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SHORT REVIEW

Vitamin D status and cardiovascular outcome

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Abstract

Introduction Vitamin D is classically involved in maintaining bone and mineral health, but it has been shown to exert many extraskeletal functions, including pleiotropic effects on cardiovascular system.

Materials and method This review aims to summarize evidences in literature about vitamin D and cardiovascular outcome.

Results and conclusions Calcitriol or 1,25$(OH)_2$D, the active hormone, binds to the specific nuclear receptor VDR, which is expressed in rat and human heart and vasculature and has effects on myocardiocytes, smooth cells, and endothelial cells. 25-Hydroxy-vitamin D (25OHD) represents the biomarker of vitamin D levels and reflects vitamin D status. There is consistent evidence that low serum 25OHD levels are associated with increased risk of cardiovascular diseases, including hypertension, coronary artery disease, ischemic heart disease, heart failure, stroke, and type 2 diabetes. Randomized-controlled trials and Mendelian randomization studies so far have not succeeded in proving a benefit of vitamin D supplementation. However, the latter investigations are affected by some methodological limitations, and therefore, it is still unclear if vitamin D deficiency has a causative role in cardiovascular diseases or is rather a marker of poor health in chronic disease.

Keywords Vitamin D · Calcitriol · Cardiovascular risk · Heart failure

Introduction

Vitamin D is a steroid hormone and a crucial regulator of skeletal and calcium homeostasis. In the last 10 years, vitamin D has been shown to produce relevant extraskeletal effects, particularly on the cardiovascular system [1–4]. These data are supported by preclinical experiments, claiming that vitamin D receptor and enzymes modulating vitamin D actions are expressed in the heart. Moreover, 1,25-dihydroxy-vitamin D (1,25$(OH)_2$D) or calcitriol, the active vitamin D metabolite, exerts interesting effects on endothelial cells, vascular smooth cells, macrophages, and cardiomyocytes [5]. Clinical evidence also supports the link between vitamin D and cardiovascular system: low levels of 25-hydroxy-vitamin D (25OHD), the biomarker of vitamin D status, are associated with increased risk of cardiovascular diseases [6] including hypertension, coronary artery disease, ischemic heart disease, heart failure (HF), and stroke [7–11]. On the other hand, the beneficial effect of vitamin D replacement has not been demonstrated so far in randomized-controlled trials (RCTs) and Mendelian randomization studies, so that the meaning of the association between a low vitamin D status and cardiovascular diseases remains to be established.

The aim of this paper is to summarize the most recent evidences about the role of vitamin D on cardiovascular outcomes, including pre-clinical data, association studies and available results from randomized clinical trials, and Mendelian randomization studies.

Cardiovascular effects of 1,25$(OH)_2$D

In the early 1980s, Robert Scragg proposed the hypothesis that the increase in cardiovascular diseases occurring in winter might be the consequence of low serum 25OHD levels, due to the reduced efficacy of sunlight radiations during that season [12]. This idea turned on a great interest in the potential cardiovascular benefits of vitamin D supplementation, leading to several publications in this field. However, the

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physiological role of vitamin D in the cardiovascular system is still unclear.

$1,25(OH)_2D$ binds to the specific nuclear receptor VDR, which is expressed in rat and human heart and has a potential role as a modulator of cardiac hypertrophy and failure. $1,25(OH)_2D$ is also directly involved in calcium-dependent cellular processes, including synthesis of calcium-binding proteins, activation of adenylate cyclase, rapid activation of voltage-dependent calcium channels, and sarcoplasmic reticulum calcium uptake and release. Notably, altered intracellular handling of ionized calcium has been shown to be a major determinant of contractile impairment in patients with HF [13] (Fig. 1).

Vascular effects of $1,25(OH)_2D$ have also been demonstrated; indeed, $1,25(OH)_2D$ can modulate the growth of smooth cells and endothelial cells [14]. In endothelial cells, $1,25(OH)_2D$ also directly stimulates nitric oxide (NO) synthase [15] and inhibits COX 1 [16], leading to vasodilation. Moreover, $1,25(OH)_2D$ may reduce oxidative stress decreasing superoxide production in the vascular wall [17] (Fig. 1).

Systemic effects of vitamin D on blood pressure can be explained by the role of $1,25(OH)_2D$ as a negative regulator of the renin-angiotensin system (RAS) (Fig. 1). Indeed, in vitro studies demonstrated that $1,25(OH)_2D$ inhibits the cAMP responsive elements in the renin promotor gene, decreasing renin gene expression [18]. These data are supported by the other recent results, showing that several nuclear receptors, including VDR, liver X receptor (LXR), and peroxisome proliferators-activated receptor (PPAR), regulate renin expression via specific elements in the renin promoter [13].

