Salahaddin university-Erbil

College of education

Chemistry department

Stage 4th

Vitamin D Function in Cardiovascular disease

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Supervisor recommendation:

I am the student's supervisor, Ibrahim Khaled Omer, I support that the student has completed all the requirements for submitting the research drawn entitled The Effect of Solvent on the Rate of some bromination Reactions according to the numbered administrative order 3/1/5/1972 on *th mar. 2024 in accordance with the instructions of Salahaddin university quality assurance and it is ready for discussion.

Supervisor: Dr. Lutfya

Signature:

Date:

Research project lecturer

Dr. Dler D. Kurda

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Abstract:

Cardiovascular disease (CVD) is a major cause of morbidity and mortality worldwide. Recently vitamin D de- ficiency has been identified as a potential risk factor for many diseases not traditionally associated with vitamin D, and CVD. This review discusses the evidence suggesting an association between low 25-hydroxyvitamin D levels and CVD and the possible mechanisms mediating it.Vitamin D deficiency has been associated with CVD risk factors such as hypertension and diabetes mellitus, with markers of subclinical atherosclerosis such as intima-media thickness and coronary calcification as well as with cardiovascular events such as myocardial infarction and stroke as well as congestive heart failure.

Introduction:

Definition of Vitamins:

Vitamins are organic micronutrients mainly synthesised by plants and microorganisms, which do not provide energy. Animals are not able to synthesise them, consequently, these essential micronutrients must be supplied by the diet in small amounts or even trace amounts (micrograms or milligrammes per day) for the maintenance of the metabolic functions for protection, for maintenance of health and proper growth of most animal cells. (Zittermann, Schleithoff et al. 2005)

Classification of Vitamins:

Vitamins are classified according to their solubility, into two groups:

1. Fat Soluble Vitamins: these are oily and hydrophobic compounds, they are stored in the liver and not excreted out of the body. Bile salts and fats are needed for their absorption. Vitamins A, D, E and K are fat soluble. (Owens, Fraser et al. 2015)

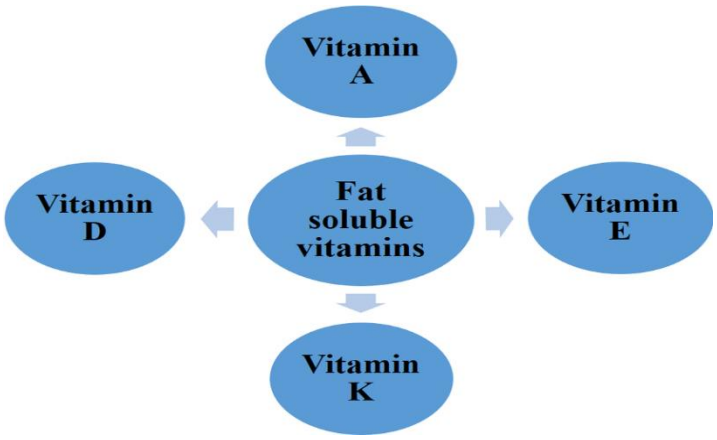


Fig1: Fat soluble vitamin.

2. Water Soluble Vitamins: Vitamin B complex and Vitamin C are water soluble. They are not stored in the body, therefore are required daily in small amounts. (Owens, Fraser et al. 2015)

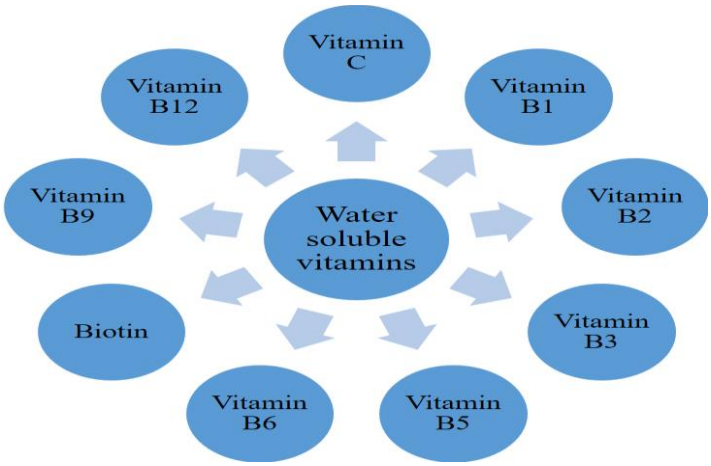


Fig 2: Water soluble vitamins.

