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VITAMIN D AND CARDIOVASCULAR DISEASES

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Abstract: A lot of attention is paid to vitamin D in the last few years due to its broader spectrum of influence in human organs. Nuclear vitamin D receptors (VDR) are proved to be a main mechanism of action. More and more evidence of the negative influence of vitamin D deficiency on cardiovascular system appears together with low vitamin D serum levels in the current population, mostly due to life style with little exposure of unprotected skin to sun light. The course of ischemic heart disease can be worsened by low serum level of vitamin D because of higher risk of myocardial infarction a cardiac failure with more frequent hospitalisations. Higher risk of arrythmias during vitamin D deficiency is explained by higher production of parathormone and its binding to receptors stimulating phospholipase C followed by increased activity of catecholamines, angiotensin II and endothelin in ischaemic myocardium. There is no evidence of any association of vitamin D and cholesterol levels, on the other hand normal level of vitamin D helps to keep the triglyceride serum concentration in normal range. Hypertension is influenced negatively by low level of vitamin D due to stimulation of renin-angiotensin-aldosteron system, parathormon secretion and lower antiiflammatory and vasculoprotective effect. The course of cardiovascular diseases can be positively modulated by keeping vitamin D level within normal range. The adequate exposure of unprotected skin to sun is recommended as natural suplement and effective source of vitamin D.

Key words: Vitamin D, vitamin D receptor, hypertension, ischemic heart disease, cardiac failure.

Introduction

In recent years increasing information has been published regarding the pleiotropic effects of vitamin D that has long been regarded as a factor playing a role in calcium level regulation in the skeletal system only. The breakthrough was the finding of vitamin D receptors (VDRs) in most human cells and organs. VDR is a nuclear receptor that is activated after binding with dihydroxycholecalciferol, the active form of vitamin D. Insufficient receptor activity caused by low vitamin D level may result in many metabolic, immunologic, cardiovascular and other disorders (1-3)

The life style of present population is characterized by spending most of the time indoors. This creates conditions favoring long-term vitamin D deficiency already starting from basic school attending years. The main source of vitamin D for the human body is solar radiation that causes the formation of cholecalciferol in the skin that is later metabolized in the liver and kidney to the active 1,25-dihydroxycholecalciferol. This accounts for 80% of the active vitamin supply, while nutrition provides only the remaining 20%, and according to some sources this ratio is even 90% to 10% (4). This is the reason for the inconsistency of the results of studies based on the evaluation of vitamin D intake from nutrition (5). It is from this findings that the lack of solar radiation is the most likely cause that the average level of vitamin D is between 40 and 50 nmol/l in Czech population. In Czech Republic normal range of vitamin D is considered as 50-200 nmol/l. This means it is gradually becoming clear that almost half of the Czech population does not reach 37,5 nmol/l as a level necessary for good-quality bone remodeling, and not even two thirds reach 75nmol/l, the considered level for normal functioning of a number of other systems (6).

Geographical regions north of 42 degree latitude provide radiation intensity that is insufficient for vitamin D synthesis over the period from November to February, while the interval of insufficient exposure is up to 6 months a year in the regions further north. Overcast sky reduces the radiation intensity by 50%. The use of sun blockers with UV protection factors above 8 results in an effective blockade of UVB component of solar radiation. In the temperate zone, sufficient vitamin D supply should be ensured with an exposure of 10% of unprotected body

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surface for 20 minutes between 10 a.m. and 3 p.m., twice a week (7, 8).

The aim of this review is to remind the role of vitamin D in the functioning cardiovascular system and also to offer the chance to modulate the treatment of cardiovascular diseases.

Mechanisms of Cardiovascular system damage associated with vitamin D deficiency.

One possible line of action of vitamin D is interference of the activated vitamin D receptor with the renin-angiotensin-aldosterone system (RAAS), by directly suppressing renin gene expression with the subsequent consequence of reduced blood pressure (9-11). Vitamin D deficiency resulted in RAAS activation with vasoconstriction, sodium and water retention, and increased arterial wall rigidity (12).

