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Vitamin D in the prevention and treatment of coronary heart disease

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Purpose of review

The pathogenesis of coronary heart disease is of multifactorial origin. Not all risk factors are probably satisfactorily understood. This article outlines beneficial vitamin D effects on cardiac function and the vasculature. In addition, human data associating serum vitamin D metabolite levels or oral vitamin D dosages or both with coronary heart disease outcome parameters are reviewed.

Recent findings

There is accumulating evidence that the vitamin D hormone calcitriol exerts important physiological effects in cardiomyocytes, vascular smooth muscle cells, and the vascular endothelium. Low levels of the calcitriol precursor 25-hydoxyvitamin D are associated with myocardial infarction, congestive heart failure, and calcific aortic stenosis. Deficient calcitriol concentrations probably contribute to the massive vascular calcification seen in chronic kidney disease. In patients with end-stage renal disease and end-stage heart failure, very low-circulating calcitriol levels or nonuse of active vitamin D or both are independently associated with high mortality rates.

Summary

Despite these exciting data, it is still too early to recommend exact dosages for the prevention or therapy of coronary heart disease. Prospective, randomized controlled trials with different amounts of vitamin D and probably with its active form calcitriol are needed to determine whether vitamin D can prevent coronary heart disease events and mortality.

Keywords

calcitriol, coronary heart disease, mortality, survival, vascular calcification, vitamin D

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Introduction

Coronary heart disease (CHD), also called coronary artery disease or ischemic heart disease, is the result of the accumulation of atheromatous plaques within the walls of the arteries that supply the myocardium with oxygen and nutrients. After decades of progression, some atheromatous plaques may rupture and may thus severely restrict the flow of oxygen carrying blood to the myocardium. As a consequence, a heart attack can occur. Myocardial infarctions are the most common cause of sudden death in western countries. In the United States and Germany, CHD is responsible for one in five deaths. The WHO estimated that in 2002, 12.6% of deaths worldwide were from CHD [1]. CHD is also one of the major causes of congestive heart failure, another prevalent disease in western countries that is characterized by failure of the heart to supply adequate blood flow and therefore oxygen delivery to peripheral tissues and organs or to do so only from elevated filling pressures. The prevalence of congestive heart failure is 2.0% in patients aged 40–59 years and rises to 12.0% in patients who are 80 years and older [2]. This review summarizes recent experimental and epidemiological evidence for a role of vitamin D in the prevention of CHD. In addition, available data concerning the effect of vitamin D on cardiovascular and total mortality are presented.

Vitamin D and the heart

The active form of vitamin D, 1,25 dihydroxyvitamin D or calcitriol, is the end product of two hydroxylation steps of vitamin D: a hepatic 25-hydroxylation and a subsequent renal 1α-hydroxylation. Calcitriol exerts genomic and nongenomic effects through a cytosolic vitamin D receptor (VDR) and a membrane bound receptor. VDRs have been found in almost all human tissues and cells, among them cardiomyocytes, endothelial cells, and vascular smooth muscle cells. Several tissues also possess an enzymatically active 25-hydroxyvitamin D-1α-hydroxylase system, among them vascular smooth muscle cells [3]. However, cardiomyocytes do not possess

such a 1-α-hydroxylase activity [4]. Therefore, the cardiac muscle strongly depends on the circulating blood concentration of calcitriol. It is noteworthy that renal calcitriol synthesis and thus circulating calcitriol concentrations become substrate dependent, that is, dependent on the circulating 25-hydroxyvitamin D [25(OH)D] concentration, in case of vitamin D deficiency/insufficiency. It is therefore an important finding that in postmenopausal women, calcitriol concentrations were reduced by approximately one-third in patients with deficient 25(OH)D levels (<25 nmol/l) compared with adequate levels (>80 nmol/l) [5•]. Moreover, in severely obese patients (BMI > 40 kg/m^2), 25(OH)D levels were 20 nmol/l lower compared with patients with a BMI less than 25 kg/m^2 [6•]. These two subgroups also differed significantly in serum calcitriol levels (by 20 pmol/l). Data are in line with the fact that both, some postmenopausal women and obese patients, have an enhanced risk for CHD.

