Vitamin D and the heart

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Gardner DG, Chen S, Glenn DJ. Vitamin D and the heart. Am J Physiol Regul Integr Comp Physiol 305: R969–R977, 2013. First published September 11, 2013; doi:10.1152/ajpregu.00322.2013.—Vitamin D receptors (VDR) are found in cells throughout the cardiovascular system. A variety of experimental studies indicate that the liganded VDR may play an important role in controlling cardiac hypertrophy and fibrosis, regulating blood pressure, and suppressing the development of atherosclerosis. Some, but not all, observational studies in humans provide support for these experimental findings, raising the possibility that vitamin D or its analogs might prove useful therapeutically in the prevention or treatment of cardiovascular disease.

Vitamin D or, more specifically, its bioactive metabolite, 1,25(OH)2 vitamin D3 [1,25(OH)2D3], is a nuclear hormone receptor ligand, which is known to have profound effects on calcium and phosphate homeostasis. From the standpoint of mineral homeostasis, vitamin D’s primary targets are located in the small bowel, bone and, to a lesser extent, kidney. However, a growing literature indicates that vitamin D receptors (VDRs) are found in a variety of cells and tissues that are either loosely related or totally unrelated to mineral homeostasis. These include malignant breast, colon, and prostate cells and normal cells of the immune system, kidney, heart, and vasculature. The heart is particularly noteworthy in that 1) plasma 25(OH) vitamin D3 [25(OH)D3] levels have been shown to correlate inversely with the incidence of a variety of cardiac disorders, including ischemic heart disease and heart failure and 2) interventional studies in a variety of cell culture systems and animal models suggest that the liganded VDR can exert antihypertrophic activity in cardiac myocytes in vitro and in vivo. The present work will review the recent literature supporting a role for the liganded VDR and, inferentially, vitamin D in the regulation of cardiac structure and function.

Experimental Studies

Expression of VDR and 1α-hydroxylase genes in heart. Early studies showed that the VDR gene is expressed in the heart (15, 48, 50, 63, 78), where it localizes to both the cardiac myocyte (19, 58) and fibroblast (15). VDR expression in both cell types increases following exposure to hypertrophic stimuli in vitro, as well as in hypertrophied hearts in vivo (15). Cardiac ventricular tissue also expresses the 1α-hydroxylase (Cyp27B1) implying that it has the capacity to produce 1,25(OH)2D3, the cognate ligand of the VDR (15), from circulating 25(OH)D3. Ventricular tissue also expresses the 25 hydroxyvitamin D-24 hydroxylase, Cyp24A1, which is responsible for producing inactive vitamin D metabolites (15). Data gathered in our laboratory suggest that the liganded VDR possesses antihypertrophic activity in the heart (see below), implying that this hormone-ligand system may operate in a negative feedback loop that regulates the magnitude and duration of the hypertrophic response.

Role of the VDR in cardiac development. Experimental studies have shown that the VDR is linked to quail cardiac atrial development (79, 80). The slow myosin heavy-chain 3 gene (MyHC3), an atrial chamber-specific gene, has been used as a marker to investigate atrial and ventricular lineage specification (21, 80, 81, 97). Slow MyHC3 is initially expressed throughout the early tubular heart. While atrial chamber-restricted expression is maintained at a constant level, down-regulation of ventricular slow MyHC3 gene expression during chamber formation (80) leads to atrial specification. Expression of the slow MyHC3 gene is achieved through the positive effects of a GATA factor-binding element in the cardiac atria and the negative effects of a vitamin D response element (VDRE) in the cardiac ventricle (80). The liganded VDR inhibits slow MyHC3 expression through a process that involves an Iroquois family homeobox gene, Irx4. Expression of Irx4 is restricted to the ventricular myocyte throughout heart development (79). Downregulation of the slow MyHC3 gene by Irx4 requires the VDRE element. Of note, Irx4 does not bind directly to the VDRE but forms an inhibitory complex through interaction with retinoid X receptor-alpha (RXRα) in the heterodimeric VDR-RXRα complex.

