Vitamin D and Its Effects on the Heart

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Clinical Case Scenario

A 67 year-old gentleman with hypertension, hyperlipidemia, heart failure with preserve ejection fraction (left ventricular ejection fraction 65%), symmetric left ventricular hypertrophy, chronic kidney disease Stage 3B presents in follow up of his multiple cardiovascular issues. He has a normal serum calcium level and his parathyroid hormone is within target range. Would this patient benefit of vitamin D treatment and if so, which form and dose of vitamin D?

Introduction

Although primarily involved in bone and mineral metabolism, both 25-hydroxy vitamin D (25[OH]D) and its active hormonal form (1,25-dihydroxy vitamin D [1,25$(OH)_2$D]) have been associated with cardiovascular effects [1]. The very high prevalence of vitamin D insufficiency or deficiency, commonly defined as <30 and <20 ng/mL [1], respectively, makes this association especially important to unravel. Since cardiovascular disease is the number one cause of mortality in the United States, the topic is particularly relevant to disease prevention strategies aimed at improving public health [2–5].

Although the vitamin D receptor (VDR) is known to be expressed in cardiomyocytes and fibroblasts [6, 7], the role of supplementation with vitamin D and/or its analogs on cardiac function has yet to be elucidated. Epidemiological data to date are inconclusive [8, 9] and randomized studies are scarce (Table 11.1 provides a summary of longitudinal studies evaluating 25(OH)D associations with cardiovascular outcomes). Furthermore, most studies aimed at establishing a link between vitamin D and cardiovascular outcomes have focused on total circulating levels of 25(OH)D, but important new information suggests that the fraction of 25(OH)D that is not bound to its specific high-affinity carrier protein may be a more appropriate indicator of vitamin D status [22]. In the current chapter we will focus on the biological pathways by which vitamin D may play a role on cardiac function as well as observational and randomized studies of vitamin D supplementation in cardiovascular disease.

Observational Studies

Observational studies can assess the exposure (25(OH)D) and outcome (i.e. cardiovascular diseases) at the same point in time (cross-sectional) or they can assess the exposure and then outcome occurring after the exposure is measured (longitudinal). The cross-sectional studies are faster, cheaper and allow us to evaluate the relationship between the variables of interest at a given time point. However, the cross-sectional studies do not provide any information regarding the timing of the events as the longitudinal studies do. All observational studies are subject to confounding, which can be best minimized by randomization to intervention or placebo. In this section we will evaluate the data supporting the effects of vitamin D in cardiovascular diseases by study type.

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Table 11.1 Summary of longitudinal studies evaluating 25(OH)D associations with cardiovascular outcomes

Study	Population	N	Male (%)	Age (years)	Baseline 25(OH)D (ng/mL)	Follow-up (years)	Exposure ([25(OH)D] in ng/mL)	Outcome	Association
Wang et al. [10]	Community-dwelling adults, no previous CVD	1,739	45	59	19.7	5.4	25(OH)D <15 vs. 25(OH)D ≥15	MI, angina, Stroke, TIA, HF	HR 1.62 (95 % CI 1.11–2.36)
Giovannucci et al. [11]	Men between 40 and 75, no current CVD	18,225	100	64	23.6	10	25(OH)D <15 vs. 25(OH)D >30	Nonfatal MI, fatal CHD	RR 2.42 (95 % CI 1.53–3.84)
Sun et al. [12]	Community-dwelling adults, free of CVD and cancer	118,864	38	n/a	n/a	21	Intake of 25(OH)D ≥600 IU/day vs. intake <100 IU/day	CHD and stroke	RR 0.84 (95 % CI 0.72, 0.97) for men; RR 1.02 (95 % CI 0.89, 1.17) for women
Brøndum-Jacobsen et al. [13]	Community dwelling adults without vitamin D fortified-diet.	10,170	44	57	17.6	29	25(OH)D <6 vs. 25(OH)D >24	Myocardial infarction	HR 1.64 (95 % CI 1.25–2.14)
Dobnig et al. [14]	Patients referred for coronary angiography	3,258	Stratified	62	Stratified	8	25(OH)D 13.3 vs. 25(OH)D 28.4	Cardiovascular death	HR 1.82 (95 % CI 1.29–2.58)
Wolf et al. [15]	Incident dialysis patients	825	53	63	21	90 days	25(OH)D <10 vs. 25(OH)D >30	Cardiovascular death	OR 1.9 (95 % CI 1.0–3.4)
van Ballegooijen et al. [16]	Community-dwelling older adults	256	Stratified	67	23	8	25(OH)D <14 vs. 25(OH)D >32	Change in LVMI	RC 9.9 (95 % CI 3.3, 16.6)
Fall et al. [17]	Elderly subjects, no previous heart disease	870	48	70	23.2	5	Baseline 25(OH)D	LVMI	B = –0.035 (95 % CI –0.915, 0.846)
Liu et al. [18]	Patients with heart failure	548	61	74	14.6	1.5	Decrease in [25(OH)D] by 4	HF hospitalization or death	HR 1.09 (95 % CI 1.00–1.16)
Pilz et al. [19]	Patients referred for coronary angiography	3,299	Stratified	Stratified	Stratified	8	25(OH)D <10 vs. 25(OH)D ≥30	HF or sudden cardiac death	HR 2.84 (95 % CI 1.20–6.74)
Forman et al. [20]	Community-dwelling adults without hypertension	1,809	Stratified	Stratified	Stratified	4	25(OH)D <15 vs. 25(OH)D ≥30	Incidence of hypertension	RR 3.18 (95 % CI 1.39 to 7.29)
Margolis et al. [21]	Postmenopausal women without hypertension	4,863	–	66	Stratified	7	Quartiles of 25(OH)D	Incidence of hypertension	Change in SBP or DBP by 25(OH)D quartile was not significantly different at any point in time

