Vitamin D and its role in cardiovascular disease

Summary
Vitamin D insufficiency is prevalent, especially among older adults and may be associated with higher risk for cardiovascular disease (CVD) and mortality. The newest worldwide statistics demonstrate a near doubling of the prevalence of vitamin D insufficiency seen just 10 yrs ago. Vitamin D plays a key role in maintaining calcium and bone homeostasis and regulation of secretion of parathyroid hormone by acting through vitamin D receptor (VDR). Expression of vitamin D receptors has been detected in multiple extra-skeletal tissues. Recent data suggest a potential role for vitamin D in the development of atherosclerosis where local production of 1,25(OH)₂D₃ (calcitriol) by macrophages may promote atherosclerotic calcification. Recently, vitamin 25(OH)D₃ assay became commercially available on immunochemistry analyzers which allows further research to elucidate the role of vitamin deficiency in the development of CVD. This review attempts to provide some explanation for: risks and mechanisms of soft tissue calcification important in atherogenesis and addresses the adverse impact of vitamin D insufficiency on skeletal and extra-skeletal health in humans.

Introduction
Vitamin D plays a key role in maintaining calcium and bone homeostasis and regulation of secretion of parathyroid hormone by acting through vitamin D receptor. Expression of vitamin D receptors has been detected in multiple extra-skeletal tissues. In recent years more attention has been paid to the association of vitamin D deficiency with the development of cardiovascular disease and many types of cancer, bacterial infections, autoimmune diseases and diabetes as well. According to the newest statistics, mean 25(OH)D₃ concentration worldwide is in the range of hypovitaminosis (50-75 nmol/L; 20-30 ng/mL) whereas in Europeans is in the range of insufficiency/mild deficiency (25-50 nmol/L; 10-20 ng/mL) (8,29). The criteria for defining levels of 25(OH)D₃ deficiency were provided by different groups (3,12,16,29) as the following: <12.5 mmol/L or <5 ng/mL; severe deficiency, 12.5-25 mmol/L or 5-10 ng/mL; moderate deficiency, 25-50 mmol/L or 10-20 ng/mL; mild deficiency, >50-75 mmol/L or >20-30 ng/mL; insufficiency/ hypovitaminosis, >75 mmol/L or >30 ng/mL; sufficiency. Few clinical studies, as yet, have shown higher prevalence of cardiovascular disease and hypertension in relation to vitamin D deficiency (27).
Recent data suggest a potential role for vitamin D in the development of atherosclerosis where local production of
1,25(OH)₂D₃ by macrophages may promote atherosclerotic calcification. Moreover, macrophages may be involved in the phenotypic changes of vascular smooth muscle cells (VSMCs) to acquire calcifying capacity. Therefore, the phenotypic changes of VSMCs in atherosclerotic plaque may contribute to the development of atherosclerotic calcification. Vascular calcification is an active process similar to osteogenesis. Similarities include presence of all the major components of bone osteoid, bone regulatory factors, and subpopulations of artery wall cells that retain osteoblastic lineage potential. Vascular calcification is increasingly recognized as a significant contributor to cardiovascular morbidity and mortality as well as a biologically regulated process potentially subject to prevention and reversal. Aortic calcification increases aortic stiffness and contributes to cardiac ischemia, left ventricular hypertrophy, heart failure, and stroke. However, it is not yet proven whether vitamin D deficiency is a cause or a consequence of cardiovascular disease and whether supplementation or treatment with VDR activators will be beneficial for patients (26).

