REVIEW

Vitamin D deficiency and myocardial diseases

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Vitamin D deficiency is common among patients with myocardial diseases because sun-induced vitamin D production in the skin and dietary intake of vitamin D is often insufficient. Knockout mice for the vitamin D receptor develop myocardial hypertrophy and dysfunction. It has also been shown that children with rickets who suffered from severe heart failure could be successfully treated with supplementation of vitamin D plus calcium. In adults, almost all patients with heart failure exhibit reduced 25-hydroxyvitamin D levels, which are used to classify the vitamin D status. In prospective studies, vitamin D deficiency was an independent risk factor for mortality, deaths due to heart failure and sudden cardiac death. Several vitamin D effects on the electrophysiology, contractility, and structure of the heart suggest that vitamin D deficiency might be a causal factor for myocardial diseases. Data from interventional trials, however, are rare and urgently needed to elucidate whether vitamin D supplementation is useful for the treatment of myocardial diseases. In our opinion, the current knowledge of the beneficial effects of vitamin D on myocardial and overall health strongly argue for vitamin D supplementation in all vitamin D-deficient patients with or at high risk for myocardial diseases.

1   Introduction

Vitamin D deficiency is commonly observed in patients suffering from myocardial diseases [1]. Sun exposure, which induces vitamin D production in the skin, is often limited in these symptomatic, housebound patients. This reduced

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Abbreviations: ANP, atrial natriuretic peptide; **ECM,** extracellular matrix; **MMP,** matrix metalloproteinase; **PTH,** parathyroid hormone; **RAS,** renin-angiotensin system; **TIMP,** tissue inhibitors of metalloproteinase; **UV-B,** ultraviolet-B; **VDR,** vitamin D receptor

ultraviolet-B (UV-B) radiation of the skin constitutes the main factor for the worldwide high prevalence of vitamin D deficiency because vitamin D intake by nutrition (*e.g.* eggs, fish or fortified food) is often too low to compensate for reduced dermal vitamin D production [2]. In particular, elderly people are prone to vitamin D deficiency because the capacity of the skin to produce vitamin D decreases with aging and malnutrition is a frequent problem.

Mounting evidence suggests that vitamin D deficiency is associated with increased cardiovascular risk and myocardial diseases, but the underlying mechanisms remain to be explored in detail [3]. Whether vitamin D deficiency is partially the cause or only the consequence of myocardial diseases is unclear. However, the vitamin D endocrine system, which regulates about 3% of the human genome, exerts widespread effects on the cardiovascular system, suggesting a possible causal relationship of vitamin D

deficiency and cardiovascular risk [3, 4]. With the current review, we aim to provide an overview of the pathophysiological mechanisms and the epidemiological data concerning vitamin D deficiency and myocardial diseases.

We performed a systematic literature search in Pubmed for relevant English language publications published until August 2009. We used the following search terms: "vitamin D" and "heart", "vitamin D" and "myocardium", "vitamin D" and "myocardial", and "vitamin D" and "cardiac". In addition, we also used the search terms "25-hydroxyvitamin D", "1,25-dihydroxyvitamin D" or "calcitriol" instead of vitamin D. We also used listed references from selected articles to expand the search. Some articles were not cited due to space limitations.