Note: *HR* hazard ration, *RR* relative risk, *OR* odds ration, *RC* regression coefficients, *CI* confidence interval, *IU* international units, *CV* cardiovascular, *CVD* cardio vascular disease, *CHD* coronary heart disease, *MI* myocardial infarction, *TIA* transient ischemic attack, *HF* heart failure, *LVMI* left ventricular mass index, *HF* heart failure, *SBP* systolic blood pressure, *DBP* diastolic blood pressure

Cross-Sectional Studies

A growing body of literature suggests that vitamin D insufficiency or deficiency may be associated with an increased risk of cardiovascular disease. However, the evidence thus far is inconclusive and subject to debate. Early studies reported a higher prevalence of hypertension in countries located in northern latitudes where populations are exposed to less sunlight than in countries nearer the equator [23, 24]. Similarly, large population studies such as the Third National Health and Nutrition Examination Survey (NHANES) identified cardiovascular risk factors (elevated blood pressure, plasma glucose and cholesterol) associated with lower 25(OH)D levels [25]. In contrast, an analysis of the Longitudinal Aging Study Amsterdam that included 1,205 participants patients older than 65 year-old did not find any association between 25(OH)D levels and blood pressure [26].

A second analysis of the NHANES database conducted by Melamed et al. included 13,331 free-living adults in the United States. These authors reported an increase in coronary artery disease (CAD) and stroke in patients with total 25(OH)D levels <20 ng/mL vs. those with 25(OH)D of >32 ng/mL [odds ratio (OR) 1.2 (95 % confidence interval (CI): 1.01–1.36)] [27]. Others have described an association between low 25(OH)D (<30 ng/mL) and heart failure (OR 1.7 [95 % 0.87–3.32]) in the same NHANES cohort [28]. In cases of extreme vitamin D deficiency (<15 ng/mL) in children (rickets), severe cardiomegaly and heart failure have been reported [29–33] Interestingly, patients with Vitamin D–resistant rickets as a result of congenital mutations in the VDR mostly die from cardiovascular diseases, but show no abnormalities in angiotensin converting enzyme activity, or in levels of angiotensin II and aldosterone [34].