Strong support for the involvement of vitamin D in the pathogenesis of cardiovascular diseases comes from observations performed in vitamin D receptor knockout mice

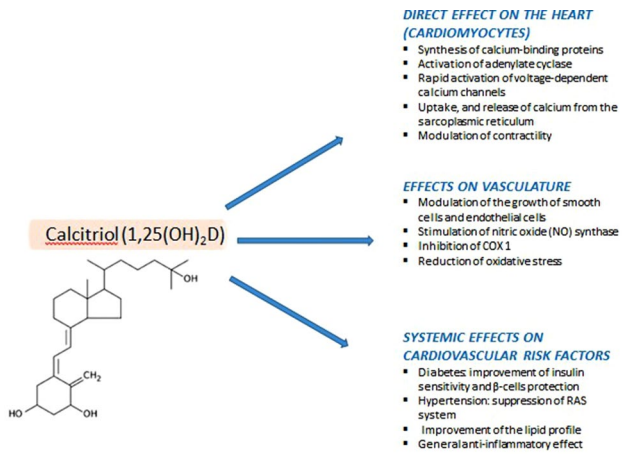

Fig. 1 Summary of the known effects of Vitamin D on cardiomyocytes and vasculature, as well as that of its systemic effects on cardiovascular risk factors

(VDR$^{-/-}$). These mice develop typical signs of HF, including activation of the RAS system, cardiac hypertrophy, high blood pressure, and increased levels of atrial natriuretic peptide. This phenotype is not modified by restoring serum calcium levels through a calcium-rich diet, suggesting a profound alteration in the endocrine system [2]. Furthermore, the development of hypertension in VDR$^{-/-}$ mice can be corrected by administration of ACE inhibitors, but only as long as vitamin D levels are sufficient [1–3].

Additional, indirect endocrine effects of vitamin D on the cardiovascular system may be mediated troughs non-specific anti-inflammatory and immunomodulating actions. $1,25(OH)_2D$ has been shown to reduce the expression of pro-inflammatory genes (TNFα, IL1, and IL6) [19] and to stimulate anti-inflammatory genes (IL10) (Fig. 1). Moreover, $1,25(OH)_2D$ inhibits TH1-17 cells and affects dendritic cell functions [20].

One more aspect to be considered is the potential role of secondary hyperparathyroidism in the setting of vitamin D deficiency. Indeed, a prevalence of 10–33% of secondary hyperparathyroidism is reported among patients with hypovitaminosis D and high PTH levels have been associated with hypertension, arrhythmias, and vascular calcifications [21–23]. Further studies are needed to clarify the specific role of calcitriol and PTH on cardiovascular outcomes in this setting.

Observational studies

Several longitudinal cohort studies demonstrated the association of vitamin D deficiency with cardiovascular events, namely HF, stroke, myocardial infarction, cardiomyopathy, and with cardiovascular mortality. In the Framingham Heart Study, published in 2008, low serum 25OHD levels (< 15 ng/mL) were associated with 60% increase in the risk of developing cardiovascular events, even after adjustment for the most important cardiovascular risk factors [24]. Using baseline data from the Third National Health and Nutrition Examination Survey (NHANES 1988–1994), including more than 15,000 subjects, Fiscella et al. showed that low levels of serum 25OHD (< 14 ng/mL) were associated with a higher risk of cardiovascular death, particularly in black people [25]. More recently, data from NHANES 2001–2010 have been published: in a cohort of 7674 subjects, and serum levels of 25OHD > 29 ng/mL were associated with a lower risk of cardiometabolic risk compared to levels of 25OHD < 17 ng/mL, after adjusting for several confounding factors [26]. In the European study, Copenaghen City Heart, conducted on more than 10,000 subjects with a follow-up up to 29 years, the lower percentiles of 25OHD were associated with an increased risk of myocardial infarction (+ 64%) and mortality for

cardiovascular diseases (+ 81%) [27]. The association between hypovitaminosis D and cardiovascular risk seemed to be valid either for men, as demonstrated by the Health Professional Follow-Up Study, and for women, as showed in a large Finnish study [28, 29]. In a small Italian study on 200 healthy women (19–50 years), serum 25OHD levels were directly correlated with serum HDL cholesterol and inversely correlated with intima–media thickness, suggesting a cardiovascular protective role for high serum 25OHD levels [30]. Among cardiovascular risk factors, obesity has a central role: several studies have been showed a clear association between low levels of vitamin D and obesity (BMI > 30 kg/m^2) [31]. This association could be due to the sequestration of the lipophilic hormone in the adipose tissue [32] and/or to a complex interplay between adipocytes and vitamin D, as suggested by some authors [33]. Indeed, there are some evidences that 1,25(OH)2D can inhibit peroxisome proliferator-activated receptor γ, thus modulating adipogenesis, but still further studies are needed to address the effects of vitamin D on adipose tissue and relation between hypovitaminosis D and obesity [34].