Experimental vitamin D effects on cardiomyocytes

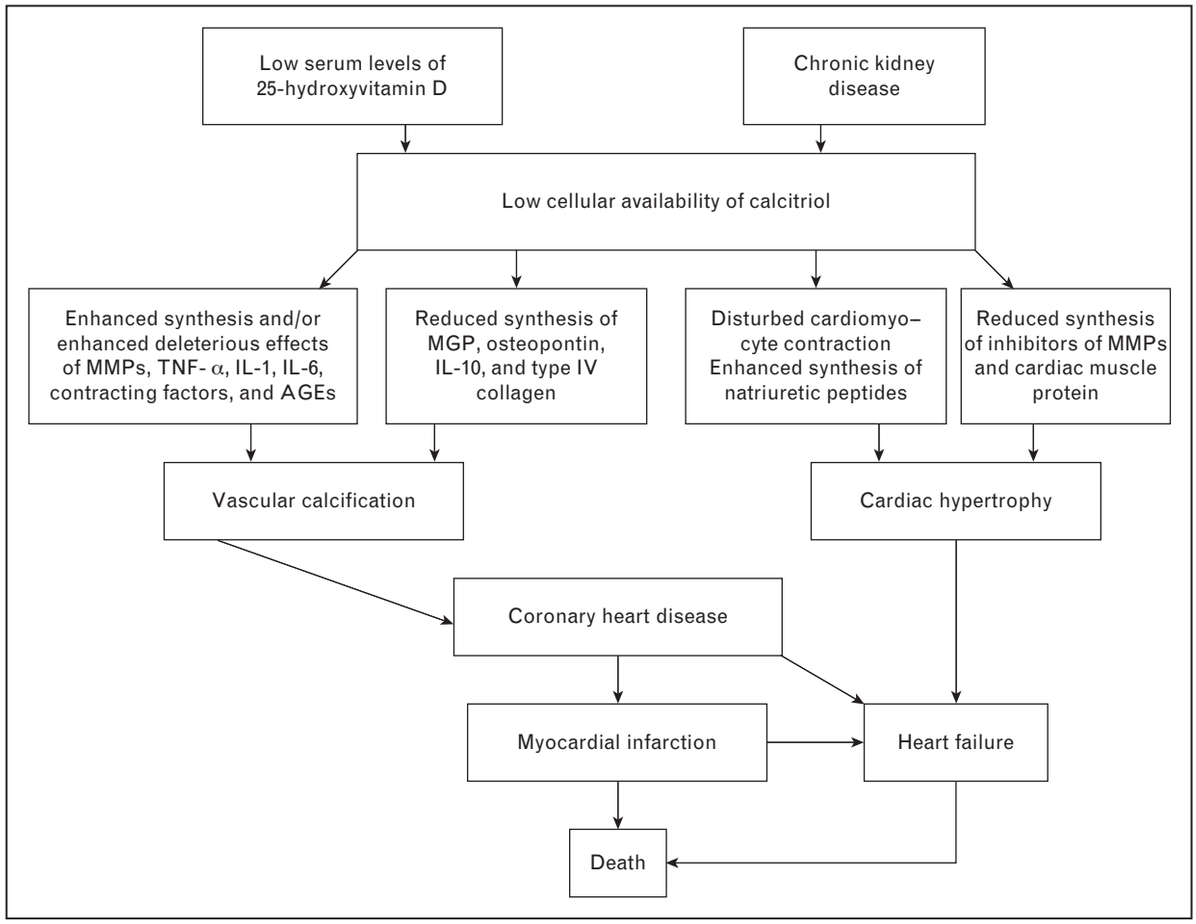
Calcitriol affects the growth, proliferation, and morphology of murine cardiomyocytes (Fig. 1). In detail, treatment with calcitriol increased the expression of the cardiac muscle protein myotrophin. Calcitriol treatment also decreased expression of atrial natriuretic peptide, a biochemical risk marker that is inversely related to cardiac function. In addition, calcitriol treatment increased expression and nuclear localization of the VDR in these cells [7]. Murine cardiomyocytes isolated from VDR knockout mice show accelerated rates of contraction and relaxation as compared with wild type mice, and calcitriol directly affected contractility in the wild type but not the knockout cardiomyocyte [8•]. Thus, calcitriol is an important hormone involved in modulating and maintaining heart cell structure and function. The aforementioned study group [9•] has also demonstrated that the heart of VDR knockout mice is hypertrophied because of cellular hypertrophy of heart myofibrils. Microarray analysis revealed tissue inhibitors of metalloproteinases were significantly underexpressed in VDR knockout mice compared with wild type mice [10]. Matrix metalloproteinases (MMPs) are connective tissue enzymes that are involved in remodeling of the vascular wall and myocardium. They function to destabilize atheromatous plaques to cause rupture and thrombosis within the lumen. Extracellular matrix remodeling mediated by MMPs contributes to progressive left ventricular remodeling, dilation, and heart failure. Experimental data suggest that calcitriol may prevent the development of cardiac hypertrophy. In spontaneously hypertensive heart failure rats, calcitriol treatment resulted in lower heart weight, myocardial collagen levels, left ventricular diameter, and cardiac output compared with untreated rats [11•].