Longitudinal Studies

Ischemic heart disease has been associated with extreme forms of vitamin D deficiency. For example in 1,739 participants of the Framingham Offspring Study, the risk of ischemic heart disease was associated with total 25(OH)D <15 ng/mL (hazard ratio [HR] of 1.62; 95 % CI 1.11–2.36, P = 0.01) compared to individuals with levels ≥15 ng/mL [10]. In a stratified analysis by diagnosis of hypertension at baseline, the association between 25(OH)D levels and ischemic heart disease was evident in patients with hypertension (HR 2.13, 95 % CI 1.30–3.48), but not in those without hypertension (HR 1.04, 95 % CI 0.55–1.96). Similar results were found in a study involving 18 225 men in the Health Professionals Follow-up Study [11] Furthermore, higher vitamin D intake from foods and supplements was associated with a decreased risk of cardiovascular disease including coronary artery disease and stroke in the Nurses Health Study and the Healthcare Professionals Follow- up Study [12]. Large global cohort studies have yielded similar findings. One such study of 10,170 women and men from the Danish general population showed that the risk for myocardial infarction was 64 % higher in participants with extreme 25(OH)D deficiency (<6 ng/mL) than participants with 25(OH)D >24 ng/mL [13]. Similarly, in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study, both low 25(OH)D and $1,25(OH)_2D$ levels were associated with cardiovascular mortality [14]. Of note, patients with extreme forms of chronic kidney disease who cannot convert 25(OH)D into the active hormonal form $1,25(OH)_2D$ also have a high risk of cardiovascular mortality [15].

Studies evaluating the role of vitamin D in patients with left ventricular hypertrophy (LVH) show mixed results. An analysis of 256 participants from the Hoorn study, which is a population-based cohort in the Netherlands, demonstrated an association between low 25(OH)D and LVH only in individuals with history of cardiovascular disease and in those with low renal function (median estimated glomerular filtration rate ≤77.5 mL/min/1.73 m^2) [16]. The effect appeared to be attenuated when adjusted for parathyroid hormone (PTH) levels. The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study suggested an association between low 25(OH)D levels and altered left ventricular (LV) geometry and function at baseline (left ventricular end-systolic diameter and left ventricular ejection fraction), but failed to show the same association after 5 years of follow up [17]. In contrast, an analysis of 711 participants from the Baltimore Longitudinal Study of Aging revealed a relationship between 25(OH)D levels and left ventricular mass index (by echocardiogram), but did not find an association with left ventricular ejection fraction or geometry [35]. Similarly, a study that utilized cardiac magnetic resonance in 992 Icelandic community dwelling individuals found an association between 25(OH)D and left ventricular mass [36]. Populations with extreme forms of 25(OH)D deficiency such as the chronic kidney disease have a higher prevalence of LVH than patients with similar risk factors with normal renal function [37]. Heart failure patients with low 25(OH)D levels have a poor prognosis and higher inflammatory markers than those with higher 25(OH)D levels [18]. Furthermore, 25(OH)D levels are negatively correlated with natriuretic peptides and New York Heart Association class [19]. However, the relationship between vitamin D and heart failure is still controversial [38].

Blood pressure and vitamin D have been inconsistently linked in longitudinal studies. A combined analysis of the Health Professionals' Follow-Up Study and the Nurses' Health Study with 1,811 patients encompassing up to 8 years of follow-up reported a 2.67 fold increase in the relative risk of hypertension when comparing individuals with 25(OH)D

Table 11.2 Summary of randomized trials evaluating 25(OH)D or 1,25(OH)2D analogs on cardiovascular outcomes

Study	N	Population	Intervention	Follow-up	Outcome	Result
Thadhani et al. [45]	227	CKD stage 3b-4	Paricalcitol 2 μg/day or Placebo	48 weeks	Change in LVMI	No effect in LVMI
Wang et al. [46]	60	CKD stage 3–4 with left ventricular hypertrophy	Paricalcitol 1 μg/day or Placebo	52 weeks	Change in LVMI	No effect in LVMI
Shedeed et al. [47]	80	Infants with chronic heart failure	Cholecalciferol 1,000 IU/day or Placebo	12 weeks	Left ventricular end-diastolic diameter	32.8 ± 4.6 mm before and 24.9 ± 3.1 mm after treatment
Larsen et al. [48]	130	Subjects with hypertension	Cholecalciferol 3,000 IU/day or Placebo	20 weeks	24 h blood pressure	BP significantly decreased in subjects with 25(OH)D <32 ng/ml
Hsia et al. [49]	36,282	Postmenopausal women	Cholecalciferol 400 IU/day or Placebo	7 years	Myocardial infarction, coronary death and stroke	No difference between groups
Trivedi et al. [50]	2,686	Men and women over 65 years	Cholecalciferol 100,000 IU/4 months or Placebo	5 years	Mortality by cardiovascular disease (fatal MI, stroke)	No difference between groups
Prince et al. [51]	302	Older women with low 25(OH)D (<24 ng/mL) and previous history of falling	Ergocalciferol 1,000 IU/day or Placebo	1 year	Ischemic heart disease (MI, angina)	No difference between groups