Metabolism, degradation and activity of vitamin D
Vitamin D and its metabolites belong structurally to the secosteroids. They are very similar in structure to steroids except that two of the B-ring carbon atoms of the typical four steroid rings are not joined. It exists in several forms among which ergocalciferol (D₂) and cholecalciferol (D₃) and its hydroxylation products are the most important. Vitamin D₂ is synthesized in plants and fungi and vitamin D₃ is synthesized in animals and humans. Vitamin D₃ is a fat soluble vitamin, produced in the skin during sun exposure (UVB) through conversion of 7-dehydrocholesterol into cholecalciferol and then after hydroxylation by 25-hydroxylase in the liver 25(OH)D₃ is synthesized. Insufficient exposure to UV-B leads to decrease of vitamin D₃ production in the skin, which is a major source of this vitamin for humans. Dietary intake is another but minor source (10-20%) of 25(OH)D₃ which is synthesized from ergocalciferol (D₂) and D₃ in the liver. Serum concentration of 25(OH)D₃ reflects the vitamin D status of the organism. 25(OH)D₃ transported in the circulation complexed with a binding protein enters the kidney where is converted to active form 1,25(OH)₂D₃ by 1-α hydroxylase (CYP27B1). Kidney synthesis of 1,25-dihydroxy vitamin D₃ takes place in the proximal renal tubule cells and is strictly regulated by serum PTH level, that stimulate the activity of 1-α hydroxylase, as well as by serum calcium, phosphate and phosphatidins such as fibroblast growth factor 23, frizzled-related protein 4, matrix extracellular phosphoglycoprotein (7,14). The absorption of renal calcium and intestinal calcium and phosphorus is increased in the presence of 1,25(OH)₂D₃. Calcitriol decreases synthesis and release of parathormone (PTH) acting directly on parathyroid gland activity and indirectly by increasing serum calcium and regulates its own production through a feedback mechanism (6). Decreasing vitamin D concentration leads to impairment of calcium and phosphorus homeostasis that in turn begins a cascade of events which rises synthesis and release of PTH into the blood and enhances synthesis of 1,25(OH)₂D₃ (21,25). Calcitriol is autonomously made in tissues and directly affects various cells via its autocrine and paracrine functions (15).

1,25(OH)₂D₃ and its precursor 25(OH)D₃ are degraded by hydroxylation at 24-position by 24-hydroxylase (CYP24). The second step is a 23-hydroxylation and oxidation giving rise to calcitrionic acid, which is biologically inactive and excreted with bile. Metabolism of vitamin D also includes the formation of the 26,23-lactone derivative or 26-hydroxylation, but the most important reaction regulating the level of vitamin D is the CYP24. This enzyme is regulated in a negative feedback by parathyroid hormone. PTH not only stimulates the 1-alpha hydroxylase but also the destruction of CYP24, thus increasing the amount of the vitamin D (6).

1,25(OH)₂D₃ acts through a specific cytosolic/nuclear receptor (VDR), a member of the steroid/thyroid hormone receptor family that mediates transcriptional gene regulation. VDR is encoded by a gene located on chromosome 12q13.1. VDR bound to vitamin D undergoes phosphorylation and conformational change facilitating its binding to the retinoid X receptor (19). The resulting heterodimer interacts with vitamin D-responsive elements in the promoter region of target genes modifying their expression (2,19). However, very recently it was suggested that while VDR binding to target sites is ligand-dependent, RXR binding is not (20). The transcriptional activity of the vitamin D receptor is regulated by a number of coactivator and corepressor complexes, which bind to the VDR in a ligand (1,25(OH)₂D₃ dependent (coactivators) or inhibited (corepressors) process (4). Vitamin D and its receptor can regulate a large number of genes in a sequential and differentiation specific fashion but the mechanism is not fully understood yet. The regulation involves processes such as innate immunity, cell growth and differentiation, extracellular matrix remodeling, intestinal calcium transport, secretory function (15,17).