Despite VDR’s well-defined role in avian heart development, the role of the VDR in mammalian heart development remains undefined; however, atrial and ventricular specification appears to be normal in the VDR−/− mouse (37), implying that if it does play a role, it may be redundant with other developmental regulatory systems in the heart.

Relationship of the liganded VDR to hypertrophy of the rodent heart. Using the neonatal rat cardiac ventricular myocyte system, we have documented that the liganded VDR suppresses myocyte hypertrophy in vitro. We have shown that...
1,25(OH)_2D_3, as well as a number of the less calcemic analogs, act in both atrial (92) and ventricular (93) myocytes to inhibit the activation of phenotypic markers associated with hypertrophy. The vasoactive peptide endothelin (ET) promotes changes in fetal gene expression and promoter activity, cell size, and protein synthesis (93) that parallel changes that occur with hypertrophy in vivo. These changes are at least partially reversed by 1,25(OH)_2D_3 or its less calcemic analogs (i.e., oxacalcitriol). Similar findings have been reported by others using cultured cardiac HL-1 myocytes (48), where 1,25(OH)_2D_3 was found to reduce cell proliferation and atrial natriuretic peptide (ANP) gene expression, a marker of the hypertrophy-sensitive fetal gene program. We have characterized the structural requirements for VDR’s antihypertrophic activity in vitro using human (h)ANP gene promoter activity as a surrogate marker of hypertrophy. Inhibition of this promoter requires an intact DNA-binding and ligand-binding domain of the VDR (17). It also requires the capacity of the liganded VDR to heterodimerize with the RXR (12) and preservation of the activation domain of the receptor, particularly in the area surrounding the coactivator binding pocket (13). Intriguingly, the same residues that are critical for association with coactivator proteins and triggering an increase in target gene transcription, also play a role in mediating the inhibitory effect on hANP promoter activity (15).

Simpson’s group using a vitamin D-deficient rat model was among the first to report a connection between vitamin D status and cardiovascular function (86). They found that when they provided Sprague-Dawley rats a low-vitamin D diet for more than 2 wk, the rats developed transient hypertension and significant hypocalcemia. Despite the fact that the rats were maintained on the same vitamin D-deficient diet, by 8 wk (and extending to 18 wk), there was no difference in blood pressure between the vitamin D-deficient group and control animals (86). Weishaar et al. (85) went on to find a significant increase in heart weight-to-body weight ratio, a reliable index of cardiac hypertrophy, in rats after 9 or 18 wk of vitamin D deficiency. They found that the hypertrophy was not accompanied by loss of soluble cardiac enzymes (e.g., creatine phosphokinase) or myocardial edema (85). It was not reversed by restoration of serum calcium to normal, nor was it prevented by normalization of serum calcium levels during the period of vitamin D deficiency. Microscopic analysis of the ventricular sections demonstrated that myofibrils from the vitamin D-deficient rats were smaller than those in vitamin D-sufficient rats, and there was a significant increase in the amount of extracellular matrix protein (85). Independent studies demonstrated that vitamin D-deficient cardiac hypertrophy is associated with myocyte hyperplasia and increased expression of the proto-oncogene c-myc (49), but the precise mechanism underlying cardiac hypertrophy in these vitamin D-deficient rats remains unknown. Extending this antihypertrophic activity to a developmental paradigm, Gezmish et al. (24) have reported that maternal vitamin D deficiency in Sprague-Dawley rats led to cardiac hypertrophy in 4-wk-old offspring. This was accompanied by an increase in cardiomyocyte number and size (24).

Both the VDR and the 1-α(OH)ase or VDR gene knockout mice consistently demonstrate cardiac hypertrophy, there is relatively little information dealing with cardiac function in these models. Zhou et al. (100) have shown impaired systolic function in 1-α(OH)ase gene knockout mice that normalized following 1,25(OH)_2D_3 administration. Paradoxically, cardiac myocytes isolated from 6-mo-old VDR knockout mice have shown accelerated rates of contraction and relaxation compared with age-matched wild-type controls (73). The same study showed that acute treatment of wild-type cardiac myocytes with vitamin D accelerates myocyte relaxation. Subsequent studies suggested that the vitamin D effect may be dependent upon an interaction between the VDR and caveolin-3 in the T-tubules and sarcolemmal membrane, operating through a rapid, nongenomic pathway (99).

