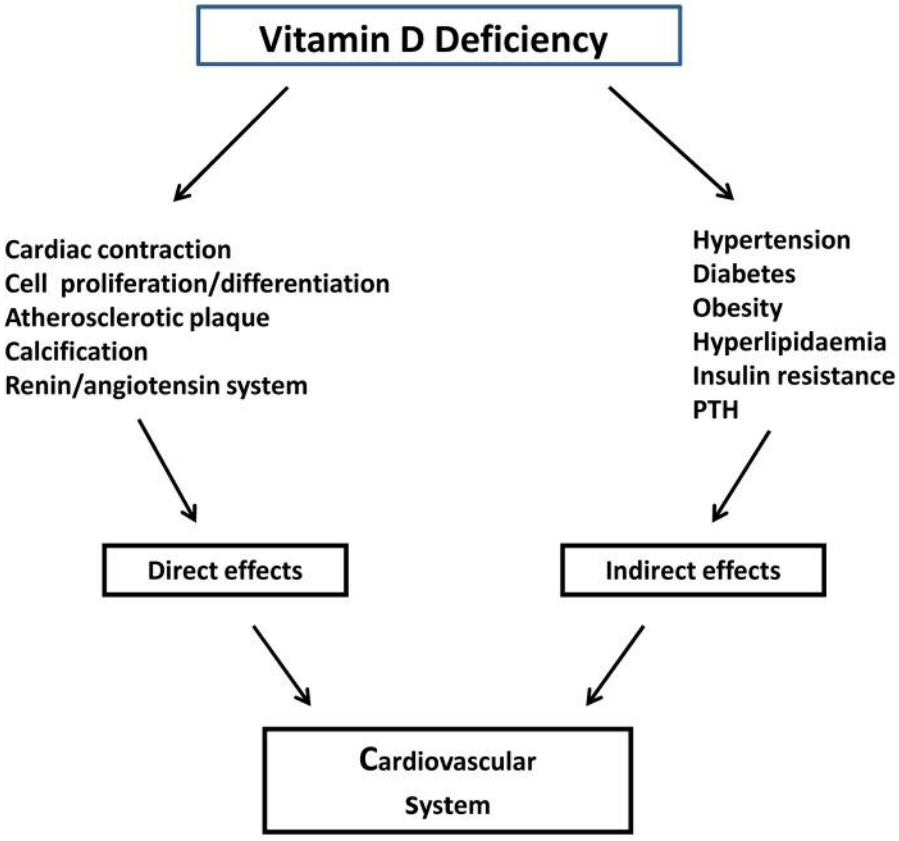

Figure 1. *Potential associations between vitamin D deficiency and cardiovascular disorders. Vitamin D deficiency affects the cardiovascular system both directly and indirectly through the multiple roles that it plays in various conditions and pathologies associated with cardiovascular system (see text for details). PTH: Parathyroid hormone.*

atrial natriuretic peptide (ANP) (23). As well as this, in rats, vitamin D-deficient diet led to a higher systolic pressure and lower calcium concentration. Interestingly supplementation of vitamin D analogs, led to reversal of these effects (24).

There has also been evidence that vitamin D can regulate matrix homeostasis. Such actions may prove to be critical in inflammatory and aneurismal diseases, where matrix destabilization is significant (25). There are several studies that suggest that calcitriol can suppress several MMPs (26). Furthermore, in VDR knockout mice, the expression of tissue inhibitor of MMP1 and tissue inhibitor of matrix metalloproteinase-3 is down-regulated, while the expression of MMP2 and MMP9 are up-regulated in cardiac muscle (27). There are also a few clinical studies that link vitamin D insufficiency with increased MP production (28-31).

Nowadays, there is evidence that associates vitamin D deficiency with several cardiovascular disorders (Figure 1). However, a causal relationship has not yet been identified. Studies have demonstrated a link between vitamin D deficiency and progression of atherothrombosis and vascular calcification (32, 33). Vitamin D has been found to regulate macrophage maturation and infiltration into the vasculature, subsequently regulating the expression of pro-inflammatory cytokines and adhesion molecules, which are critical components in the progression of atherosclerosis (34). These findings are also in line with observations that vitamin-D deficient patients have increased plaque instability and incidence of myocardial infarction. Interestingly, vitamin D supplementation therapy resulted in improvement of inflammatory biomarkers in patients with heart failure (35).

There have been large-scale studies that support the association of low levels of vitamin D with both prevalent and incident CVD (31, 36). Vitamin D deficiency has also been linked to traditional risk factors for CVD such as dyslipidaemia, hypertension and diabetes mellitus (37). Several studies demonstrated that higher vitamin D concentrations are associated with an improved lipid profiling. However, recent meta-analyses have demonstrated there is little evidence for this beneficial effect (38, 39). In addition, cross-sectional studies have also revealed an

association between vitamin D deficiency and diabetes mellitus (40-42). In prospective studies, a clear link between vitamin D levels and coronary heart disease (CHD) in a dose-response manner has been established (43-45). Furthermore, a meta-analysis of 12 prospective studies confirmed an increased 33% change for CHD in patients with the lowest quartile of vitamin D levels (46). Meta-analyses of several studies focusing on cerebrovascular disease have revealed similar patterns (47-49). Recently, plasma 25-hydroxyvitamin D was associated with mortality in patients with suspected stable *angina pectoris* (50).

Conclusion

Vitamin D is a vitamin/hormone with complex action and through its VDR can exert significant cellular effects on multiple biological systems, including the cardiovascular system. Preliminary findings suggest that it is a critical regulator of several cellular components of the cardiovascular system, affecting cellular function, MMP production and inflammatory responses. Clinical trials are required in order to fully establish a clear relationship between vitamin D level and cardiovascular events. It is possible that in the near future, the vitamin D/VDR system may be a potent therapeutic target not only for CVD, but also potentially for several more inflammatory diseases.

Declaration of Interest

The Authors declare that they do not have any competing interests in regard to this article.

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