Note: *HD* hemodialysis, *IU* international units, *LV* left ventricle, *LVMI* left ventricular mass index, *LVEDD* left ventricular end diastolic diameter, *MI* myocardial infarction, *CKD* chronic kidney disease, *BP* blood pressure

<15 vs. >30 ng/mL [20] In contrast, the Women's Health Initiative study reported no association between 25(OH)D and hypertension [21]. In the Norwegian Tromso study (n = 2,385), no difference in the incidence of hypertension was found in participants with lower vs. higher quartiles of 25(OH)D after 14 years, except for a small increase (4 mmHg) in systolic blood pressure when the lowest (<16 ng/mL) vs. the highest 25(OH)D quartiles (>25 ng/mL) were compared [39].

It is important to note that none of these studies evaluated the role of vitamin D repletion in the aforementioned outcomes. Observational studies cannot rule out other characteristics of these populations that may explain the associated cardiovascular effects. Well-designed randomized trials are needed to confirm or rule out the suspected associations [40].

Clinical Trials

Nonrandomized Open-Label Trials

A few small open-label studies have been conducted. One included 27 infants with vitamin D deficient rickets and ten controls. Both groups were administered one dose of 600,000 IU cholecalciferol and calcium for 2 weeks and showed an improvement in ejection fraction [41] Another study administered 50,000 units of cholecalciferol weekly for 12 weeks to 30 chronic hemodialysis patients with 25(OH)D levels <30 ng/mL followed by 20,000 IU weekly for another 12 weeks [37]. Interestingly, a significant reduction in left ventricular hypertrophy (by echocardiogram) and inflammatory markers was detected at 6 months. Similarly, several small short-term studies in hemodialysis patients with hyperparathyroidism experienced reductions in left ventricular hypertrophy after treatment with $1,25(OH)_2D$ for 3 months [42, 43], or cholecalciferol for 1 year [44].

Randomized Trials

Randomized trials evaluating the effects of intervention with either 25(OH)D or active $1,25(OH)_2D$ analogs on cardiovascular outcomes as a primary objective are very scarce (Table 11.2). Supported by extensive animal experiments and observational human studies suggesting an effect of vitamin D on left ventricular hypertrophy [10, 52–54], PRIMO (Paricalcitol Capsule Benefits in Renal Failure–Induced Cardiac Morbidity) was one of the first large randomized trials designed to evaluate the cardiac effects of vitamin D repletion. In PRIMO, 227 patients with Stage 3b-4 chronic kidney disease were randomized to receive either the active vitamin D compound paricalcitol or placebo for 48 weeks to evaluate its effect on left ventricular mass index (LVMI) [45]. Despite the supporting data in both animal and human studies, PRIMO found no effect of paricalcitol