Vitamin D and cardiac events

During the last decade, it became clear that deficient serum concentrations of vitamin D metabolites are prevalent not only in specific patients groups but also in the general population in western countries and throughout the world [12•]. The by far most important reason for this phenomenon is an inadequate skin exposure to solar ultraviolet B radiation, as ultraviolet B-induced skin synthesis is the major source of vitamin D for humans. Ecological studies have reported higher rates of CHD with increasing distance from the equator, a phenomenon that can be attributed to the higher prevalence of vitamin D deficiency in regions with less exposure to sunlight.

In a nonrandomized prospective study in 1739 Framingham Offspring Study participants, individuals with low 25(OH)D levels (<37.5 nmol/l) had a multivariable-adjusted hazard ratio of 1.62 for incident cardiovascular disease such as myocardial infarction, coronary insufficiency, and heart failure compared with those with 25(OH)D levels of at least 37.5 nmol/l [13•]. In the Women's Health Initiative study, however, myocardial infarction, ischemic attack, hospitalization rate for heart failure, and cardiovascular death could not be prevented by supplementation with 1000 mg calcium and 10 μg vitamin D daily compared with the placebo group [14]. But several limitations such as the low daily vitamin D dose and the lack of measurements of serum 25(OH)D levels or of calcitriol or of both of the vitamin D arm of this study makes data interpretation difficult [15•]. In a nested case–control study among male participants of the Health Professionals Follow-up Study [16•], men with low 25(OH)D levels (≤37.5 nmol/l) had a relative risk of 2.09 [95% confidence interval (CI) 1.24–3.54] of myocardial infarction compared with those considered to be sufficient (≤75 nmol/l), after adjustment for various lifestyle and other risk factors. Very recently, data on all-cause and cardiovascular mortality in association with vitamin D status have been published from a prospective cohort study of 3258 consecutive male and female patients scheduled for coronary angiography [17••]. During a median follow-up period of 7.7 years, 737 patients (22.6%) died, including 463 deaths from cardiovascular causes. Multivariate-adjusted hazard ratios for patients in the lower two 25(OH)D quartiles (median, 19.0 and 33.3 nmol/l) were higher for all-cause mortality (hazard ratio 2.08; 95% CI 1.60–2.70; and hazard ratio 1.53, 95% CI 1.17–2.01, respectively) and for cardiovascular mortality (hazard ratio 2.22; 95% CI 1.57–3.13; and hazard ratio 1.82, 95% CI 1.29–2.58, respectively) compared with patients in the highest 25(OH)D quartile (median, 71.0 nmol/l). Similar results were obtained for patients in the lowest calcitriol quartile. A trend toward lower mortality was already observed in a British vitamin D intervention trial [18]. The vitamin D group received one capsule containing 2500 μg vitamin D_3 every

Figure 1 Biochemical and clinical effects of low calcitriol availability on cardiac and vascular function



AGEs, advanced glycation end products; IL-1, interleukin-1; IL-2, interleukin-2; MGP, matrix Gla protein; MMP, matrix metalloproteinases; TNF, tumor necrosis factor.