Chemistry of Vitamin D:

Vitamin D is represented by cholecalciferol (vitamin D3) and ergocalciferol (vitamin D2), which are structurally similar secosteroids derived from the UV irradiation of provitamin D sterols. (Secosteroids are steroids in which one of the rings has broken.) In vertebrates, vitamin D3 is produced in vivo by the action of sunlight on 7-dehydrocholesterol in the skin. Vitamin D2 is produced in plants, fungi and yeasts by the solar irradiation of ergosterol. Vitamin D3 and vitamin D2 differ structurally only in the C-17 side chain, which in vitamin D2 has a double bond and an additional methyl group. (Georghiou 1977, Palomer), (González-Clemente et al. 2008)

Biological Functions of Vitamin D:

Vitamin D increases the gut uptake of ingested calcium and phosphorus and improves calcium reabsorption by the kidney, thus resulting in the elevation of both mineral elements in plasma. As a consequence, the major biological actions of this vitamin include maintenance of mineral homeostasis and regulation of bone remodelling. Also, many other vitamin D targets have been reported, such as heart, stomach, liver, brain, skin, pancreatic islets (b cells), thyroid, parathyroid and adrenal glands and immune cells (figure). Remarkably, some of these tissues and cell types, including brain, activated lymphocytes (T and B cells), macrophages and skin, comain not only theand phosphorus and improves calcium reabsorption by the kidney, thus resulting in the elevation of both mineral elements in plasma. As a consequence, the major biological actions of this vitamin include maintenance of mineral homeostasis and regulation of bone remodellin. Also, many other vitamin D targets have been reported, such as heart, stomach, liver, brain, skin, pancreatic islets (b cells), thyroid, parathyroid and adrenal glands and immune cells (figure). Remarkably, some of these tissues and cell types, including brain, activated lymphocytes (T and B cells), macrophages and skin, contain not only the nuclear VDR but also the enzymes required for its synthesis. (Holick 2010)