**Relationship of liganded VDR to profibrotic activity in the rodent heart.** Vitamin D regulates myocardial extracellular matrix integrity through its effects on the expression of matrix metalloproteinases (MMPs), as well as tissue inhibitors of metalloproteinases (TIMPs) (84). Imbalance in the expression of MMPs and TIMPs in the myocardium is associated with the initiation and progression of both diastolic and systolic dysfunction in the heart (6). Neonatal rat cardiac fibroblasts express the VDR gene (15), and this expression is increased following exposure to the prohypertrophic/profibrotic agonist ET (15). Interestingly, pretreatment with 1,25(OH)_2D_3 leads to a reduction in preproendothelin gene expression (~20% decrease in the VDR knockout mice. The reasons behind these seemingly discrepant results (37, 62) remain undefined. Chen and coworkers have recently documented that isolated deletion of the VDR within the cardiac myocyte leads to cardiac hypertrophy and activation of the fetal gene program without increased cardiac renin gene expression (16).

While all studies with the 1-α(OH)ase or VDR gene knockout mice consistently demonstrate cardiac hypertrophy, there is relatively little information dealing with cardiac function in these models. Zhou et al. (100) have shown impaired systolic function in 1-α(OH)ase gene knockout mice that normalized following 1,25(OH)_2D_3 administration. Paradoxically, cardiac myocytes isolated from 6-mo-old VDR knockout mice have shown accelerated rates of contraction and relaxation compared with age-matched wild-type controls (73). The same study showed that acute treatment of wild-type cardiac myocytes with vitamin D accelerates myocyte relaxation. Subsequent studies suggested that the vitamin D effect may be dependent upon an interaction between the VDR and caveolin-3 in the T-tubules and sarcolemmal membrane, operating through a rapid, nongenomic pathway (99).
crease in preproendothelin mRNA levels relative to vehicle-treated controls; Gardner, DG, unpublished data) in cultured cardiac fibroblasts. This suggests a negative feedback loop in which activation of pathological hypertrophy/fibrosis, accompanied by an increase in preproendothelin gene expression, leads to an increase in VDR expression. VDR, in turn, feeds back to suppress ET gene expression and, by inference, the prohypertrophic and profibrotic activities that it promotes. As noted above, rats with vitamin D deficiency develop cardiac hypertrophy in association with interstitial fibrosis (85). VDR gene knockout mice display an increase in myocardial interstitial fibrosis (57) with increased expression of cardiac MMP-2 and MMP-9 and reduced expression of TIMP-1 and TIMP-3, suggesting that vitamin D plays an important role in suppressing remodeling activity in the myocardium. This is consistent with a study in humans, which showed an inverse correlation between circulating MMP-9 levels and 25(OH)D3 concentrations (71).

**Relationship of the liganded VDR to atherosclerosis.** Atherosclerotic involvement of the coronary arteries represents the leading cause of cardiovascular disease worldwide. Recent experimental studies suggest that vitamin D may impact the development of atherosclerotic disease.

Oh et al. (51), using macrophages from obese, diabetic, hypertensive patients with vitamin D deficiency, showed that 1,25(OH)2D3 suppressed foam cell formation by reducing acetylated or oxidized low-density lipoprotein (LDL) cholesterol uptake in diabetic but not in nondiabetic subjects. This resulted from downregulation of JNK activity, improved insulin signaling, reduced oxidized LDL-derived cholesterol uptake, as well as suppression of macrophage endoplasmic reticulum (ER) stress and promotion of an antiatherogenic monocye/macrophage phenotype (51, 59). More recently, Szeto et al. (66) showed that VDR deficiency (i.e., VDR/−/− genetic background) accelerated the atherosclerotic process in the low-density lipoprotein receptor-deficient (LDLR/−/−) mouse. This effect appeared to operate through a mechanism involving suppression of the renin-angiotensin system in the macrophage cell.