HF is a major cardiovascular disease with a poor prognosis. In 2012, Gotsman et al. evaluated the prevalence of vitamin D deficiency in a large cohort of HF patients, and described the seasonal variation in serum 25OHD levels and the impact of vitamin D deficiency and supplementation on mortality. They demonstrated that serum 25OHD D levels are low in the general population and even lower in patients with HF, and that vitamin D deficiency was a significant predictor of reduced survival. Moreover, vitamin D supplementation was associated with an improved outcome in terms of mortality [35]. We recently evaluated an Italian cohort of 261 patients with HF and showed that low serum levels of 25OHD are inversely correlated with the Metabolic Exercise Cardiac Kidney Index (MECKI), a validated score of mortality [36]. Moreover, in a subgroup of these patients, we also evaluated cardiovascular outcomes: patients with HF had mean serum levels of 25OHD statistically lower than healthy subjects (45.2 ± 23.7 nmol/L vs 58.2 ± 24.0 nmol/L, $P < 0.001$) and a higher prevalence of vitamin D insufficiency (serum 25OHF < 20 ng/mL) (61.1% vs 39.5%, $P < 0.001$), that was associated with reduced survival [37].

Several meta-analyses published between 2012 and 2018 [7, 27, 38–42] summarized results obtained in a large number of subjects, ranging from 26,916 in the study of Gaksch et al. [42] to more than 180,000 in the study of Zhang et al. [41]. All meta-analyses confirmed a consistent association between a low vitamin D status and cardiovascular endpoints (myocardial infarction, hypertension, and HF) and/or mortality.

Table 1 summarizes the results of the most important observational studies.

Randomized clinical trials (RCT) and vitamin D supplementation in cardiovascular diseases

As discussed above, observational studies show a clear association between a low vitamin D status and cardiovascular diseases, but this is not sufficient to establish a causal relationship. RCTs are required to prove the benefit of vitamin D supplementation on cardiovascular outcomes. Several RCTs are available in the literature, but most of them were not designed to evaluate extra-skeletal endpoints, and their interpretation is not simple.

The Women' Health Initiative, designed for skeletal primary endpoints, also considered cardiovascular events as secondary endpoints. In this study, more than 36,000 women were randomized to 400 UI of vitamin D plus 1000 mg calcium daily or placebo: there was no difference between the two arms, in term of coronary events and stroke [43]. Subsequently, an analysis of the same database, including only women not already taking vitamin D and calcium at the baseline, found an increased risk for cardiovascular events in the supplementation arm [44]. In the Cochrane review, vitamin D supplementation significantly reduced all-cause mortality compared with placebo or no intervention, but had no significant effect on cardiovascular mortality (risk ratio 0.98, 95% CI 0.90–1.07; $n = 47{,}267$) [45].

The VIDA study is a randomized, double-blind, placebo-controlled trial conducted in New Zealand. Adult patients were randomized to cholecalciferol 100,000 UI/monthly or placebo: the results after 3 years of follow-up have recently been published, showing no beneficial effect of vitamin D supplementation on any cardiovascular endpoint [46].

A meta-analysis focused on HF and vitamin D status showed that vitamin D supplementation was associated with a decrease of serum levels of PTH, TNFα, and CRP, even if the beneficial effects on left-ventricular function and exercise tolerance were limited [47].

The RECORD study included 5260 participants and concluded that the daily supplementation with 800 UI of cholecalciferol was protective against HF [HRs 95% = 0.75 0.75 (0.58, 0.97)] but not against myocardial infarction or stroke [HR = 0.97 (0.75,1.26), and 1.06 (0.8, 1.32) respectively, 48]. Shleithoff et al. studied a cohort ($n = 123$) of patients with HF, randomized to daily supplementation with 2000 IU vitamin D ($n = 61$) or placebo ($n = 62$) for 9 months, and observed decreased proinflammatory cytokines in the active group, without changes in ventricular function and biochemical markers (LV ejection fraction, LV end-diastolic diameter, VO2max,

Table 1 Data from RCTs exploring the effects of vitamin D supplementation on cardiovascular events and/or mortality