Vascular smooth muscle cells and endothelial cells express receptors for vitamin D and the ability to convert circulating 25-OH D to 1,25-OH D. (13, 14).

Another mechanisms of action of vitamin D considered is its influence on calcium metabolism. Decreasing vitamin D level results in reduced serum calcium level and secondary hyperparathyroidism. Parathormone promotes myocyte hypertrophy and vascular remodeling (15). Long-lasting reduced vitamin D level was associated with higher occurrence of strokes (16).

Vitamin D is vital for the synthesis of contractile proteins in the myocardiocyte by activating of basic intracellular mechanisms of calcium metabolism and energy production as factors participating in the creation of appropriate myocardial ventricle geometry and efficient myocardial activity (17). Vitamin D is also important for the regulation of expression of genes coding cytokine and hormone synthesis that participate in the pathogenesis of cardiac failure – natriuretic peptide, the already mentioned renin, as well as other factors (18).

Regarding the possible mechanisms of cardiovascular damage due to long-term low vitamin D levels, the analogy with mice is considered. Comparing model where the animals deprived of vitamin D receptors developed cardiovascular damage more rapidly as a result of accelerated atherosclerosis, increased inflammatory reaction and increased parathormone level. Vitamin D supplementation was associated with anti-sclerotic, anti-inflammatory, direct cardioprotective and parathormone suppressive effects. (1)

Similar results were obtained in cross-sectional studies in patients with cardiovascular diseases where a correlation analysis demonstrated a significant inverse relationship between vitamin D level and inflammatory activity, oxidative stress, or the presence of vascular and intercellular adhesive molecules (19).

Another structure that might be influenced by reduced vitamin D levels is the cardiac valvular apparatus. Vitamin D deficiency results in reduced calcium levels and increases phosphate levels. A study that included almost 2,000 subjects free of cardiac damage investigated with echocardiography demonstrated that every rise of serum phosphate level above 50mmol/l of was associated with increased risk of aortic valve atherosclerosis and concerned only the levels of phosphorus, while neither calcium and vitamin D levels nor parathormone levels showed the above mentioned relationship (20).

Long-term follow-up of a sample of 10,000 subjects aiming at revealing the relationships of vitamin D-related cardiovascular damage, found that low vitamin D level was associated with not only significantly higher occurrence rates of hypertension, coronary damage, cardiomyopathy, but also diabetes mellitus. (21) Vitamin D deficiency was also a significant predictor of the overall mortality. Vitamin D supplementation resulted in significantly improved survival, especially in patients with demonstrated deficit (22)

In the population of 2,312 elderly patients a group of 384 patients was found with significantly reduced vitamin D level and significantly increased parathormone activity. An analysis of the occurrence of cardiovascular complications demonstrated that every 25-mmol/l reduction of vitamin D level was associated with a 9% increase in mortality and a 25% increase in the risk of myocardial infarction. Parathormone values higher than 65ng/l were associated with a 30% increase risk of cardiac failure (23).

Vitamin D and coronary artery disease

Numerous studies have demonstrated a significant relationship between low vitamin D levels and the magnitude of the seriousness of both acute and chronic forms of coronary artery disease. For example, vitamin D level follow-up in patients who were indicated for coronary artery interventional procedures have shown that patients with low vitamin D level had significantly increased risk of cardiac failure and future sudden cardiac death compared to patients with vitamin D levels in the normal range (24).

