VITAMIN D: CARDIOVASCULAR EFFECTS AND BEYOND

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BACKGROUND

The importance of vitamin Din mineral metabolism has been known for a long time. Deficiency of this compound can cause rickets in children and both osteomalacia and osteoporosis in adults, leading to increased risk of fracture.1 A significant number of pediatric and adult patients have vitamin D deficiency due to decreased sun exposure, reduced dietary intake, malabsorption, drug intake (anticonvulsants), and renal and hepatic disease.2

Recently, better understanding of the physiology of vitamin D and the discovery of new receptor sites in many organs/ tissues have underscored vitamin D's multiple beneficial effects, including improved cardiovascular health.3 Moreover, studies have reported that correction of vitamin D deficiency has resulted in decreased risk of cancer and diabetes,4•6 improvement in the immune system,7 and improved muscle function.8 We summarize herein some of these observational studies.

SYNTHESIS AND METABOLISM OF VITAMIN D

Solar ultraviolet radiation exposure transforms 7-dehydrocholesterol in the skin into vitamin Dy Excessive sun exposure degrades chi compound into inactive products, which is why excess sun exposure does not result in vitamin D intoxication. Vitamins D_2 and D_3 from dietary sources are mixed with chylomicrons and transported via the lymphatic system into the venous circulation. Vitamin D_3 obtained from the skin and by nutritional sources is stored and released from fat cells and transferred to the liver by a vitamin D binding protein. Subsequently by the effect of D-25 hydroxylase, vitamin D is converted into 25(0H) D_3' the levels of which can be readily measured as a marker of vitamin D concentration, with normal values being 30-60 ng/ml. This inactive form of circulating vitamin D needs to be converted into an active compound at the level of the kidney, whereby the action of 25(0H) D-1a hydroxylase becomes 1,25(0H)2D3, the biologically active form. Also considered "hormone D," $1,25(0H)_2D$ is responsible for calcium/phosph rus and parathyroid hormone homeostasis (Figure 1).[9]

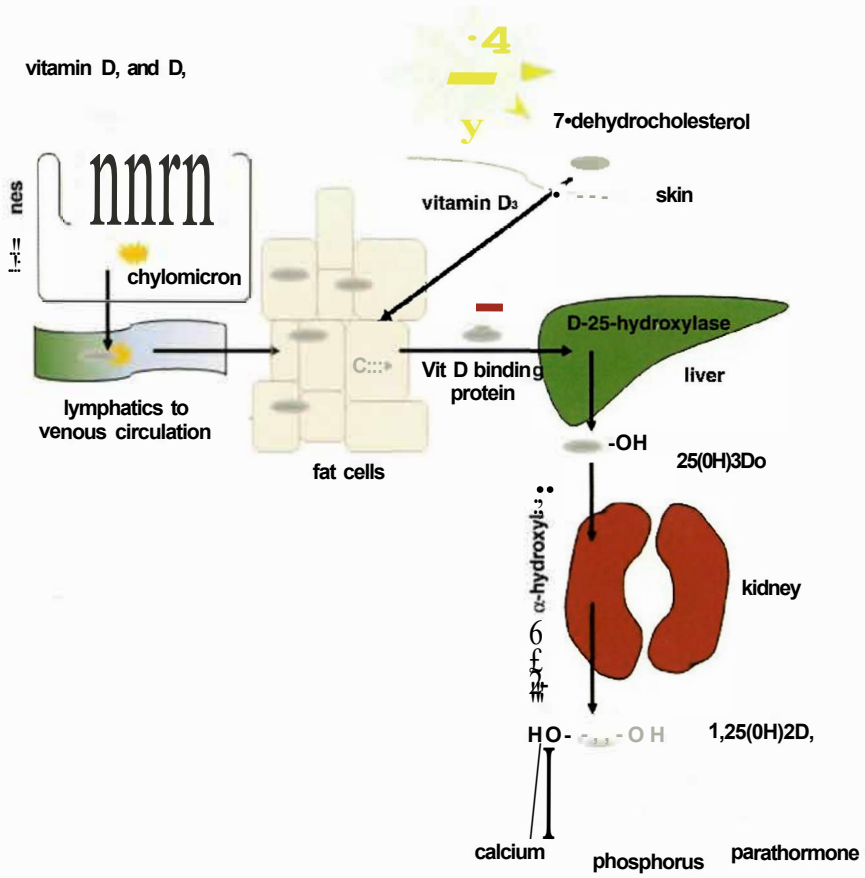


Figure 1. The biologically active form of vitamin D - $1,25(OH)_2D_3$ (or "hormone D"} - is responsible for calcium/phosphorus and parathyroid hormone homeostasis.9

Over the years, vitamin D (hormone D) analogues have become an important therapy in suppressing the devastating effects of excess parathormone production, a consequence of secondary hyperparathyroidism that is invariably present in patients with chronic kidney disease. The vitamin D analogues currently available are shown in Table 1.