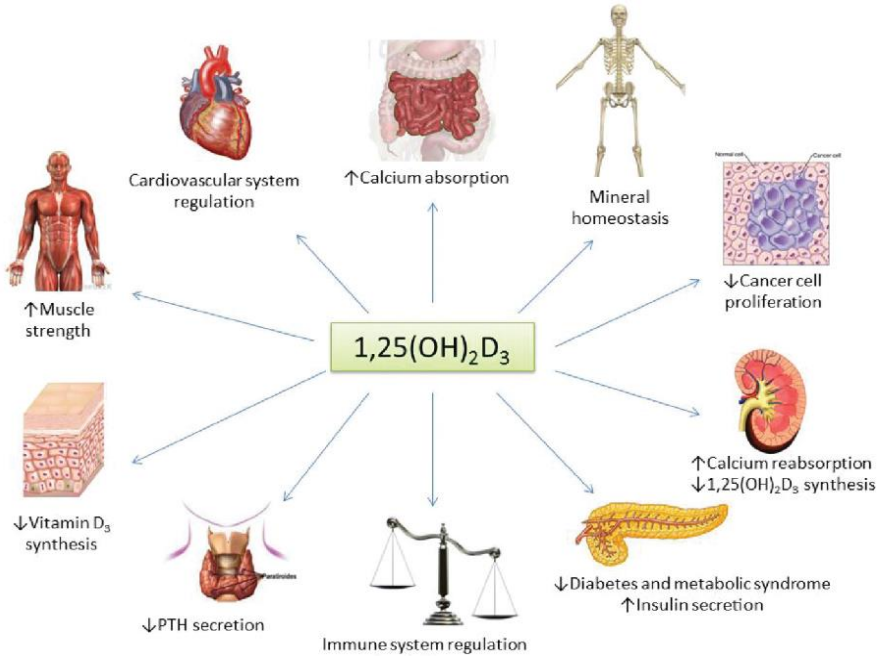
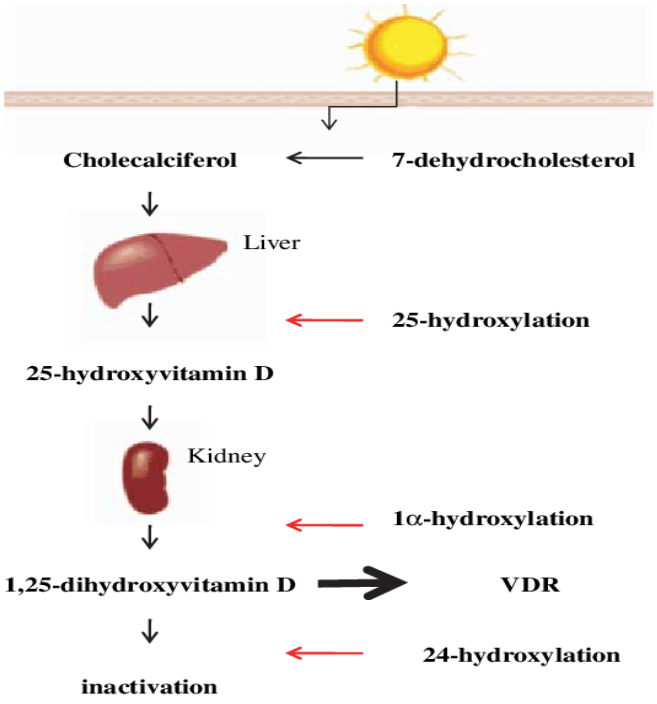


Fig3: Principal target and action of vitamin D.

Metabolism of Vitamin D:

Vitamin D can be obtained from food sources of vegetable origin (vitamin D2, also known as ergocalciferol) or animal (vitamin D3, also known as cholecalciferol). The best food sources are fatty fish and their oils. However, small amounts can also be found in butter and egg yolk. Cow's milk and human milk are relatively poor in vitamin D. Skim milk, in particular, often does not contain vitamin D Therefore, the main source of circulating VD is endogenous synthesis in the skin, where ultraviolet B (UVB) wavelength of sunlight initiates conversion of 7-dehydrocholesterol to inactive VD (cholecalciferol). Only small amounts of cholecalciferol are present in some dietary products, so in the absence of adequate sunlight, the supply of VD largely depends on fortification of dietary products or individual use of oral VD supplements. Cholecalciferol undergoes two hydroxylation steps to form the active VD compound 1,25(OH). The first hydroxylation process takes place in the liver and forms 25 1 droxyvitamin D3found in butter and egg yolk. Cow's milk and human milk are relatively poor in vitamin D. Skim inilk, a particular, often does not contain vitamin D [10].Therefore, the main source of circulating VD is endogenous synthesis in the skin, where ultraviolet B (UVB) wavelength of sunlight initiates conversion of 7-dehydrocholesterol to inactive VD (cholecalciferol). Only small amounts of cholecalciferol are present in some dietary products, so in the absence of adequate sunlight, the

supply of VD largely depends on fortification of dietary products or individual use of oral VD supplements. Cholecalciferol undergoes two hydroxylation steps to form the active VD compound 1,25(OH). The first hydroxylation process takes place in the liver and forms 25-hydroxyvitamin D3 (25(OH)D_3), while the second hydroxylation step, which produces the final active metabolite, occurs predominantly in the kidney. These reactions are brought about by 25-hydroxylase in the liver and la- hydroxylase in the kidney. The activated form of VD 1,25(OH)$_2$$D_3$ mediates its effect through the VD receptor (VDR) until inactivated by 24-hydroxylation. The table below indicates the factors involved in VD metabolism. (Fraser 1980),(Jones 2012)