2   Basic vitamin D metabolism

The main vitamin D source accounting for approx. 80–90% of circulating vitamin D metabolites is sunlight-induced vitamin D production in the skin. In detail, UV-B radiation induces conversion of 7-dehydrocholesterol to provitamin D3, which spontaneously isomerizes to vitamin D3 (cholecalciferol). Certain foodstuffs such as fatty fish or cod-liver oil also contain vitamin D3 [2]. Further sources for vitamin D are plants and fungi in which vitamin D2 (ergocalciferol) is produced by UV-B-induced conversion of ergosterol [2]. Vitamin D (vitamin D2 or vitamin D3) is hydroxylated to 25-hydroxyvitamin D (25[OH]D) in the liver. 25(OH)D is the main circulating vitamin D metabolite and is used for the classification of the vitamin D status into vitamin D sufficient (25[OH]D ≥ 30 ng/mL), vitamin D insufficient (20–29 ng/mL) and vitamin D deficient (< 20 ng/mL) (to convert ng/mL into nmol/L multiply by 2.496) [2]. 25(OH)D is further hydroxylated to 1,25-dihydroxyvitamin D (1,25[OH]2D) which is the most active vitamin D metabolite. This latter 1α-hydroxylation of 25(OH)D takes place in most tissues and cells of the body but blood levels of 1,25(OH)D are mainly determined by renal 1α-hydroxylase activity. Importantly, circulating 25(OH)D levels are a main determinant of extrarenal tissue levels of 1,25(OH)2D and are thus the best indicator of whole body vitamin D status [2]. Activity of 1α-hydroxylase is, however, also regulated by several inflammatory and hormonal mechanisms including, *i.e.* fibroblast growth factor 23, which suppresses 1α-hydroxylase activity [2]. Finally, 1,25(OH)2D, which is a steroid hormone, binds to the vitamin D receptor (VDR) which is expressed in most cells of the body. Liganded VDR forms a complex with the retinoid X receptor and regulates about 3% of the human genome by binding to vitamin D responsive elements [4]. In addition, there also exist non-genomic effects of the vitamin D endocrine system, which are less well characterized [2, 4]. Notably, catabolization of 1,25(OH)2D and 25(OH)D to biologically inactive calcitroic acid is catalyzed by 24-hydroxylase [2].

3   Myocardial VDR expression and metabolism

Several studies have shown that cardiac myocytes express a functional VDR, which is primarily located in the nucleus and within, or adjacent to the *t*-tubules [5–11]. Cardiac fibroblasts also express the VDR. Importantly, myocardial hypertrophy is associated with an increased expression of the VDR in cardiac myocytes as well as in cardiac fibroblasts [11]. Furthermore, it has been shown that cardiac myocytes and fibroblasts express the enzymes 1α-hydroxylase and 24-hydroxylase [11, 12]. Considering that the conversion of 25(OH)D to 1,25(OH)2D by 1α-hydroxylase in extrarenal tissues is mainly dependent on substrate availability, this latter finding suggests that, apart from 1,25(OH)2D plasma levels, the concentrations of circulating 25(OH)D levels might be a significant determinant of vitamin D effects in the myocardium.

4   Direct vitamin D effects on the myocardium

4.1   Antihypertrophic effects and modulation of differentiation and proliferation of cardiomyocytes

Myocardial hypertrophy develops in the course of heart failure. 1,25(OH)2D was shown to exert antihypertrophic effects on cardiomyocytes and reduced the expression of several genes which are upregulated in myocardial hypertrophy [9, 13]. Suppression of the cardiac renin-angiotensin system (RAS) and of natriuretic peptides, which are described below in detail, may partially mediate these antihypertrophic effects of vitamin D. Apart from this, vitamin D exerts various effects on the growth and differentiation of cardiomyocytes, which are largely suggested to improve myocardial structure and function [14–19]. One beneficial key mechanism of vitamin D is to inhibit overwhelming proliferation of cardiomyocytes [14, 16, 17]. Anti-proliferative properties of vitamin D are at least in part mediated by the suppression of proto-oncogenes such as c-myc, which was found to be reduced after 1,25(OH)2D treatment of cardiomyocytes [9, 14, 16, 17]. It should, however, be noted that adult cardiomyocytes usually do not proliferate in contrast to neonatal cardiomyocytes which were used for the key experiments in this field [16].

4.2   Vitamin D effects on the cardiac RAS

The RAS is important for regulating blood pressure and mineral metabolism. Increased activation of the cardiac RAS system was observed in VDR knockout mice and has been linked to the development of myocardial hypertrophy [20]. In detail, Xiang *et al.* showed that cardiac renin mRNA was

significantly increased in mice lacking the VDR [20]. Regulatory mechanisms of renin expression by 1,25(OH)2D in cardiomyocytes remain to be explored in detail. By now, Yuan *et al.* have shown that liganded VDR suppresses renin expression by binding to the transcription factor CREB in mesangial cells of the kidney [21]. Notably, renin expression is usually induced by cAMP binding to protein kinase A. The latter phosphorylates CREB resulting in the recruitment of the co-activators CBP/p300 to promote transcription of the renin gene [22]. Interestingly, treatment with the active vitamin D compound paricalcitol resulted in down-regulation of several components of the RAS in the kidney of 5/6 nephrectomized rats: renin, renin receptor, angiotensinogen, and angiotensin II type 1 receptor [23, 24].