4 months over 5 years (equivalent to 21 μg vitamin D per day). In subgroup analysis, serum 25(OH)D concentrations were 21 nmol/l higher in the active vitamin D group compared with the placebo group. The rate ratios for cardiovascular diseases, cancers, and colorectal cancers incidences were 0.90 (0.77–1.06), 1.11 (0.86–1.42), and 1.02 (0.60–1.74), respectively. For mortality, these ratios were 0.84 (0.65–1.20), 0.86 (0.61–1.20), and 0.62 (0.24–1.60), respectively. Hence, though statistical significance was not achieved, incidence rate ratios were always close to 1.0, whereas mortality rate ratios were always lower, suggesting that the protective effect of vitamin D on cardiovascular and cancer mortality is more effective than its effect on disease incidence. In line with this suggestion, a metaanalysis of controlled clinical trials came to the conclusion that vitamin D supplementation reduced total mortality in middle aged to elderly adults by 7% during a trial size-adjusted mean of 5.7 years [19••]. In the vitamin D-supplemented patients and controls, mean serum 25(OH)D concentrations increased by 40 nmol/l and decreased by 6.5 nmol/l, respectively. Although the authors could not evaluate cause-specific mortality, the relatively immediate effect of a large enough magnitude to influence total mortality would suggest a preventive effect on CHD mortality.

Vitamin D and congestive heart failure

The aforementioned experimental data and several clinical results indicate that adequate vitamin D metabolite levels may contribute to the prevention of congestive heart failure (CHF). In a recent study in 43 men and 17 women with left ventricular ejection fraction of 40% or less, longer 6-min walk distance was correlated with higher 25(OH)D levels [20•]. The 6-min walk distance is a frequently used test in heart failure patients to assess functional cardiac outcome. Other independent variables of the 6-min walk distance were age, sex, and highly sensitive C-reactive protein levels. A case-controlled study [21•] showed that lifestyle factors associated with adequate vitamin D status such as membership in a sports club, frequent summer holidays, and living in rural areas were less frequently reported for the period of childhood,

adolescence, and young adulthood by CHF patients compared with healthy controls. Data indicate that vitamin D insufficiency/deficiency is a causal factor of CHF and not just the result of disease-related alterations.

Very low serum calcitriol levels (<37.5 pmol/l) have frequently been found in end-stage heart failure patients [22••]. In this study, patients in the highest calcitriol tertile had a hazard ratio for an event (death or cardiac transplantation) of only 0.506 (95% CI 0.334–0.767) compared with patients in the lowest calcitriol tertile, after adjustment for potential confounders. Data support the assumption that low vitamin D metabolite levels are a risk factor for survival and that vitamin D seems to be a very important protective factor for cellular health.

Vitamin D and the vasculature

Classical risk factors in the pathogenesis of CHD are smoking, dyslipoproteinemia, hypertension, disturbed glucose metabolism, and proinflammatory processes. Until recently, vascular calcification was considered to be a passive process that occurred as a nonspecific response to vascular damage without clinical significance. However, there is now accumulating evidence that vascular calcification is an active process [23••]. Almost all angiographically atherosclerotic lesions are calcified [24]. Vascular calcification can cause thrombosis, arterial rupture, and myocardial infarction. In general, the development of tissue calcification requires a preexisting injury as an inducer, whereas further progression requires the presence of other promoter factors such as hyperphosphatemia and hypercalcemia or a deficiency in calcification repressor factors or both [25].

Experimental vitamin D effects on the vasculature

Beside the heart, the vasculature is an important target tissue for vitamin D. Available data concerning protective effects of vitamin D on the vasculature have recently been summarized [23••]. These effects include calcitriol-mediated downregulation of MMPs and proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α (Fig. 1). The effects also include upregulation of the anti-inflammatory cytokine IL-10 and of inhibitors of vascular calcification such as matrix Gla protein (MGP), osteopontin, and type IV collagen in vascular smooth muscle cells and osteoblast-like cells. In addition, calcitriol blunts the deleterious impact of advanced glycation end products (AGEs) on endothelial cells [26•]. AGEs are believed to induce vascular dysfunction in diabetic and uremic patients and may explain the link between hyperglycemia and the development of vascular complications.