Gene name	Vitamin D metabolism	Protein function	Chromosomal location human	Chromosomal location mice	KO model
CYP2R1	Activation	25-hydroxylase	11p15.2	11	–
CYP27A1	Activation	25-hydroxylase	2q33-qter	1	–
CYP27B1	Activation	1α-hydroxylase	12q13.1-q13.3	10	+
VDR	Mediator	Receptor	12q13.11	15	+
CYP24A1	Inactivation	24-hydroxylase	20q13	2	+

Sources of Vitamin D:

1-A major source of vitamin D for most humans comes from exposure of the skin to sunlight

2-eggs

3-milk

4-mushroom

5-tuna and salmon and caviar

6-cod liver oil

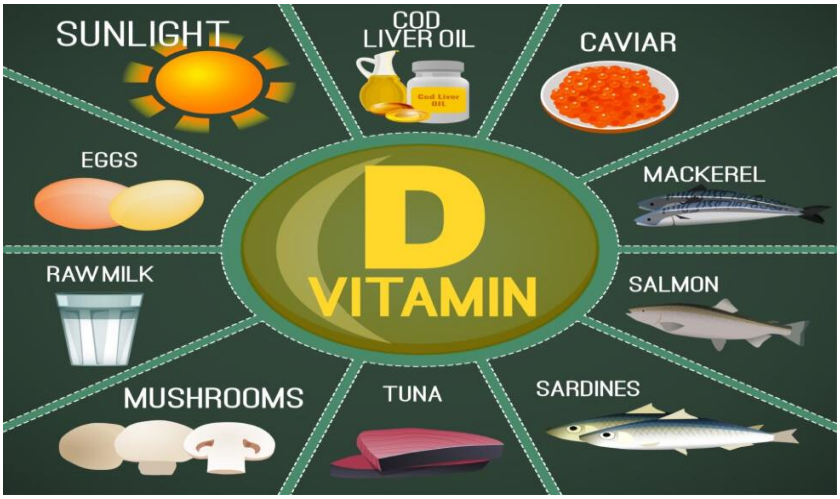


Fig5: sources of vitamin D {Benedik, 2021}

Stages of vitamin D status:

The different stages of vitamin D status can be classified as deficiency, insufficiency, hypovitaminosis, adequacy, and toxicity.Vitamin D deficiency is characterized by a lack of the active vitamin D metabolite calcitriol in its target cells. Physiologic circulating 25(OH)D levels are necessary to satisfy the tissue's requirement to produce an adequate amount of calcitriol. In the case of vitamin D deficiency, severe clinical symptoms such as rickets, osteomacia , myopathy, severe secondary hyperparathyroidism (SHPT) (serum PTH>65 pg/ml), and calcium malabsorption are seen. Moreover, renal synthesis of calcitriol becomes substrate dependent, i.e.

dependent on the circulating 25(OH)D concentration. Based on results obtained in the 8th decade of the 20th century in elderly subjects, it has been hypothesized that a substrate-dependent reduction in serum calcitriol levels may occur if the circulating serum 25(OH)D level falls below 30–40 nmol/l .Recently performed studies support this concept also for other age groups. Children and young adults with mean 25(OH)D levels of 30 and 32 nmol/l in winter showed a significant increase in serum calcitriol in summer in parallel with a rise in serum 25(OH)D. Moreover, vitamin D supplementation resulted in a 25(OH)D rise of 39 nmol/l and a calcitriol increase of 36 p mol/l in women with initial serum 25(OH)D of 26 nmol/l. On the other hand, serum calcitriol remained constant in subjects with initial serum 25(OH)D of approximately 50 nmol/l, despite a marked rise in serum 25(OH)D following vitamin D supplementation). (Lips 2004)