4.3 Vitamin D effects on gene expression of natriuretic peptides

Natriuretic peptides are secreted by cardiomyocytes due to volume overload and increased atrial and/or ventricular pressure. After previous observations suggesting an involvement of 1,25(OH)2D in the regulation of atrial natriuretic peptides (ANPs) [25], Li and Gardner showed that the liganded VDR suppressed ANP transcription by binding to the promoter region of this gene [26]. Further studies confirmed that 1,25(OH)2D inhibits the secretion of natriuretic peptides in atrial and ventricular myocytes [13, 27]. It was demonstrated that the inhibition of the ANP promoter activity requires the DNA-binding and the ligand-binding domain of the VDR [28]. Heterodimerization of the VDR with the retinoid X receptor and binding of coactivators (GRIP-1 and steroid receptor coactivator 1) were also shown to be important for the suppression of the ANP transcription [29, 30]. Given that natriuretic peptides exert anti-hypertrophic effects, it could be speculated that the above-described vitamin D mediated suppression of natriuretic peptides might be harmful. However, Chen *et al.* concluded that the vitamin D-dependent suppression of ANP reflects a global antagonism of myocardial hypertrophy rather than an isolated inhibition of the ANP gene [31]. This notion is supported by studies showing that vitamin D treatment suppresses several genes that are upregulated in patients with heart failure [9, 13]. Interestingly, liganded VDR was also shown to increase the expression and activity of the type 1 natriuretic peptide receptor-A, which exerts anti-hypertensive effects, suppresses the RAS, and inhibits myocardial hypertrophy and fibrosis [31].

4.4 Vitamin D effects on cardiac contractility and calcium handling

Calcium flux and calcium homeostasis are crucial for the electrophysiology and contractility of the heart. 1,25(OH)2D was shown to increase the Ca^{2+} uptake in cardiac ventricular

cells. This uptake was mediated by nongenomic effects leading to the opening of Ca^{2+} channels, and by genomic effects requiring the *de novo* synthesis of proteins related to Ca^{2+} cycling in the myocardium [32–34]. 1,25(OH)2D effects on cardiac contractility and intracellular calcium handling were studied in adult rat cardiomyocytes [35]. The main finding was an accelerated relaxation in response to acute (5–60 min) and sustained (for at least 2 days) administration of calcitriol [35]. It was shown that protein kinase C mediated the phosphorylation of Troponin T, which decreases myofilament Ca^{2+} sensitivity, and of phospholamban, which increases Ca^{2+} sequestration into the sarcoplasmatic reticulum. These effects are mainly responsible for the acute (nongenomic) effects of calcitriol on myocardial contractility [35]. Sustained effects of calcitriol on myocyte relaxation were independent of phosphorylation of Ca^{2+} cycling proteins and remain to be explored in further studies. In this context, it should be noted that 1,25(OH)2D alters gene expression of protein kinase C isoforms *via* a genomic vitamin D effect that may hypothetically influence cardiac contractile performance. This accelerated relaxation of cardiomyocytes induced by calcitriol might be important for the maintenance of normal diastolic function because relaxation in the diastole is crucial for an adequate blood inflow into the heart. Apart from this, compelling evidence exists that 1,25(OH)2D increases intracellular calcium by modulating cardiac β-adrenergic pathways [36–40]. These pathways involve the activation of the adenylatcylase by receptor coupled G proteins [36–40]. Subsequent increases of cAMP activate protein kinase A, which phosphorylates subunits of the L-type Ca^{2+} channel, lead to increased calcium influx into the cardiomyocytes [36–40].