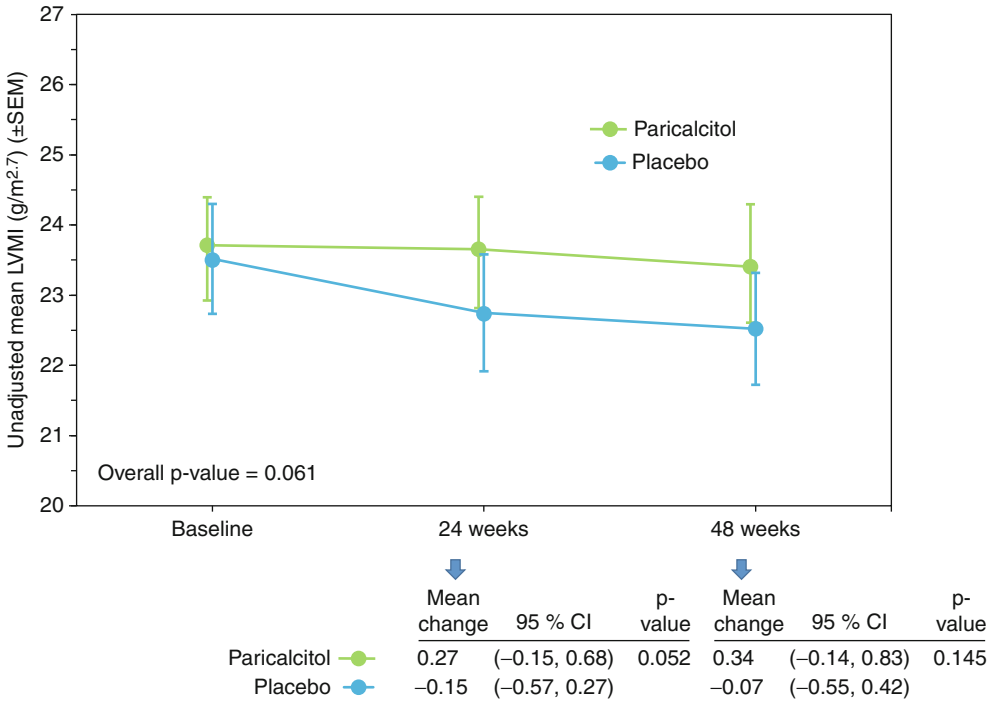

Fig. 11.1 Unadjusted mean left ventricular mass index (*LVMI*) at baseline, week 24, and week 48 by treatment group

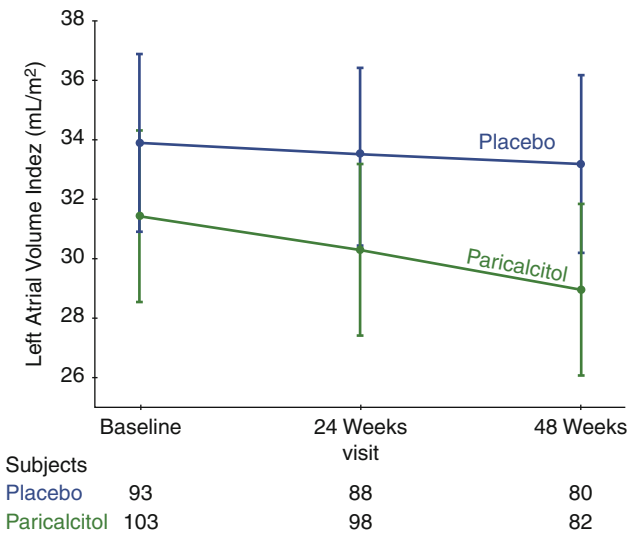

Fig. 11.2 Adjusted mean left atrial volume index (LAVi) at baseline, week 24, and week 48 by treatment group (Reprinted from Tamez et al. [55] with permission from Elsevier, Mosby, Inc; Copyright © 2012 Mosby, Inc. Terms and Conditions)

on LVMI (Fig. 11.1). All patients met left ventricular hypertrophy criteria by echocardiogram at baseline, but not by cardiac magnetic resonance, which may explain why this was a negative trial. A smaller study that included patients with severe LVH showed similar results [46]. A sub-analysis of PRIMO revealed significant reductions in left atrial volume index (Fig. 11.2), natriuretic peptides and cardiovascular hospitalizations (mostly due to heart failure) in the paricalcitol group [55]. Another very small study in children with severe heart failure and vitamin D deficiency randomized participants to either 12 weeks of cholecalciferol 1,000 IU or placebo and found a significant improvement in the heart failure score and left ventricular ejection fraction, among other parameters [47].

A handful of studies have evaluated the effect of cholecalciferol on blood pressure. A recent study in Denmark randomized 130 patients to 3,000 IU of cholecalciferol or placebo for 20 weeks. Although treatment with cholecalciferol was associated with a non-significant reduction in blood pressure compared to placebo, a post-hoc subset analysis restricted to vitamin D deficient patients (<32 ng/mL) revealed a small but statistically significant reduction in both systolic and diastolic blood pressure (4 and 3 mmHg respectively) [48]. Secondary analyses of other studies have yielded mixed results [56].

No studies have yet evaluated prevention of ischemic heart disease or cardiovascular mortality as the primary outcome. The Women's Health Initiative randomized 36,282 postmenopausal women to calcium and vitamin D 200 IU twice daily or to placebo and found no significant difference in the rate of myocardial infarction, angina or stroke (secondary outcomes) after 7 years of follow up [49]. Similarly, another study of 2,686 participants (men and women) who were randomized to 100 000 IU of cholecalciferol or placebo administered every 4 months over 5 years found a non-significant improvement in all-cause mortality