Weng et al. (87) have shown that vitamin D-deficient mice fed a high-fat diet had elevated plasma renin levels, increased systolic and diastolic blood pressure, and a 2–8-fold greater incidence of atherosclerosis in the aortic arch, thoracic aorta, and abdominal aorta compared with vitamin D-sufficient mice. This was accompanied by increased macrophage infiltration into atherosclerotic plaques. Of note, treatment of vitamin D-deficient mice on the high-fat diet with either paricalcitol or doxercalciferol for 2 mo displayed reduced natriuretic peptide gene expression and a 65–80% reduction in left ventricular (LV) wall thickness (34). When either of these vitamin D analogs was paired with losartan, reversal of hypertrophy was virtually complete. 1,25(OH)2D3 treatment of spontaneously hypertensive-heart failure-prone (SHR-HFP) rats, fed a high-salt diet, resulted in reduced myocyte hypertrophy, left ventricular diameter, and improved stroke volume (40).

Mice subjected to transverse aortic constriction develop significant cardiac hypertrophy and fibrosis. Noteworthy, treatment with paricalcitol failed to reverse hypertrophy. However, it did reduce cardiac ANP gene expression, as well as expression of a number of extracellular matrix proteins (i.e., fibronectin, collagen III, and TIMP-1), and it was successful in reducing fibrosis and improving indices of LV contraction and relaxation (44). An intriguing study from Gupta et al. (27) showed that vitamin D deficiency induces cardiac hypertrophy, as well as inflammation in epicardial fat, in hypercholesterolemic swine. Noteworthy, the epicardial inflammation was associated with diminished suppressor of cytokine signaling 3 gene expression.

In uremic rats, which express low levels of the 1α(ΩH)ase in the kidney, treatment with paricalcitol prevented left ventricular hypertrophy (47).

Collectively, these findings are consistent with the notion that 1,25(OH)2D3, as well as its less hypercalcemic analogs, can reduce cardiac hypertrophy in these well-defined experimental models. Table 1 summarizes the studies supporting the antihypertrophic activity of the VDR ligands.

1,25(OH)2D3 and its analogs suppress cardiac fibrosis. Cardiac fibrosis is frequently seen together with cardiac hypertrophy, and it plays a major role in contributing to the dysfunctional state seen in advanced cardiomyopathy. 1,25(OH)2D3 has been shown to possess both anti-inflammatory (20, 95) and
antifibrotic (98) activity in different experimental models. However, 1,25(OH)2D3 and its analogs have demonstrated inconsistent results in the suppression of cardiac fibrosis. Koleganova et al. (33) showed that treatment with subhypercalcemic doses of 1,25(OH)2D3 reduced interstitial fibrosis of the heart in subtotally nephrectomized rats. A second group showed that paricalcitol prevented left ventricular hypertrophy, as well as myocardial and perivascular fibrosis in uremic rats (47). Interestingly, these findings have been linked to upregulation of VDR gene expression, reduced myocardial proliferating cell nuclear antigen labeling (an index of cellular proliferative activity) and reduced myocardial oxidative stress (57).

In an acute myocarditis-induced, extensive fibrosis model, treatment of infected, susceptible mice with the vitamin D analog ZK 191784 resulted in a reduction in myocardial expression of osteopontin, metalloproteinase-3, TIMP-1, urinary plasminogen activator, and procollagen-Iα (65), all of which have been associated with fibrosis. An independent study showed that paricalcitol reversed interstitial fibrosis and extracellular matrix protein expression in an aortic constriction model of cardiac hypertrophy (44). By way of contrast, Repo et al. (58) reported that paricalcitol aggravated cardiac perivascular fibrosis in rats with renal insufficiency, a model that is typically associated with low 1,25(OH)2D3 levels. In another study, while treatment with 1,25(OH)2D3 led to decreased cardiac hypertrophy in the SHR-HFP rat, there was no significant reduction in myocardial collagen content (40). Collectively, the experimental data have provided mixed results (Table 1). While these studies have raised the possibility that vitamin D possesses antifibrotic activity in the heart, definitive proof of this hypothesis has proven difficult to demonstrate.