4.5 Vitamin D effects on extracellular matrix turnover

Myocardial extracellular matrix (ECM) turnover is regulated by vitamin D effects on the expression of both matrix metalloproteinases (MMPs), which hydrolyze ECM proteins, and tissue inhibitors of metalloproteinases (TIMPs) [41]. Dysbalances in MMPs and TIMPs are related to the complex processes of the initiation and progression of both diastolic and systolic heart failure (for review see [42]). In VDR knockout mice, dysregulated MMP/TIMP expression, which was characterized by upregulation of MMP-2 and MMP-9 as well as downregulation of TIMP-1 and TIMP-3, was associated with myocardial fibrosis and hypertrophy [43]. TIMP-2 upregulation, and increased expression of ADAMTS-1, which degrades type 1 collagen, was also observed in VDR knockout mice [41]. Hence, vitamin D influences ECM turnover and this might hypothetically be beneficial for myocardial structure and function [41]. This is in line with a study in humans, which showed an inverse correlation of MMP-9 levels and 25(OH)D concentrations [44]. In the same study, MMP-9 decreased by 66.8% and TIMP-1 decreased by 39.8% after 1 year of vitamin D supplementation [44].

4.6 Other molecular effects of vitamin D on the myocardium

Expression of myosin, a major contractile protein of the myocardium, is also regulated by vitamin D [45–47]. These effects on myosin gene expression might partially underlie the associations of vitamin D status and myocardial contractility, which have been observed in rodents [45–47]. In addition, vitamin D is involved in the regulation of myocardial energy metabolism with one study showing that optimal mitochondrial function in chicken heart is vitamin D dependent [48, 49].

The above-described direct effects of vitamin D on myocardial structure and function are shown in Fig. 1.

5 Indirect effects of vitamin D on the myocardium

Vitamin D deficiency might also contribute to myocardial diseases by various indirect effects on the myocardium, which are related to disturbances of calcium homeostasis, classic cardiovascular risk factors, atherosclerosis, infections or autoimmunological processes (Fig. 2).

Elevated parathyroid hormone (PTH) levels are commonly observed in patients with vitamin D deficiency to maintain normal serum calcium levels despite insufficient vitamin D effects on calcium metabolism [50]. Secondary hyperparathyroidism has been associated with increased risk of cardiovascular diseases [50]. Deleterious PTH effects on the vessels and the myocardium suggest that increased PTH is a causal pathophysiologic link between vitamin D deficiency and myocardial diseases [50].

Apart from this, accumulating evidence exists that vitamin D deficiency indirectly contributes to the development of arterial hypertension, diabetes mellitus, dyslipidemia, and other cardiovascular risk factors [51–53]. It was also shown that vitamin D exerts direct anti-atherosclerotic effects on endothelial and vascular smooth muscle cells [3, 4, 51]. Hence, it is conceivable that vitamin D might prevent ischemic myocardial diseases by direct anti-atherosclerotic effects and by beneficial effects on cardiovascular risk factors. However, associations of vitamin D deficiency with vascular diseases have not been consistently observed and there exists some controversy about the causality of the link between the low 25(OH)D levels and the development of atherosclerosis [3, 51, 54].

Several infectious diseases can affect the myocardium and the cardiac valves and can thus contribute to myocardial diseases by causing arrhythmias, myocardial dysfunction, and valvular heart diseases. Given that vitamin D plays an important role for the immune system including resistance to infectious diseases, it could be hypothesized that a sufficient vitamin D status might prevent myocardial diseases by reducing the incidence of infections of the heart [55]. Moreover, the increased prevalence of autoimmune diseases in vitamin D-deficient individuals and the proposed involvement of autoimmunological processes in the development of heart diseases suggest that anti-autoimmunological properties of vitamin D might be another protective mechanism against myocardial diseases [4, 56]. Finally, further evidence exists that vitamin D exerts anti-inflammatory and anti-oxidative effects on the myocardium [1–4].