Effect of vitamin D on skeletal health
Vitamin D plays a key role in the system involving interactions among the kidney, bone, parathyroid gland and intestine that maintain extracellular concentration of calcium within narrow range and are essential for normal cellular physiology and skeletal integrity. It is well known that osteocalcin, a major bone matrix protein, is vitamin D-dependent. If necessary, active vitamin D₃ together with PTH stimulates mobilization of calcium from bone to maintain normocalcemia. Mineral homeostasis is maintained through a feedback mechanism regulating 1,25(OH)₂D₃ concentration and stimulation of 24-hydroxylase action to produce 24,25(OH)₂D₃. Hypercalcemia leads to release of calcitonin from thyroid gland which blocks calcium mobilization from the bone and stimulates conversion of 25(OH)D₃ to 1,25(OH)₂D₃ mediated...
by 1-α-hydroxylase for noncalcemic effects. Interaction of 1,25(OH)$_2$D$_3$ with VDR significantly increases the efficiency of intestinal calcium and phosphate absorption which is critical for the proper bone matrix mineralization.

Vitamin D deficiency causes an increase of serum PTH leading to bone resorption, osteoporosis and fractures (1).

**Extra-skeletal effects of vitamin D**

VDR receptors have been discovered in numerous organs and tissues that were not considered earlier as targets for vitamin D such as parathyroid glands, pancreatic β cells and thyroid C cells, arterial smooth muscle cells and cardiomyocytes, stomach, oesophagus and intestine, liver cells, kidney, testis, ovary and uterus, T and B cells, bone marrow and thymus, lung alveolar cells, macrophages and keratinocytes, breast and colon tissue, brain neurons (7). In some tissues, 1-α-hydroxylase mediated conversion of 25(OH)D$_3$ into the active 1,25(OH)$_2$D$_3$ was found (5,7,10,11). However, this vitamin D3 is supposed to act only locally and is not released into the circulation (11,13).

1,25(OH)$_2$D$_3$ was found to effect directly or indirectly on hundreds different genes responsible for regulation of cellular proliferation, differentiation, apoptosis and for angiogenesis (10,11). Active form of vitamin D was shown to diminish cell multiplication and to induce terminal differentiation as well as induce apoptosis of cancer cells. The concentration of 1,25(OH)$_2$D$_3$ is maintained by expression of 24-hydroxylase which in turn converts 25(OH)D$_3$ to inactive metabolite (9). Thus effect on calcium homeostasis is prevented.

On the other hand, 1,25(OH)$_2$D$_3$ produced in the kidneys is released into the circulation and may decrease renin synthesis and rise insulin secretion from the pancreatic β-cells (9).

Vitamin D may potentially modulate parathyroid gland function. Administration of 1,25(OH)$_2$D$_3$ inhibits parathyroid cell growth and PTH synthesis whereas vitamin D deficiency results in hyperplasia of the gland, increased PTH synthesis and secretion (7). Parathyroid cell growth may be arrested by 1,25(OH)$_2$D$_3$ in the complicated mechanism involving mitogenic signals, specific suppressors of cell growth and cell membrane and nuclear growth signals from epidermal growth factor receptor (7).

**Vitamin D: its role in vascular calcification**

Cardiovascular disease is a major cause of morbidity and mortality worldwide. A few clinical studies have shown that there may be an association between cardiovascular disease and vitamin D status, and recent evidence suggests that vitamin D can play a role in reducing the risk of cardiovascular disease (27). Vitamin D is involved in the pathogenesis of cardiovascular diseases and arterial hypertension. Among possible mechanisms effects on the renin gene expression, smooth muscle cell proliferation, inflammation, thrombosis and vascular remodeling are mainly affected by vitamin D deficiency (27). 1,25(OH)$_2$D$_3$ affects the number of genes appropriate to the vessel wall, including vascular endothelial growth factor, matrix metalloproteinase type 9, myosin, and structural proteins, such as elastin and type I collagen. It has been demonstrated that vitamin D has an effect on myocardial contractile function, regulation of natriuretic peptide secretion, extracellular matrix remodelling and regulation of inflammatory cytokines (23).