### Clinical Studies

**Cardiovascular disease.** A growing literature suggests an association between low 25 (OH) D3 levels and the risk of cardiovascular disease (CVD) and, more specifically, ischemic cardiac disease. However, this area remains highly controversial with a number of studies supporting (4, 9, 25, 30, 35, 43, 46, 64, 82, 83, 101) and questioning this association (24, 38, 54, 64, 74, 75, 98). Analysis of a cross section of the NHANES III population revealed an association between vitamin D deficiency [25(OH)D3 < 20 ng/ml] and coronary artery disease (CAD), defined as self-reported angina, myocardial infarction (MI) or stroke with an odds ratio of 1.20 (95% CI: 1.01–1.36) (45). Similar findings were reported in the Health Professionals Follow-Up Study. In that study, the relative risk (RR) for nonfatal MI or fatal CVD was 2.42 (95% CI 1.53–3.84) in those with vitamin D deficiency (25). Analysis of more than 100,000 participants from the Nurses’ Health Study and the Health Professionals Follow-Up Study showed that a higher total vitamin D intake (from foods and supplements) was associated with a decreased risk of CVD, including CAD and stroke, although the effect appeared to be confined to men (64).

In the Framingham Offspring Study the rate of cardiovascular events was also higher in those patients with 25(OH)D3 levels <15 ng/ml, although the association was confined to patients with hypertension, RR 2.13, (95% CI: 1.30–3.48). A study of more than 10,000 men and women from the Danish general population compared cardiovascular risk in individuals with plasma 25(OH)D3 levels at 1–4th percentile with those at the 50–100th percentile (9). The multivariable adjusted risk was increased by 40% for ischemic heart disease, 64% for myocardial infarction, 81% for stroke, and 18% for total cardiovascular disease.

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDR knockout mice</td>
<td>N/A</td>
<td>Cardiac hypertrophy, increased myocyte size, and cardiac fibrosis</td>
<td>16, 94</td>
</tr>
<tr>
<td>1α-hydroxylase knockout mice</td>
<td>Captopril</td>
<td>Reduced cardiac hypertrophy and myocyte size</td>
<td>100</td>
</tr>
<tr>
<td>1α-hydroxylase knockout mice</td>
<td>N/A</td>
<td>Cardiac hypertrophy, increased myocyte size, and impaired systolic function</td>
<td>44</td>
</tr>
<tr>
<td>Mice with transverse aortic constriction</td>
<td>N/A</td>
<td>Cardiac hypertrophy and fibrosis</td>
<td>16, 94</td>
</tr>
<tr>
<td>Mice with transverse aortic constriction</td>
<td>Paricalcitol</td>
<td>No effect on hypertrophy, but reduced fibrosis and improved cardiac function</td>
<td>14</td>
</tr>
<tr>
<td>ANG II-treated mice</td>
<td>N/A</td>
<td>Cardiac hypertrophy and fibrosis</td>
<td>16, 94</td>
</tr>
<tr>
<td>ANG II-treated mice</td>
<td>ZK191784</td>
<td>Reduced fibrosis and expression of fibrotic markers</td>
<td>16, 94</td>
</tr>
<tr>
<td>Vitamin D-deficient hypercholesterolemic swine</td>
<td>N/A</td>
<td>Cardiac hypertrophy and epicardial inflammation</td>
<td>85</td>
</tr>
<tr>
<td>Vitamin D-deficient rats</td>
<td>N/A</td>
<td>Cardiac hypertrophy, increased myofibril size, and matrix protein production</td>
<td>24</td>
</tr>
<tr>
<td>Maternal vitamin D deficiency in rats</td>
<td>N/A</td>
<td>Cardiac hypertrophy, increased cardiomyocyte number and size</td>
<td>34, 40, 56</td>
</tr>
<tr>
<td>SHR/SHR-HFP</td>
<td>Paricalcitol or Doxercalciferol or Losartan</td>
<td>Reduced hypertension and improved cardiac function, but no change in collagen content</td>
<td>33, 47, 58</td>
</tr>
<tr>
<td>Uremic rats</td>
<td>N/A</td>
<td>Cardiac hypertrophy and fibrosis, increased LV diameter and stroke volume</td>
<td>34, 40, 56</td>
</tr>
<tr>
<td>Dahl salt-sensitive rats</td>
<td>Paricalcitol or Losartan</td>
<td>Partially reversed cardiac hypertrophy and fibrosis</td>
<td>5, 7, 18</td>
</tr>
</tbody>
</table>