6 Vitamin D and myocardial dysfunction in animal studies

6.1 VDR and 1α-hydroxylase knockout models

VDR as well as 1α-hydroxylase knockout mice displayed myocardial hypertrophy which persisted even after normalization of calcium and phosphorus levels [4, 10, 22, 57–59]. Furthermore, myocardial dysfunction characterized by increased contractility in VDR knockout mice and impaired
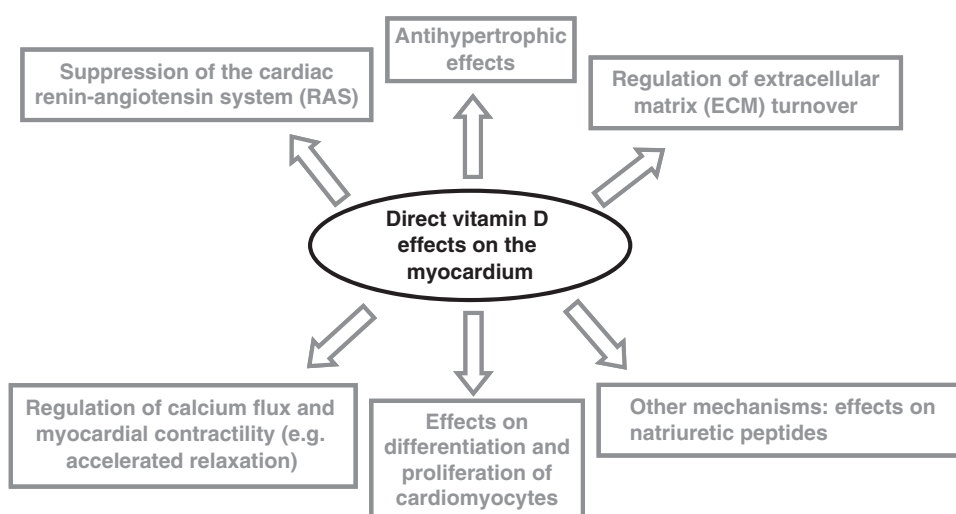

Figure 1. Direct effects of vitamin D on the myocardium.

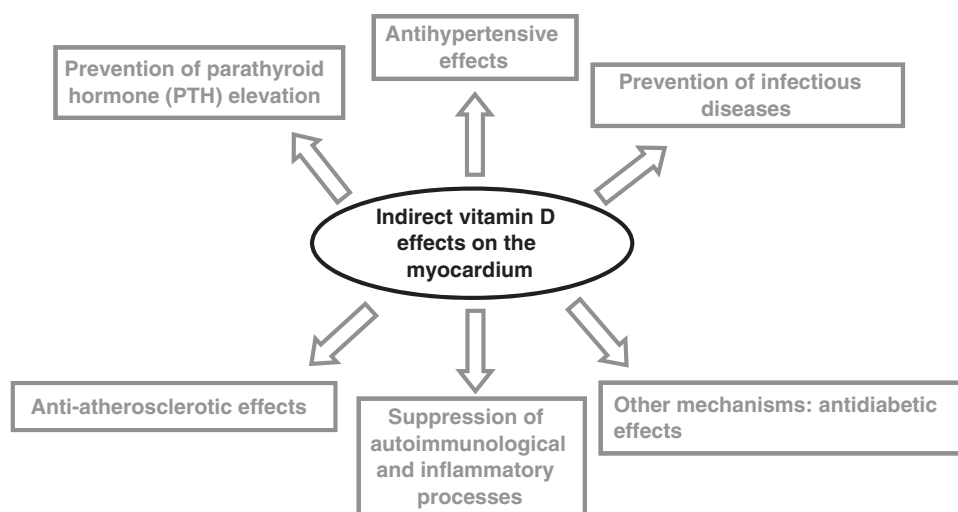*Mol. Nutr. Food Res.* 2010, *54*, 1103–1113

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Figure 2. Indirect effects of vitamin D on the myocardium.

systolic function in 1α-hydroxylase knockout mice have been observed [10, 58, 59]. These latter myocardial pathologies in the knockout models seem to be mainly mediated by increased RAS activation because inhibition of the RAS normalized myocardial structure and function [22, 58, 59].