In experimental studies with rings of spontaneously hypertensive rats aorta, calcitriol treatment reduced the acetylcholine-induced and ATP-induced endothelium-dependent contractions [27•]. Moreover, the acetylcholine-induced release of prostacyclin was reduced by the acute administration of calcitriol. Calcitriol also reduced the increase in cytosolic free calcium concentration caused by acetylcholine. These data demonstrate that calcitriol modulates vascular tone by reducing calcium influx into the endothelium and hence decreasing the production of endothelium-derived contracting factors.

Vitamin D deficiency and vascular calcification in chronic kidney disease

Obviously, chronic kidney disease (CKD) can be considered as a human model for the effects of calcitriol deficiency on vascular calcification and CHD mortality. In CKD, both calcitriol deficiency and vascular calcification are extremely common. Disturbances in mineral homeostasis such as hyperphosphatemia and hyperparathyroidism seem to be secondary to calcitriol deficiency and are obviously key factors for medial calcification [23••]. End-stage renal disease (stage 5 CKD) results in glomerular filtration rates below 15 ml/min/1.73 m^2. As a consequence, circulating calcitriol levels fall below 37.5 pmol/l (reference range 40–150 pmol/l). In end-stage renal disease, the age-standardized risk for cardiovascular events and mortality is 37 times and 10–20 times, respectively, higher than in the general population [23••].

Children on dialysis with calcitriol levels below 40 pmol/l or above 150 pmol/l had significantly higher cardiac calcification score than controls and patients with calcitriol levels in the reference range [28••]. A mouse model of CKD-stimulated atherosclerotic cardiovascular mineralization demonstrated that treatment with calcitriol and one of its analogs, paricalcitol, was protective against aortic calcification at dosages sufficient to correct secondary hyperparathyroidism. However, higher dosages stimulated aortic calcification [29•]. Data support the assumption that both inadequately low and high vitamin D concentrations are associated with deleterious effects on the vasculature [30•]. In non-CKD patients, lower serum 25(OH)D levels and higher serum parathyroid hormone (PTH) levels were independently associated with calcific aortic stenosis [31•]. In patients with type 2 diabetes and low vitamin D status [25(OH)D levels < 50 nmol/l], vitamin D treatment with a single oral vitamin D_2 bolus of 100 000 IU (1500 μg vitamin D_2) improved endothelial function, measured by flow mediated vasodilatation, in a double-blind, parallel group, randomized trial [32•].

Treatment with active vitamin D and total mortality in chronic kidney disease

Wolf *et al.* [33••] reported that in CKD, serum 25(OH)D levels of at least 25 nmol/l or serum calcitriol levels of at

least 37.5 pmol/l were associated with reduced risk of early mortality compared with patients who were untreated and had 25(OH)D and calcitriol levels below these respective values. Some studies indicate that treatment of CKD with active vitamin D (0.25–0.75 μg/d) reduces all-cause mortality by 16–24% and cardiovascular mortality by 70% [30•]. Data also indicate that the differences in survival between patients treated with different forms of active vitamin D (calcitriol, doxercalciferol, and paricalcitol) are small [34]. In a recent study [35•], patients receiving treatment with calcitriol, 0.25–0.5 μg/day, for a median duration of 2.1 years, had a significant lower incidence rate ratio [adjusted relative risk (RR) 0.35, 95% CI 0.23–0.54] for predialysis mortality than untreated patients. Although calcitriol appears to be associated with greater survival, results have to be confirmed by the use of prospective, randomized trials.

Conclusion

Several experimental studies demonstrate that the vitamin D hormone calcitriol plays a pivotal role for normal physiology of cardiomyocytes and the vasculature. Low vitamin D metabolite levels are associated with various CHD outcome parameters such as myocardial infarction, congestive heart failure, and cardiovascular mortality. There are also exciting data that vitamin D may reduce total mortality, especially in patients with deficient calcitriol levels. However, it is still too early to recommend exact dosages for the prevention or therapy of CHD, as prospective, randomized controlled trials with adequate amounts of vitamin D are lacking.

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