VDR, vitamin D receptor; SHR, spontaneously hypertensive rats; HFP, heart failure-prone.
ventricular hypertrophy, cardiomyopathy, and heart failure. Given the antihypertrophic activity that VDR ligands have demonstrated in the preclinical studies, it was an obvious move to determine whether the same antihypertrophic activity was operative in human subjects (i.e., a more selective segment of CVD). Even here, results have been mixed. In a longitudinal study of 256 subjects of the Hoorn Study, a population-based cohort in the Netherlands, low-serum 25(OH)D\(_3\) levels were associated with higher left ventricular mass index (LVMI) after 8 yr of follow up, but only in subjects without prior CVD and in subjects with low kidney function (76). The effect in the latter group was attenuated after adjustment for parathyroid hormone levels, leading the authors to conclude that no strong association exists between 25(OH)D\(_3\) levels and myocardial structure and function. In the PIVUS study, another community-based study, of 870 participants without prior CVD, impaired left ventricular end-systolic dimension, fractional shortening, and ejection fraction were all associated with low 25(OH)D\(_3\) levels at baseline, but the latter were not associated with changes in LV geometry or function over the ensuing 5-yr period (22). A third population-based study from the Baltimore Longitudinal Study of Aging found that in a group of largely vitamin D-sufficient subjects without CVD, left ventricular geometry was optimal at intermediate 25(OH)D\(_3\) levels and deteriorated at the extremes of plasma 25(OH)D\(_3\) levels (2). In contrast, in a more recent study of an older Icelandic population, 25(OH)VD\(_3\) was not associated with LV mass or thickness as measured by MRI (77). Interestingly, serum PTH was associated with both greater LV mass and decreased function in this study.

CVD is the leading cause of death in patients with chronic kidney disease (27, 28), and some element of cardiac hypertrophy is present in most patients with advanced kidney disease. Park et al. (52) were the first to demonstrate that administration of 1,25(OH)\(_2\)D\(_3\) to hemodialysis patients with secondary hyperparathyroidism resulted in a dramatic reduction of left ventricular hypertrophy, as well as reduction in plasma renin, ANG II, and ANP levels. These changes correlated strongly with reductions in plasma parathyroid hormone (PTH) levels. Similar findings of antihypertrophic effects of vitamin D in renal failure patients have been reported by two other groups (36, 42). It is notable that in the study from Lemmilä et al. (36), the reductions in ventricular hypertrophy were confined to those individuals with elevated PTH levels (36). However, Bucherles et al. (10) showed that hemodialysis patients with low vitamin D levels, displayed findings of concentric left ventricular hypertrophy and a high level of inflammation (high sensitivity CRP, IL-6, and serum albumin were used as markers), even in the absence of high immunoreactive PTH levels (<300 pg/ml). Cholecalciferol supplementation in a subset (30 subjects) of these patients suppressed levels of the inflammatory markers and left ventricular hypertrophy (14). Thadhani and the PRIMO investigators (69) carried out a multinational, double-blind, randomized, placebo-controlled trial among 227 patients with chronic kidney disease, mild-to-moderate LV hypertrophy and preserved LV ejection fraction. Study participants received paricalcitol or placebo over a 48-wk period. They found that treatment with paricalcitol reduced PTH levels effectively, but there was no effect on left ventricular mass index, a metric of cardiac hypertrophy, or diastolic function assessed by echocardiography. Noteworthy, hypercalcemia was more common in the paricalcitol- vs. placebo-treated group. Follow-up analysis of 196 patients from this same group showed that paricalcitol did promote a reduction in left atrial volume index and attenuated the rise in B-type natriuretic peptide (BNP) levels (68). A summary of these studies is presented in Table 2.