6.2 Vitamin D-deficient rats

Weishaar and Simpson examined cardiovascular changes of rats kept on a vitamin D-deficient diet for up to 9 wk [60]. Elevated serum creatinine phosphokinase and a significant increase in aortic ring and cardiac contractility were observed in the vitamin D-deficient rats [60]. This increased cardiac contractility could not be prevented by maintenance of serum calcium at normal levels [61]. Calcium-independent cardiac hypertrophy with increased myocardial collagen content, shortening of the QT interval and reduced inotropic effects of glycosids were also demonstrated in vitamin D-deficient rats [62–64]. Hochhauser *et al.* showed that the increased myocardial contractility in vitamin D-deficient chicken hearts was also associated with reduced ATP and creatine phosphate levels, indicating that vitamin D deficiency is associated with an energy deficit within the myocardium [65]. However, a following study of the same group showed only a minimal decline of ATP and creatine phosphate levels and their experiments suggested that the effects of vitamin D deficiency on myocardial function were mainly driven by indirect effects on calcium homeostasis [66]. Interestingly, despite sufficient calcium supplementation, a maternal consumption of a low vitamin D diet resulted in a significant retardation of the metabolic potential and of contractile proteins in the neonatal rat heart [67]. Apart from this, the noradrenergic chronotropic response of rat atria was significantly reduced by a vitamin D depleted diet [68].

Some animal studies have already evaluated the effect of active vitamin D treatment on myocardial structure and function [69–72]. In uremic rats, treatment with the active vitamin D analog paricalcitol protected against cardiac oxidative injury [70]. In detail, paricalcitol inhibited the superoxide-generating enzyme NADPH oxidase in the heart and increased antioxidative glutathione as well as cardiac copper/zinc superoxide dismutase activity [70]. In addition, Bodyak *et al.* showed that paricalcitol treatment reduced abnormalities in left ventricular structure and function in Dahl salt-sensitive rats [71]. Effects of 1,25(OH)2D treatment were studied in spontaneously hypertensive heart failure-prone rats, which developed heart enlargement, myocardial collagen accumulation, left ventricular dilation, and increases in stroke volume after a high-salt diet [72]. 1,25(OH)2D treatment resulted in significant improvements of these cardiac abnormalities by reducing cardiomyocyte hypertrophy, left ventricular diameter, and stroke volume [72]. Myocardial collagen content was nonsignificantly reduced and serum calcium levels were within the normal range in the control as well as in the treatment group [72].

7 Vitamin D and myocardial dysfunction in humans

7.1 Vitamin D deficiency and cardiomyopathy in infants

Several case reports highlight pediatric cardiomyopathies, which are associated with vitamin D deficiency or rickets [73–81]. Importantly, children with vitamin D deficiency associated heart failure showed in most cases a significant clinical improvement after vitamin D and calcium supplementation [73–80]. A post mortem examination of a child who died due to vitamin D deficiency associated cardiomyopathy showed a large pericardial effusion and an enlarged heart with a dilated and concentric hypertrophic left ventricle [73]. There was a mild increase in interstitial fibrous tissue, particularly in the subendocardial regions

and the cardiomyocytes were thin and elongated in keeping with dilated cardiomyopathy [73].