Another study compared the occurrence rate and course of coronary artery disease after the patients underwent coronary intervention. Patients with demonstrated coronary artery disease had vitamin D levels that were overall significantly lower than in the control group, and detailed analysis according to actual vitamin D levels showed a 2.5 times higher coronary artery risk in patients in the lowest quartile as compared with those in the highest quartile. The study has also demonstrated a significant inverse relationship between the levels of vitamin D on the one hand and triglyceride levels, BMI and body weight on the other, and vegetarians were found to have significantly lower

vitamin D levels (25). The conclusions of this study provide an independent confirmation of the results of a multicentric vitamin D level follow-up in patients who had already sustained myocardial infarction, where 96% of these patients were found to have vitamin D level that were lower than the normal range (26)

In the case of an already developed cardiac failure a vicious circle sets in where reduced patient mobility results in lower skin exposure to solar radiation and thus in further reductions of vitamin D levels (27). The greatest positive gain of vitamin D supplementation may be expected in the group of patients with serum levels below 50-70 mmol/l (28). This patient group has also the highest mortality rates and risk of repeated hospital stay for recurrent cardiac decompensation (29)

The relationship with low serum vitamin D levels and the pathogenesis of both acute and chronic forms has been described to depend on mechanisms influencing the synthesis of the natriuretic peptide, contractility, the renin-angiotensin-aldosterone system, on endothelial function, on the activity of inflammatory response, and increased blood pressure is reported by many authors. Most of these authors also point out the lack of prospective interventional studies that would demonstrate the effect of vitamin D supplementation on improved prognosis, and call for such studies to be carried out (16, 18, 19, 24, 27, 30, 31).

The predictive value of vitamin D levels for risk of CHD was assessed by Framingham risk score in 178 overweight postmenopausal women and no relationship was found (32).

However, based on the evidence supporting the effect of vitamin D, some authors now do recommend that the therapy of all forms of coronary artery disease, consider the serum level of vitamin D, and when this is found to be low, the treatment schedule be extended to include an adequate vitamin D supply (18, 33). The American Heart Association emphasizes that all women at cardiovascular risk should maintain a healthy lifestyle and avoid smoking, their blood pressure, hyperlipidemia and diabetes should be aggressively treated and preventive drug therapies including daily aspirin, HRT, vitamin D and omega-3 fatty acid supplements should be administered (34)

Vitamin D and dyslipidemia

Direct influence of vitamin D on the level of cholesterol has not been reliably demonstrated, not even an indirect one, through the anticipated mutual interaction with statins. In patients with renal failure, however, a positive influence of vitamin D on the reduction of triglyceride level has been found (35).

Vitamin D and arrhythmia

Regarding the ever more obvious relationship between vitamin D and cardiovascular system function, attention has also been paid to the possibility of a possible relationship with the increasing occurrence of atrial fibrillation. As part of the Framingham study a group of almost 3,000 individuals with mean age of 65 years has been followed-up for nine years regarding the incidence of newly developed atrial fibrillation. A multivariate analysis failed to demonstrate any relationship between vitamin D level and the risk of atrial fibrillation (36). On the other hand, it is necessary to consider the mutual relationship of vitamin D and maintenance of stable serum calcium or magnesium levels that are known as important cardiac rhythm stabilizers (37). It has also been shown that higher serum parathormone levels provoked by low vitamin D levels are associated with negative impact. Receptor binding results in the stimulation of phospholipase C, with subsequent increase of the activities of catecholamine, angiotensin II and endothelin, with possible arrhythmogenic activity in the ischemic myocardium (38). The study NHANES has also confirmed, in a sample of

37000 subjects, and as a secondary finding, significant influence of low vitamin D level on increased pulse rate and systolic blood pressure, with subsequent increase of myocardial oxygen consumption, and ensuing deepening of ischemia in an already present coronary damage (39).

Vitamin D and hypertension

The relationship between vitamin D and blood pressure has also been explained through the mediation of the renin–angiotensin system, and through its effect on parathormone secretion, and the anti-inflammatory and vasculoprotective effects of vitamin D.

Low vitamin D levels were associated with blood pressure increase by 2-6 mmHg, and low levels have also been shown to be an independent risk factor for hypertension. Regarding the high occurrence rates of both hypertension and vitamin D deficiency in the elderly population, it is possible to consider the possibility of positive modulation of antihypertensive therapy with maintaining vitamin D levels in the normal range (40).