Stages of vitamin D status	**25(OH)D concentrations (nmol/l)**	**Biochemical/clinical symptoms**
Deficiency	0–25	Severe hyperparathyroidism, calcium malabsorption, rickets, osteomalacia, myopathy
Insufficiency	>25–50.0	Elevated PTH levels, low intestinal calcium absorption rates, reduced bone mineral density, subclinical myopathy
Hypovitaminosis D	>50–70 to100	Low body stores of vitamin D, slightly elevated PTH levels
Adequacy	70–100 to 250	No disturbances of vitamin D-dependent functions
Toxicity	>250	Intestinal calcium hyperabsorption, hypercalcemia

Table 1. Suggested terminology to describe vitamin D status according to circulating 25(OH)D concentrations. (Lips 2004)

To convert values for 25-hydroxyvitamin D to ng/ml, divide by 2.50.

Vitamin D effects on heart and blood vessels:

Evidence is accumulating that vitamin D may also exert various direct effects on the cardiovascular system. Heart and blood vessels are target tissues for vitamin D and express both VDR and 1x-hydroxylase. 2,44-47 In the following, we summarize expire- mental and observational clinical studies on the role of vitamin D for the heart and blood vessels. Vitamin D receptor-knockout and 12-hydroxylase-knockout mice develop heart failure despite normalized calcium lev- ells. 2,45,48,49 Increased activation of the RAAS seems to be the Medi- acting pathway because RAAS blockade with, for example, the angiotensin-converting enzyme (ACE)-inhibitor captopril reverses cardiac abnormalities in these mouse models. 2,48,49 Preliminary data published in abstract form suggest that even cardiomyocyte- specific VDR-knockout mice develop myocardial damage.50 The crucial role of vitamin D for myocardial health is further supported by increased VDR expression in myocardial hypertrophy. 45,46 VDR expression increased in cardiac myocytes and fibroblasts after treat- ment with the pro-hypertrophic vasoactive peptide endothelin. 46 Experimental studies documented antihypertrophic and antipole- erative actions of vitamin D metabolites, which downregulate sev- eral genes involved in the development of myocardial hypertrophy. 45,51 VDR activation modulates cardiac calcium flux and thereby induces an accelerated relaxation of cardiomyocytes, which may improve diastolic function of the heart45,52 Vitamin D- mediated regulation of cardiac extracellular matrix turnover may also be important to maintain cardiac health.45.53 In this context, a study of 171 healthy British Bangladeshi adults showed that matrix metalloproteinase-9 is elevated in vitamin D deficient individuals but is significantly decreased after vitamin D supplementation. 53 Several clinical studies confirmed that heart failure patients have a poor vitamin D status, but whether vitamin D deficiency is only the consequence of heart failure or possibly contribute to myocardial diseases is unclear.45 Interventional trials produced inconsistent----results on the effect of vitamin D on parameters of myocardial, structure and function warranting further large-scale RCTs. Vitamin D may also protect against atherosclerosis, vascular cal- cification and endothelial dysfunction. Antiatherosclerotic vita- min D effects may include (i) inhibition of macrophage cholesterol uptake and foam cell formation, (ii) downregulation of vascular smooth

muscle cell proliferation and migration, and (iii) suppres sion of inflammation triggered endothelial activation and expres sion of endothelial adhesion molecules, 4.54-56 Vitamin D effects may also protect against endothelial dysfunction, for example, by antioxidative actions and by inhibiting lipid peroxidation. 4.37 Finally, vitamin D may reduce vascular calcification, for example, by inhibiting bone morphogenic proteins, but data on this topic are somewhat controversial. 458 This could be attributed to the fact that both a poor vitamin D status as well as vitamin D intoxication may contribute to vascular calcification, although it should be noted that the largest study on vitamin D plus calcium supplemen- tation found no effect on coronary artery calcification. 54.59, Observational and interventional studies showed inconsistent results regarding the association of vitamin D with vessel diseases [e.g. inconclusive data on 25(OH)D and carotid intima-media thickness], 4001 Several, but not all, interventional studies showed that vitamin D supplementation improves endothelial func- tion. Hence, we need further RCTs before we can draw final conclusions on the effect of vitamin D on the vasculature.