Study	No of subjects	Conclusions
Observational studies and meta-analyses		
Wang et al. [21]	1739	Low serum 25OHD levels (< 15 ng/mL) were associated with 60% increase in the risk of developing cardiovascular events, even after adjustment for the most important cardiovascular risk factors
Fishella et al. [22]	> 15,000	Low levels of serum 25OHD (< 14 ng/mL) were associated with a higher risk of cardiovascular death, particularly in black race
Al-Khalidi et al. [23]	7674	High serum levels of 25OHD were associated with a lower risk of cardiometabolic risk compared to low levels of 25OHD (adjusted for confounding factors)
Brøndum-Jacobsen et al. [24]	> 10,000	Lower percentiles of 25OHD were associated with an increased risk of myocardial infarction (+64%) and mortality for cardiovascular diseases (+81%)
Gaksch et al. (meta-analysis on 8 studies) [35]	26,916	Adjusted hazard ratios (with 95% confidence interval) for cardiovascular mortality on the base of 25OHD levels: < 12 ng/mL: RR 3.2, 12–20 ng/mL: RR 1.8, 20–30 ng/mL: RR 1.3
Zhang et al. (meta-analysis on 34 studies) [34]	180,667	Serum 25(OH)D concentration was inversely associated with total CVD events and CVD mortality from the observed studies
Randomized-controlled trials (RCTs)		
Hsia et al. [36]	36,282	400 UI of vitamin D + 1000 mg calcium daily or placebo: no difference of coronary events and stroke
Bolland et al. [37]	16,718	Part of the same population of Hsia et al. including only women not taking supplements at baseline: increased risk for cardiovascular events in the supplementation arm
Scragg et al. [39]	5108	Vitamin D3 100,000 UI/monthly or placebo: no beneficial effect of vitamin D supplementation on any cardiovascular endpoint
Bjelakovic et al. (meta-analysis on 56 RCTs) [38]	> 90,000	Vitamin D3 supplementation significantly reduced all-cause mortality compared with placebo or no intervention, but had no significant effect on cardiovascular mortality

NT-proBNP) [4]. Using the same dosage, Schroten et al. described a significant decrease of PRA and plasma renin concentration in patients with HF [49]. Dalbeni et al. found that 6 months of vitamin D supplementation significantly improved ejection fraction in elderly patients with HF [50] and Shedeed et al. reported that young patients with HF achieved marked improvement in both cardiac function and inflammatory markers (left-ventricular end-diastolic diameter, LV end-systolic diameter, LV ejection fraction, myocardial performance index, interleukin-10, PTH, interleukin-6, and TNFa) after 12 months of vitamin D analogues [51].

The VINDICATE study, a double-blind, placebo-controlled, trial in HF patients randomized to 4000 IU of vitamin D/daily or placebo for 12 months has shown a statistically significant improvement of left-ventricle (LV) ejection fraction, dimension, and volume in the supplemented group, without any change in the 6-min walk test, that was the primary endpoint [52].

Overall, the evidence about the benefit of vitamin D supplementation on cardiovascular health is not conclusive. This may be accounted for by substantial limitations in the experimental design: cardiovascular diseases were not the principal focus of these trials, and in some cases, the cardiovascular endpoints were not pre-specified; different dosage and different preparations of vitamin D were used; serum 25OHD was not always measured at the baseline and/or in the follow-up.

Table 1 summarizes the results of RCTs exploring the effects of vitamin D supplementation on cardiovascular events and/or mortality.

Mendelian randomization studies

Mendelian randomization studies could help to understand the role of vitamin D in cardiovascular diseases, because, with this approach, the effects of the genetic-dependent lifelong vitamin D status are analysed, with limited confounding lifestyle factors. In the Copenaghen Study by Brøndum-Jacobsen et al. 92,416 participants were genotyped using SNPs in the *DCHR7* and in the *CYP2R1* genes. In that cohort, low serum levels of 25OHD were associated with an increased risk of ischemic heart disease, but there was no evidence that the ischemic risk was due to genetically reduced serum 25OHD levels [53]. Similar conclusions were reached in a large (30,000 subjects) Canadian study, concerning the association of genetically low serum 25OHD levels and an increased risk of coronary artery diseases [54]. At variance, a meta-analysis summarizing the results of 146,581 individuals to evaluate the association between genetically determined 25OHD levels and blood pressure found that increased serum levels of 25OHD were associated with a lower risk of hypertension [55]. Finally, Ooi et al. reported that genetically elevated non-fasting remnant

cholesterol was associated with low serum 25OHD, and suggested that vitamin D deficiency could be a marker of the individual atherogenic setting [56].

Conclusions

It is still controversial whether a low vitamin D status has a causative role in cardiovascular diseases and whether vitamin D supplementation could be of benefit. Despite a strong association between hypovitaminosis D and poor cardiovascular outcomes, Mendelian randomization studies do not support a causative role and interventional investigation has not definitely proved a beneficial effect. Vitamin D deficiency could simply be a general marker of poor health in patients with chronic cardiovascular diseases. Many methodological issues are, however, still open, particularly the accuracy of serum 25OHD assays, the cut-off values used to define vitamin D deficiency, and the adequacy of the dosages and reparations used as vitamin D supplementation. Large ongoing RCTs, specifically designed to evaluate vitamin D effects on cardiovascular end-points, will hopefully shed light on the current uncertainties and controversies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This manuscript is a review of the literature and does not contain original research either on animal or on human subjects.

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