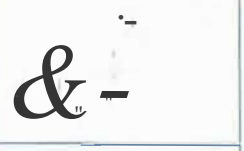
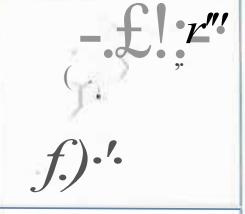
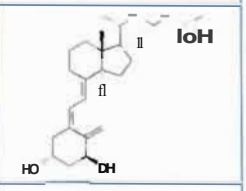
	Generic	Brand name	Chemical structure
Vitamin D_2	ergocalciferol		
Vitamin 0_3	cholecalciferol		
1,25-dihydroxycholecalciferol	calcitriol	Rocaltrol® Calcijex® Decostriol®	
	doxercalciferol	Hectorol®	
	paricalcitol	Zemplar®	

Table 1. Vitamin D analogues

CARDIOVASCULAR EFFECTS OF VITAMIN D: INFLAMMATION/ ATHEROSCLEROSIS/ VITAMIN D AND THE INFLAMMATORY PROCESS

Inflammation has been recognized as an important mechanism in the genesis and progression of atherosclerosis and the atheromatous plaque. Macrophages and T cells lead to the formation of foam cells and atheromatous lesions in the arterial endothelium that ultimately release cytokines such as interleukin (IL-1), IL-4, IL-6, interferon (INF-y) and tumor necrosis factor (TNF-a). This, in turn, results in smooch muscle cell proliferation, plaque formation, and release of amyloid A and c-reactive protein (CRP), a predictor of cardiovascular outcomes.[10-11]

Vitamin D inhibits vascular smooth muscle cell proliferation, increases IL-10 production, and decreases IL-6, 11-12, INF-y and TNF-CI. production, resulting in less inflammation.[12] Vitamin D also has a modulatory effect on the expression of tissue matrix metalloproreinases (MMP's).[13] These enzymes are involved in remodeling the vascular wall and myocardium and can break down collagen within the atherosclerotic lesion, causing rupture and thrombosis. An inverse relationship between elevated concentration of MMP's and low vitamin D levels has been found in populations with increased incidence of coronary artery disease,[14] which further supports the protective role of vitamin D against atherosclerosis. Endothelial progenitor cells (EPC's) are associated with cardiovascular health, and CRP has a detrimental effect on their differentiation and survival. This highlights vitamin D's positive cardiovascular function not only in preventing and reducing inflammation but also in stimulating EPC's from the bone marrow.[11]

Recently, using a low dose of vitamin D supplement (200 JU BID) and calcium (500 mg **daily)** was shown to neither increase nor decrease coronary or cerebrovascular risk in healthy postmenopausal women over a seven-year period.[1&] On the other hand, reduction in proteinuria (an accepted marker of cardiovascular disease) was achieved by the use of oral paracalcitol therapy independent of renin-angiotensin blockadeT In a cohort of CKD-V D patients (end-stage renal failure on dialysis), the use of vitamin D reduced the risk for cardiovascular death and improved survival.18

REN IN-ANG IOTENSIN SYSTEM AND VITAMIN D

There is a well-known inverse relationship between vitamin D levels and both the renin-angiotensin system and blood pressure levels. Vitamin D and calcium reduced blood pressure in normotensive vitamin O-deficient women[19] and in hypertensive men.[20] Among CKD-V D hypertensive patients, treatment with intravenous calcitriol for 15 weeks showed regression of LVH and reduc-

tion of renin/angiotensin II levels,[21] another reason why vitamin D has a positive impact on the cardiovascular system.

The proposed mechanism for the salutary effects of $1,25(OH)_2O_3$ is mediated by a direct suppression of the renin gene expression, which is independent of the effects of vitamin D on calcium.[22]

PERIPHERAL ARTERY DISEASE AND VITAMIN D

There are two forms of arterial calcification: calcification of the intima (atherosclerosis) and calcification of the media (Monckeberg's sclerosis) that is most commonly seen among the elderly, diabetics, and patients with chronic kidney disease. The latter is a predictor of lower limb amputation and cardiovascular mortality.[23]