VITAMIN D AND CARDIOVASCULAR DISEASE

RISK FACTORS:

Vitamin D and Diabetes:

Recent evidence from animal and human studies suggest that vitamin D may be involved in the pathogenesis of diabe- tes mellitus .How could this association be mediated? There are many possible pathways, thoroughly discussed in a recent review .In brief, 1 option would be through the binding of circulating 1,25(OH)2D to the ß-cell VDR, or through conversion and activation of 25(OH)D by la- hydroxylase, which has been shown to be expressed in β- cells. Furthermore, vitamin D can act by promoting insulin secretion, a calcium-dependent process, indirectly through the regulation of extracellular calcium levels and calcium flux through the B-cell. Alternatively, vitamin D might in- crease peripheral insulin action by stimulating the expression of insulin receptors. Moreover, vitamin D has well docu- mented immunomodulatory effects [29, 30]. which could act protectively against autoimmune (type 1) and inflammation- associated (type 2) diabetes Available data on a potential inverse association between type 1 diabetes risk and vitamin D intake in early life are not consistent .A recent meta-analysis showed an inverse

associa- tion between 25(OH)D levels and prevalent type 2 diabetes (OR 0.36; 95% CI 0.16 to 0.80). Pittas et al. also showed a significant inverse association between vitamin D intake and risk of type 2 diabetes in the Nurses' Health Study cohort (N = 83,806) after adjusting for age, body mass index (BMI) and non-dietary covariates .However, results regarding the effects of vitamin D supplementation on glucose toler- ance have been inconsistent . (Schleithoff, Zittermann et al. 2006)

Vitamin D and Hypertension:

There is substantial evidence supporting a relation be- tween vitamin D and blood pressure. For example, in the INTERSALT study, which examined > 10,000 subjects from around the world, systolic and diastolic blood pressure val- ues were significantly and positively associated with distance from the equator and it is known that vitamin D synthesis also declines with increasing distance from the equator . Furthermore, there are geographic differences in blood pressure among individuals of African origin, with those residing closer to the equator having lower blood pressure than those residing in northern regions Cross-sectional studies also showed an inverse association of vitamin D con- centrations and blood pressure. Moreover, a number of studies have shown seasonal blood pressure variations within the same population, with values peaking in winter and fall. (Pittas, Harris et al. 2007)

Vitamin D and Inflammation:

C-reactive protein (CRP) is associated with atherosclero- sis either as a marker of inflammation or even playing a causal role .There seems to be no association between 25(OH)D levels and CRP.One study however, in patients with type 2 diabetes found that patients with low 25(OH)D levels (<15 ng/ml) had higher high sensitivity CRP (hsCRP) levels compared with their vitamin D- sufficient counterparts.Although vitamin D supplemen- tation has been shown to decrease CRP levels in 2 small clinical trials the majority of existing data suggests the lack of such an association .However, vitamin D supplementation has been shown to down-regulate nuclear factor-KB activity and to increase the anti-inflammatory cy- tokine interleukin (IL)-10 levels and decrease the pro- inflammatory cytokines IL-6, IL-12, interferon-y and TNF-α Moreover, an inverse association has been shown between vitamin D levels and urinary isoprostane concentra- tion, a marker of oxidative stress . (Kuneš, Tremblay et al. 1991)

VITAMIN D RECEPTOR POLYMORPHISMS AND ATHEROSCLEROSIS:

Recent studies have indicated many polymorphisms of the VDR exist, with 3 adjacent restriction fragment length polymorphisms for BsmI, Apal and TaqI, at the 3' end of the VDR gene being the most frequently studied .The data regarding an association between VDR polymorphisms and atherosclerosis are contradictory. For example the BB geno- type of the BsmI polymorphism was associated with in- creased carotid intima-media thickness (IMT) in Mexican American women but was not associated with preva- lence and severity of CHD in a large cohort (n = 3441) of German subjects phenotyped by angiography. Further- more, 1 study found an association between the B allele of the BsmI polymorphism and aortic valve calcification. Additional studies are needed before firm conclusions can be drawn regarding the role of VDR polymorphisms and car- diovascular disease. (Uitterlinden, Fang et al. 2004)