7.2 Vitamin D deficiency and heart failure in adults

Several studies showed an increased prevalence of vitamin D deficiency among patients suffering from heart failure [1]. Zittermann *et al.* found significantly reduced 25(OH)D and 1,25(OH)2D levels in 54 heart-failure patients when compared with 34 age-, sex-, and BMI-matched controls [82]. In a study among 102 African Americans, vitamin D deficiency was observed in 84–96% of heart-failure patients, whereas only one-third of the healthy controls was vitamin D deficient [83]. Two further studies among African Americans also showed a high prevalence of vitamin D deficiency in patients with heart failure [84, 85]. Interestingly, not all heart-failure patients with vitamin D deficiency show elevations in PTH levels but those with secondary hyperparathyroidism have more severe forms of heart failure [83–85]. In a cohort of over 3000 patients referred for coronary angiography 25(OH)D as well as 1,25(OH)D were inversely correlated with left ventricular dysfunction, New York Heart Association functional class and N-terminal pro-B type natriuretic peptide (NT-pro-BNP) [86]. In the National Health and Nutrition Examination Survey (NHANES), a population-based study in the US including 8351 persons, 25(OH)D levels were significantly reduced in patients with self-reported heart failure with the highest prevalence of vitamin D deficiency in patients suffering from both, coronary heart disease and heart failure [87]. Poor vitamin D status was also highly prevalent in patients with congestive heart failure undergoing evaluation for cardiac transplantation [88]. In that study, low 25(OH)D levels were associated with more severe congestive heart failure and with impaired exercise capacity. Moreover, in a cross-sectional analysis of 60 patients with mild to moderate heart failure, 25(OH)D levels were an independent predictor of the 6-min walk distance, which is a validated measure of aerobic capacity [89]. Results from a study among 150 patients with congestive heart failure and 150 age-, sex-, and race-matched controls showed that life-style factors associated with low 25(OH)D levels in earlier life (childhood, adolescence, and adulthood) including residence in large towns, low physical activity, and low frequency of summer holidays were significantly more common in heart-failure patients than in controls [90]. These data suggest that vitamin D deficiency is present before heart failure develops and this supports the hypothesis that low 25(OH)D levels are a cause and not only a consequence of myocardial dysfunction. Prospective studies addressing the associations of vitamin D levels and myocardial diseases are sparse. Among 3299 patients referred for coronary angiography, low 25(OH)D as well as low 1,25(OH)2D levels were prospectively and independent of cardiovascular risk factors associated with an increased risk of death due to heart failure and of sudden cardiac death

[86]. Furthermore, low 1,25(OH)2D concentrations were associated with increased mortality in 510 patients from a specialized heart center and were an independent predictor of death and the need for cardiac transplantation in 383 end-stage congestive heart-failure patients [91, 92]. In addition, low calcitriol levels were also associated with increased 1-year mortality in 171 cardiac transplant recipients [93]. In that latter study, calcitriol deficiency was associated with low 25(OH)D levels, renal impairment, and inflammation, which are all highly prevalent among the ageing population [93].

7.3 Vitamin D or 25(OH)D supplementation and myocardial function

Effects of 25(OH)D supplementation on left ventricular function were first studied in ten hemodialysis patients [94]. Five patients were treated for 8 months with 100 µg 25(OH)D daily and five patients served as the control group. At the end of the study, there was a significant improvement of left ventricular function with decreased end-diastolic and end-systolic diameters in patients receiving 25(OH)D treatment, whereas there was no significant change in echocardiagraphic parameters in the control group [94]. Schleithoff *et al.* performed a randomized double-blind placebo-controlled trial to evaluate the impact of vitamin D supplementation on survival and biochemical and hemodynamic parameters [95]. In total, 123 heart-failure patients were randomly assigned to either receive 2000 IU (50 µg) vitamin D3 daily or placebo and 500 mg calcium was supplemented in all study participants. After a treatment period of 9 months, interleukin-10, an anti-inflammatory cytokine suggested to be cardioprotective, was significantly reduced in the treatment group. TNF-α, a pro-inflammatory cytokine that may contribute to congestive heart failure, remained unchanged in the treatment group but increased significantly in the placebo group. Survival rates, left ventricular ejection fraction, and natriuretic peptides were not significantly affected by vitamin D supplementation in that study. In contrast, vitamin D supplementation with 2000 IU (50 µg) daily or 60 000 (1500 µg) IU monthly in 53 lactating women was associated with a significant decline in NT-proBNP levels [96]. That study was, however, lacking a placebo group and there was no significant correlation between the changes from baseline in 25(OH)D levels and NT-proBNP [96].