Vitamin D deficiency has been strongly linked to heart failure in a variety of observational studies (38), although its causal relationship to heart failure remains highly controversial (1). Heart failure has been reported in infants with rickets (3, 11, 28, 31, 39), although, in this setting, profound hypocalcemia may contribute to the observed cardiac dysfunction. In one

Cardiac hypertrophy, cardiomyopathy, and heart failure.
study, vitamin D supplementation (vs. placebo) in 80 infants with congestive heart failure (71), all of whom had baseline 25(OH)D3 levels that were below the lower end of the reference range, led to a significant improvement in heart failure score, several echocardiographic indices of myocardial function, including left ventricular ejection fraction, and the serum cytokine profile (61). It is noteworthy that patients with hereditary vitamin D-resistant rickets, who harbor mutations of the VDR gene, showed no abnormalities in circulating plasma renin activity, angiotensin-converting enzyme activity, ANG II, or aldosterone levels; nor was there evidence of hypertension or echocardiographic pathology (72).

In cross-sectional studies, vitamin D deficiency has been linked to the presence of heart failure (19) (53). In a study drawn from the NHANES III database, vitamin D insufficiency, defined as 25(OH)D3 < 30 ng/ml was associated with an OR of 1.7 (95% CI: 0.87–3.32) for heart failure and 3.52 (95% CI: 0.87–3.32) for heart failure and 3.52 (95% CI: 0.87–3.32) for heart failure (88). Interestingly, a recent report linked a functional polymorphism in the 1-α(OH)ase gene, the rate-limiting step in the synthesis of active 1,25(OH)2D3, with increased risk for heart failure (89). A short-term randomized, controlled trial examining the effects of vitamin D supplementation (2.500 IU/day) on endothelial function, arterial stiffness, or inflammation—indirect measures of cardiovascular health—showed no effect of the supplementation (23). A similar small randomized study comparing calcium and vitamin D supplementation showed statistically significant reductions in TNF-α and increases in the anti-inflammatory cytokine IL-10 in the vitamin D treatment group; however, no change in LV function was observed (60). In a study from Zia et al. (113), a small group of 14 African-American subjects with vitamin D deficiency [25(OH)D3 levels, 14.4 ± 1.3 ng/ml at entry] and dilated cardiomyopathy with reduced ejection fraction (EF) (<35%) were treated with oral ergocalciferol for 8 wk followed by a maintenance phase of cholecalciferol plus calcium carbonate supplementation for 6 wk. Treated patients demonstrated increased 25(OH)D3 levels, reduced PTH, and plasma 8-isoprostane (a biomarker of lipid peroxidation) levels and improvement of EF (from 24.3 ± 1.7% to 31.3 ± 4.3%). Gotsman et al. (26) studied more than 3,000 heart failure patients in an Israeli health mainte-