VITAMIN D AND PRECLINICAL CARDIOVAS- CULAR DISEASE

Coronary calcification and carotid IMT are two estab- lished and reliable markers of subclinical atherosclerosis. There is strong evidence suggesting an association be- tween low vitamin D concentrations with subclinical athero- sclerosis. A study of 390 patients with type 2 diabetes and 390 non-diabetic controls showed that subjects with low 25(OH)D levels (< 15 ng/ml, 37.5 nmol/l) had significantly increased IMT when compared with their vitamin D- sufficient counterparts. Interestingly, patients with type 2 diabetes also had significantly more often than the non-diabetic controls low 25(OH)D levels (< 15 ng/ml, 37.5 nmol/l). Regarding coronary artery calcification, Wat- son et al. in a study of 173 subjects at high or moderate risk for CHD found that 1,25(OH)2D levels were inversely correlated with coronary artery calcification as evaluated by electron beam computed tomography. The authors suggested that vitamin D deficiency may be the factor explaining the proposed association between osteoporosis and vascular calcification. Similar results were reported in a study of 283 high-risk subjects, where an inverse association between 1,25(OH)2D levels and coronary calcium was also identified. (Bouillon, Carmeliet et al. 2008)

VITAMIN D AND CLINICAL CARDIOVASCULAR:
DISEASE:

There are several lines of evidence suggesting an associa- tion between vitamin D and the pathogenesis of CVD. Vita- min D receptors have a broad tissue distribution that includes cardiomyocytes, VSMC and endothelial cells and in vitro studies have shown that active vitamin D inhibits car- diac myocyte hypertrophy .Furthermore, vitamin D has been shown to inhibit the renin-angiotensin system and to have anticoagulant properties .Moreover, it has been shown that vitamin D supplementation improves the cytokine profile (CRP, TNF-a concentrations) of patients with congestive heart failure . Experimental studies have suggested that low 25(OH)D influences the activity/ expres- sion of macrophages and lymphocytes in atheroscleroticplaques, thus promoting chronic inflammation in the artery wall .Interestingly, van de Berghe et al. have shown that vitamin D supplementa- tion significantly reduces serum levels of CRP, IL-6 and tissue matrix metalloproteinases. Finally, a model of vitamin D deficiency, the vitamin D-24-hydroxylase transgenic rat, develops aortic atherosclerosis . Vitamin D-24- hydroxylase (CYP24) catalyzes the conversion of 25(OH)D to 24,25(OH)2D in the kidney and is involved in the break-down of 1,25(OH)2D, the active form of vitamin D.Low serum 25(OH)D levels have recently been found to be associated with a higher prevalence of peripheral arterial disease (PAD) .The authors analyzed data from 4389 participants of the NHANES 2001-2004. After multivariate adjustments for demographics, comorbidities, physical activ- ity levels and laboratory measures, the prevalence ratio of PAD for the lowest compared to the highest 25(OH)D quar- tile (< 17.8 and ≥ 29.2 ng/ml, respectively) was 1.80, and for each 10 ng/ml lower 25(OH)D level, the multivariate- adjusted prevalence ratio of PAD was 1.35. Two previous smaller cross-sectional studies showed similar results. (Xiang, Kong et al. 2005)

Discussion:

In summary, while much evidence supports a potential antiatherosclerotic effect of vitamin D and several mecha- nisms to this effect have been suggested, prospective, pla- cebo-controlled

randomized as well as mechanistic studies are needed to confirm this association. The same holds true for its role in congestive heart failure. Since vitamin D defi- ciency is both, easy to screen and treat, the confirmation of such an association could have important implications for both, patient care and health policy. Already at the present time food regulatory agencies should consider if fortification of nutrients should be adopted. The scientific community and drug regulators should reiterate the question whether current upper safety limits need to be corrected. This would enable higher vitamin D daily doses through self-medication.

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