Another possible mechanism underlying the development of increased blood pressure in vitamin D deficiency is the increased aortic rigidity, demonstrated recently by Czech authors in subjects with reduced serum levels of 25-hydroxyvitamin D, independently of age and gender (41). Still another possible explanation s for the contribution of vitamin D to blood pressure control are the already demonstrated factors such as endothelial dysfunction, increased tendency to vascular and myocardial cell calcification and higher inflammatory

activity associated with low vitamin D levels (42).

To summarize the effect of vitamin D on cardiovascular outcomes the meta analysis of 51 studies was done to pool the relative risks (RR) and the weighted mean differences across trials. Trial data available to date are unable to demonstrate a statistically significant reduction in mortality and cardiovascular risk associated with vitamin D. The quality of the available evidence is low to moderate at best. (43)

Studies based on vitamin D dietary or supplement intake show inconsistent results as well, but this is not surprising if we consider rather higher proportion of activation of vitamin D by exposure than contribution of oral intake (44,45)

Main findings of studies mentioned in this article are summarized in Table 1.

Conclusion

The pleiotropic effects of vitamin D could be extended to include also the positive influence of physiological vitamin D levels on the cardiovascular system.

Maintaining the vitamin D level in the normal range can contribute to better outcome of patients with coronary artery disease, arterial hypertension, arrhythmias and also cardiac failure, but prospective intervention studies are necessary according to almost all authors´ opinion. The adequate exposure to solar radiation should be considered as more important for the maintenance of sufficient vitamin D levels than vitamin D intake in foods.

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Table 1
Main findings of trials studying vitamin D effects on cardiovascular system

Author	Design	Number of pts	Duration	Condition	Outcome	Findings
Dobnig (19)	prospective	3258	7,7 yrs	low vitamin D serum level	all cause mortality, CV mortality	HR 2,02 all cause HR 2,22 CV in lowest quartile
Pilz (1)	crosssectional	3299	7,7 yrs	vit D status	SCD, heart failure	HR 2,84 for SCD
Kestenbaum (23)	prospective	2312	14 yrs	low vitamin D serum level, high parathormone serum level	all cause mortality, CV mortality, MI, HF	low vit D 29% greater risk of mortality, high parathormone 30% greater risk of CF
Liu (29)	prospective	548	18 months	low vitamin D serum level	Combined endpoint – all cause mortality and HF	HR 1,1 per 10nmol/l decrease of vitamin D level
Vacek (22)	prospective	10899	5 yrs 8 months	vit D deficiency	all cause mortality	OR 2,64
Sun (44)	crossectional	118864	22 yrs	dietary or/and supplemental vitamin D > 600 IU/d	CVD risk	RR 0,72 in men p=0,009 RR 0,89 in women p=0,17
Mayer (41)	crossectional	560		vitamin D serum level	aortic stiffness	significant negative association
Elamin (44)	meta-analysis	51 trials		serum vitamin D level	death, MI, stroke	no association
author	design	No of pts	duration	condition	outcome	findings
Shanker (25)	crossectional	528		vitamin D serum level	VDR polymorphism CHD	VDR – NS CHD – 2,54 higher risk of lowest quartile vitamin D level
Lee (26)	crossectional	239	6 months	low vitamin D serum level at the admission because of MI		96% of admitted patients
Messenger (45)	prospective	3094	4,4 yrs	vitamin D serum level, vitamin D intake	CVA CVD CHD	no association
Liu (29)	prospective	548	18 months	vitamin D serum level < 75nmol/l	PRA CRP	independent predictors of low vitamin D level p=0,048, p=0,006
Truesdell (32)	crossectional	178		vitamin D serum level	FRS	no association p=0.981
Akin (46)	crossectional	239		vitamin D serum level	CHD severity – Gensini score	r= - 0,416 p < 0,001

PRA – plasmatic renin activity, CRP – C reactive protein, CVA – cerebrovascular attack, CVD – cardiovascular disease, CHD – coronary heart disease, VDR - vitamin D receptor, Framingham risk score, HF – heart failure, MI – myocardial infarction, HR – hazard ratio, RR – relative risk, CV – cardivascular, SCD – sudden cardiac death

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