7.4 Active vitamin D treatment and myocardial function

The influence of 1,α-hydroxycholecalciferol on left ventricular function was examined in 12 hemodialysis patients. After 6 wk of daily intake of 1 µg 1,α-hydroxycholecalciferol, fractional fiber shortening increased by 8% and mean

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velocity of fiber shortening increased by 9% ($p < 0.05$ for both) [97]. In another study, 15 hemodialysis patients with secondary hyperparathyroidism received 2 µg calcitriol twice weekly intravenously after hemodialysis [98]. After a treatment period of 15 wk, there was a statistically significant decrease of interventricular wall thickness, left ventricular posterior wall thickness, and left ventricular mass. There were, however, no significant changes in cardiac output and blood pressure in that study, but the investigators noted a significant decrease in plasma renin activity, angiotensin II, and ANP levels after calcitriol treatment. In a further study among ten hemodialysis patients, 1–2 µg calcitriol was intravenously injected one to three times a week for a treatment period of 3–4.5 months [99]. There were no statistically significant changes in left ventricular dimensions and function before and after treatment. However, in a subgroup of five patients with the highest PTH levels, fractional shortening significantly increased and left ventricular end systolic diameter significantly decreased after calcitriol therapy. Decreases in left ventricular mass and reductions in the corrected maximal QT interval and the corrected QT dispersion were observed in 25 hemodialysis patients, who received 2 µg intravenous calcitriol weekly twice for 15 wk, whereas there was no effect in 25 age-, sex-, hemodialysis duration-, and BMI-matched controls [100]. In that study, however, myocardial contractility parameters did not significantly change. Furthermore, treatment of 15 hemodialysis patients with an active vitamin D compound (paracalcitol) for 12 months was associated with an improvement in diastolic function and a reduction of septal and posterior wall thickness, whereas there was no effect on left ventricular ejection fraction [71].

8 Clinical consequences and summary

We presented evidence that vitamin D deficiency is associated with an increased risk of myocardial diseases. This is in line with prospective population-based studies which showed that low 25(OH)D levels are an independent risk factor for cardiovascular events and cardiovascular mortality [101–103]. We are aware that discussing the causality of vitamin D deficiency for chronic diseases is a difficult task because sun exposure is the main determinant of vitamin D status and is usually inversely correlated with the severity of illness. However, several pathophysiological effects of vitamin D deficiency suggest that a poor vitamin D status might indeed be a causal factor in the pathogenesis of myocardial diseases. Interventional trials have largely but not consistently shown that vitamin D treatment improves myocardial structure and function, but further larger studies are still needed to draw a final conclusion about the causality of vitamin D deficiency for myocardial diseases.

Hence, the burning question arises how we should treat our patients until such large randomized controlled trials are published. In this context, it should be considered that vitamin D deficiency predicts all-cause mortality in the general population [104]. Moreover, a meta-analysis of vitamin D supplementation trials showed a significant reduction of total mortality in the treatment group [105]. We are of the opinion that our review provides a reasonable rationale to speculate that the link between vitamin D deficiency and mortality is partially driven by vitamin D effects on the myocardium. Besides, it is also important to point out that apart from bone and skeletal health, vitamin D exerts beneficial effects which are relevant for several chronic diseases [2–4, 106]. Given that vitamin D supplementation is relatively easy, cheap, and safe, we therefore recommend vitamin D supplementation for all vitamin D-deficient patients with or at high risk for myocardial diseases to maintain 25(OH)D levels of at least 30 ng/mL.

For practical use of vitamin D supplementation, it can be estimated that intakes of 1000 IU vitamin D (25 µg) daily increase 25(OH)D levels by approximately 10 ng/mL (25 nmol/L) [107]. Some authors recommend loading doses of vitamin D (*i.e.* 50 000 IU weekly once for 8 wk) before starting maintenance therapy [2, 3]. This latter loading dose is considered absolutely safe because vitamin D intoxication with hypercalcemia, renal damage, and vascular calcification is not observed until 25(OH)D levels are greater than 150 ng/mL [2, 108, 109]. Furthermore, it should also be noted that daily, weekly, or monthly dosing regimens can equally raise 25(OH)D levels [110]. Importantly, excessive sun exposure can produce up to 20 000 IU vitamin D *per* day but even short-term exposure to suberythemal doses of UV-B can effectively treat and prevent vitamin D deficiency [2, 106].

The authors have declared no conflict of interest.

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