Low concentration of available calcitriol disturbs contraction of cardiomyocytes and increases natriuretic peptide synthesis that may lead to cardiac hypertrophy and subsequent
heart failure (18). Treatment with vitamin D leads to the rise in the expression of the cardiac muscle protein myotrophin, and the decreased expression of atrial natriuretic peptide, which is inversely associated with cardiac function. More than that vitamin D intake increases expression and nuclear localization of the VDR in cardiomyocytes (18).

Calcification of arterial intima that leads to formation of plaque and its rupture is associated with cardiovascular events. On the other hand, proliferation of vascular smooth muscle cells and calcification of arterial media affects vessel wall stiffness. Osteoblasts and vascular smooth muscle cells derive from a similar precursor. Vascular smooth muscle cells may undergo transformation into osteoblast-like cells which produce several bone matrix proteins that regulate mineralization. After initiation of mineralization process increased serum calcium and phosphate concentrations accelerate vessel calcification that leads to its abnormal stiffness (26). Vascular smooth muscle cells were shown to express VDR. Low concentration of available 1,25(OH)2D3 results in vascular calcification through enhanced synthesis of parathormone, matrix metaloproteinases, TNF-α, collagen type I and osteopontin and reduced synthesis of matrix-Gla protein and fetuin-A - inhibitors of vascular calcification, II-10 and type IV collagen (26,29). It seems that 1,25(OH)2D3 through interaction with VDR plays an important role in the process of vascular calcification. This is supported by the in vitro studies with the use of VDR agonists that may inhibit vascular calcification (26). It was reported that treatment with VDR agonists reduces differentiation of osteoblast-like cells, stimulates synthesis of matrix-Gla protein, an inhibitor of vascular calcification (26).

The renin-angiotensin-aldosterone system (RAAS) regulates extracellular volume homeostasis, which contributes to blood pressure stability. Overactivity of this system is involved in the pathophysiology of cardio-renal disease. Vitamin D receptor activators (VDRas) beyond suppression of the RAAS may also have anti-inflammatory and anti-fibrotic effects (18). The primary physiological function of the renin-angiotensin system is to maintain vascular resistance by regulating actions of angiotensin II on the peripheral vasculature, heart, central nervous system, kidney and adrenal glands. In mice, vitamin D is an inhibitor of the renin - angiotensin system, and vitamin D receptor knock-out mice develop cardiac hypertrophy (22). Recent study have shown that renin expression and plasma angiotensin II production are elevated in VDR-null mice, and that inhibition of vitamin D biosynthesis leads to renin upregulation. Tan et al. (24) suggested that administration of vitamin D analog with a RAS inhibitor to inhibit the reactive renin increase should produce additive therapeutic effects and reduce renal injury. Hypovitaminosis D enhances renin expression and concentration of natriuretic peptide and angiotensin II, as well, leading to myocardial hypertrophy. Treatment with VDR activators may be beneficial in patients with cardiovascular disease decreasing vascular calcification, cardiac hypertrophy, renin-angiotensin system and preventing thrombosis. Also evidence from limited data suggests that vitamin D supplements at moderate to high doses may reduce CVD risk (28).

Conclusion:
Clinical studies support a plausible role for improving vitamin D status in CVD prevention in the population. Available data indicate that mortality is more than twice as high in individuals with vitamin D deficiency compared with those who have sufficient vitamin D. Supplementation of vitamin D at moderate to high doses may reduce CVD risk. High prevalence of vitamin D deficiency and molecular mechanisms linking this to cardiometabolic risk suggest that treatment of vitamin D deficiency is a promising field to explore.

References


---

**Adres Autorów:**

Katedra i Zakład Diagnostyki Laboratoryjnej
Collegium Medicum w Bydgoszczy
ul. M. Skłodowskiej-Curie 9
85-094 Bydgoszcz

tel. (52) 585 36 85
e-mail: odes@cm.umk.pl

(Praca wpłynęła do Redakcji: 2010-04-12)
(Praca przekazana do opublikowania: 2010-05-19)