### Table 2. Clinical studies of vitamin D effects on cardiac hypertrophy

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>n</th>
<th>Primary Measure</th>
<th>Outcomes</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort van Ballegooijen et al.</td>
<td>Older age</td>
<td>256</td>
<td>25(OH)D3</td>
<td>Increased LVMI</td>
<td>76</td>
</tr>
<tr>
<td>Fall et al.</td>
<td>Older age</td>
<td>870</td>
<td>25(OH)D3</td>
<td>Increased LVESD, FS, EF</td>
<td>22</td>
</tr>
<tr>
<td>Ameri et al.</td>
<td>Subjects without CVD</td>
<td>711</td>
<td>25(OH)D3</td>
<td>Increased LVMI, LV thickness</td>
<td>2</td>
</tr>
<tr>
<td>van Ballegooijen et al.</td>
<td>Older age</td>
<td>969</td>
<td>25(OH)D3</td>
<td>No association detected with LV</td>
<td>77</td>
</tr>
<tr>
<td>Interventional</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Park et al.</td>
<td>ESRD with secondary HPT</td>
<td>Treatment (15) Controls (10)</td>
<td>Calcitriol treatment</td>
<td>Decreased IVW, LVPW, LV thickness, and LVM</td>
<td>52</td>
</tr>
<tr>
<td>Lemmilä et al.</td>
<td>ESRD</td>
<td>10</td>
<td>Calcitriol treatment</td>
<td>Decreased IVW, LVPW, LV thickness, and LV dimension</td>
<td>36</td>
</tr>
<tr>
<td>Bucharles et al.</td>
<td>ESRD</td>
<td>30</td>
<td>Cholecalciferol treatment</td>
<td>Decreased LVM</td>
<td>10</td>
</tr>
<tr>
<td>Matias et al.</td>
<td>ESRD</td>
<td>158</td>
<td>Paricalcitol treatment</td>
<td>Decreased LVM</td>
<td>42</td>
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<tr>
<td>Randomized control</td>
<td>Thadhani et al.</td>
<td></td>
<td>Paricalcitol or placebo treatment</td>
<td>No change in LVMI or diastolic function</td>
<td>69</td>
</tr>
</tbody>
</table>

LV, left ventricular; LVMI, left ventricular mass index; LVESD, left ventricular end systolic volume; LVEF, left ventricular ejection fraction; FS, fractional shortening; EF, ejection fraction; IVW, intraventricular wall; LVPW, left ventricular posterior wall; HPT, hyperparathyroidism; ESRD, end-stage renal disease; CKD, chronic kidney disease; 25(OH)D3, 25-hydroxyvitamin D3; CVD, cardiovascular disease.

- **Fig. 1.** A: Vitamin D receptor (VDR) binds retinoid X receptor (RXR) at the vitamin D receptor element (VDRE) to regulate gene expression. B: vitamin D deficiency and/or VDR gene deletion affects the heart, vasculature, and immune system, which may, in turn, contribute to the development of heart failure, hypertension, and increased atherosclerosis.
nance organization and established that vitamin D deficiency was an independent predictor of mortality in patients with heart failure (HR 1.52; CI 1.21–1.92; P < 0.0001) and in the control group (HR 1.91; CI 1.48–2.46; P < 0.00001). Intriguingly, vitamin D supplementation in 1,783 patients was independently associated with reduced mortality in the heart failure patients (HR 0.68; CI 0.54–0.85; P < 0.0001). Heart failure is also associated with skeletal myopathy that can lead to poor exercise tolerance. Witham et al. (90) showed that treatment of elderly vitamin D-deficient, heart failure patients with vitamin D$_2$ for 10 wk failed to improve functional capacity or quality of life in this patient population. Quality of life was, in fact, slightly, but significantly, worse in the vitamin D-supplemented group. In aggregate, data gathered to date indicate that there is an inverse relationship between 25(OH)D levels and the presence of heart failure; however, studies carried out to date have not been able to demonstrate a palliative effect of vitamin D supplementation on the various clinical parameters associated with heart failure.

Conclusion

A growing body of data suggests that vitamin D and VDR, its cognate receptor, play an important role in the regulation of cardiovascular homeostasis. The ability of this hormonal system to inhibit the renin-angiotensin system, control blood pressure, inhibit cellular proliferation and hypertrophy, reduce fibrosis, and suppress immune function suggests a variety of plausible mechanisms that could contribute to these palliative effects (Fig. 1). However, the cardioprotective “hypothesis” has not been without controversy and results to date have been inconclusive. While the preponderance of evidence gathered from the experimental studies have supported the hypothesis, and the clinical epidemiological studies have established a clear link between low vitamin D levels and CVD, it remains to be determined whether the latter are mechanistically linked and, inferentially, whether CVD is treatable with supplemental vitamin D. We anxiously await the results of clinical trials, currently under way, to help define the role of vitamin D and its analogs in the prevention and treatment of CVD.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

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Review

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