The association between osteoporosis and vascular calcification has become an interesting research topic. In general, vitamin D deficiency results in decreased calcium absorption from the bowel, leading ɷ hypocalcemia and ultimately eliciting parathyroid hormone release. The latter is then responsible for calcium mobilization from bone (osteoporosis) and subsequent deposition in the arteries. There is also PTH-mediated osteoclastic cell activity in the arterial wall resulting from proteins in arterial tissues that are associated with bone metabolism.[26] Inhibitors of bone resorption, like the bisphosphonates, have been shown ɷ inhibit calcification of the arterial media in animal models.[24] However, none of these drugs have any direct effect on arterial smooth muscle cells. On the ocher hand, $1a-25(OH\backslash D_3$ may act direccly on those cells or other osceoclastic-like cells within the arterial wall, worsening the vascular injury. Thus, although vitamin D is essential for "cardiovascular health," excess amounts could have detrimental effects, particularly on elastogenesis and vascular injury.[25]

CARDIAC HYPERTROPHY AND VITAMIN D

Studies evaluating N-terminal proatrial natriuretic peptide, LVH severity, and vitamin D levels showed that patients with reduced circulating levels of $25(OH)D_3$ had the most severe congestive heart failure.[27] Moreover, experimental studies evaluating the role of vitamin D in myocyte proliferation and hypertrophy have shown that vitamin D deficiency induced myocardial hypertrophy and extracellular matrix production.[28] These findings suggest that vitamin D plays an important role in cardiac homeostasis, and its deficiency may increase the risk of cardiac hypertrophy.

VITAMIN D AND CANCER

Epidemiologic studies have shown that individuals living in high latitudes, thus having decreased sun exposure, have a high incidence of vitamin D deficiency. This has been associated with an increased occurrence of colon, prostate, and breast cancer as well as non-Hodgkin's lymphoma. Moreover, the mortality rate from those cancers is higher among individuals with vitamin D deficiency.4 This beneficial effect of vitamin D stems from the fact chat during malignant cell transformation, $1,25(OH)_2O_3$ inhibits angiogenesis and induces organized cell death (apoptosis), therefore diminishing malignant cell survival.[29]

VITAMIN D AND DIABETES

Studies in Finland showed that children who were receiving 2,000 TU of vitamin D daily, beginning at age one and followed for 31 years, reduced their risk of Type I diabetes by 80%.'5 Conversely, children with vitamin D deficiency had a markedly increased risk of developing diabetes.

In general, vitamin D deficiency has been associated with insulin resistance, decreased insulin release, and the metabolic syndrome. Type II diabetes risk was also significantly reduced among adults taking 800 IU daily compared to 400 IU.[6]

VITAMIN D AND MUSCLE FUNCTION

Muscle function requires normal levels of vitamin D, and it is well established char vitamin D deficiency causes muscle weakness.[38]

Well-designed studies have unequivocally shown the beneficial role of vitamin D supplements (800 TU plus calcium) in preventing falls among elderly patients who achieve vitamin D levels of 40 ng/ml.[39] Another randomized trial performed in nursing home residents over a period of five months showed similar results.[40]

VITAMIN D AND THE IMMUNE SYSTEM

Multiple sclerosis,[30] rheumatoid arthritis,31 and osreoarchritis[32] are known to be more prevalent in people living in higher latitudes, and all have been shown to be prevented by maintaining higher-than-normal vitamin D levels via oral supplementation.

Vitamin D-triggered antimicrobial response is another example of the immune-mediated effects of this compound.33

Other conditions associated with vitamin D deficiency include schizophrenia and depression.34•3' In addition, individuals with low levels of vitamin D have reported a poorly described pain syndrome that is not relieved by the conventional use of analge.sics but improved with vitamin D supplementation.36 Based on the capability of $1,25(OH)_2O_3$ to regulate cellular proliferation, its use has also been advocated in the treatment of psoriasis.[37]

CONCLUSIONS

The studies presented suggest that vitamin D deficiency is a common occurrence, particularly in the elderly. Since this has multiple systemic consequences

for the cardiovascular system and other organs/systems, levels of vitamin D_3 (25-(0H)D and not 1,25(0H),D) should be measured during the an;ual metabolic profile evaluation.

The Institute ofMedicine recommendations for vitamin D supplementation reported in 1997 have been revised. Vitamin D levels can be subdivided as follows: Levels less than 15 ng/ml are considered insufficiency, and levels between 15-30 ng/ml should be considered as deficiency. For those individuals with vitamin D insufficiency (less than 15 ng/ml), intake of ergocalciferol 50,000 JU orally weekly for four weeks, and then 50,000 IU orally monthly has been suggested.[41] A meta-analysis reviewing randomized controlled trials with vitamin D supplementation showed a decrease in all-cause mortality in adults and older individuals.[42] However, patients with hypercalcemia or calcium-containing srones should avoid exposure to vitamin D supplementation.

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