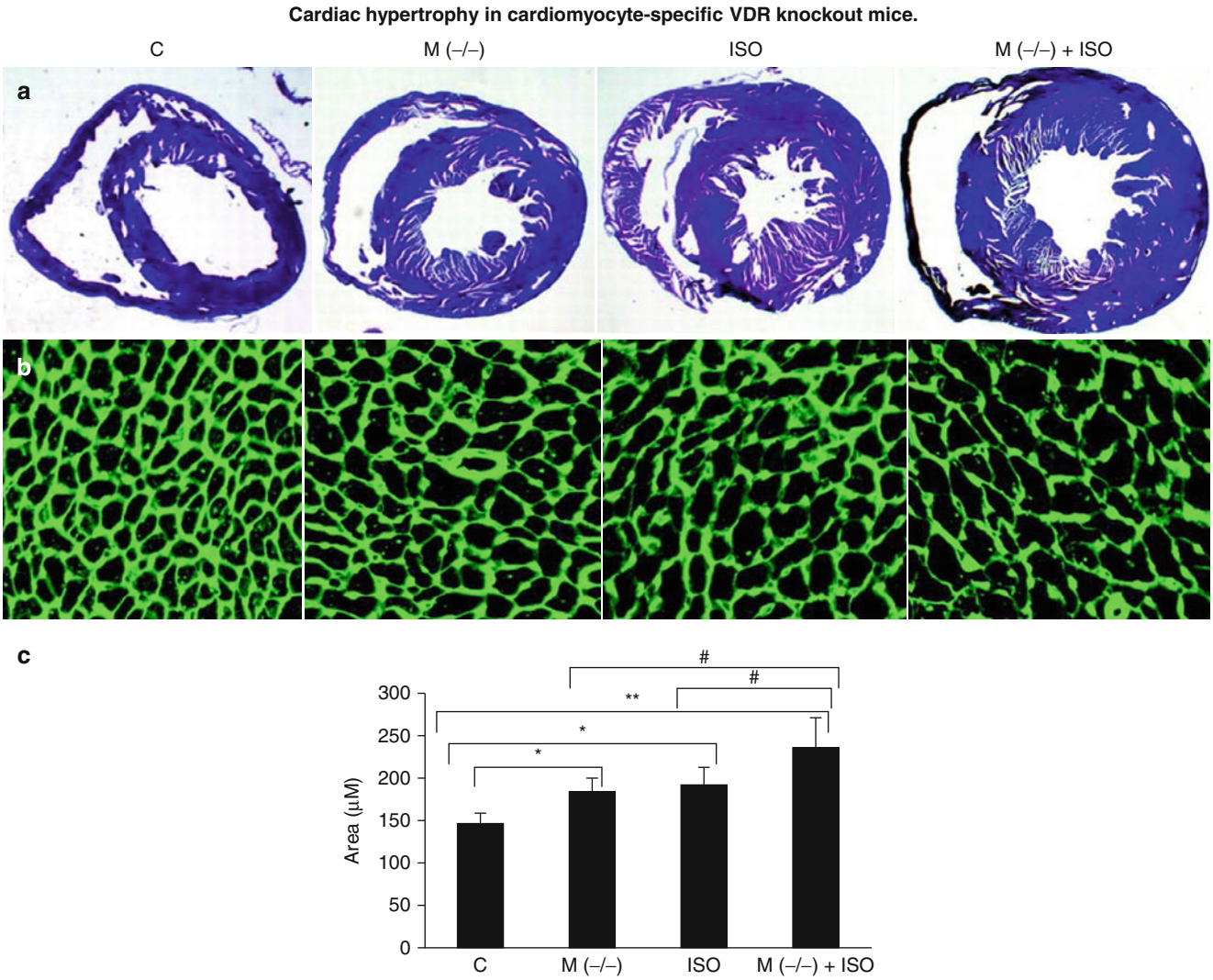

Fig. 11.3 Cardiac hypertrophy in cardiomyocyte-specific VDR knockout mice. (**a**) Left ventricular sections of hearts from mice with genotype indicated were stained by hematoxylin and eosin. Representative sections are shown. (**b**) Cardiac sections were stained with fluorescein isothiocyanate-conjugated wheat germ agglutinin, which delineates cell dimensions by staining glycoprotein enveloping individual myocytes. Representative photomicrographs are shown. (**c**) Individual myocyte size was assessed using Image J (National Institutes of Health). The mean myocyte area was evaluated by measurement of 400 cells per heart (4–5 hearts per genotype). Bar graphs displaying mean and standard deviation from 8 to 12 mice per group are shown. *P < 0.05, **P < 0.01 versus control, #P < 0.05 versus M(−/−)+ISO. *M(−/−)* indicates MLC-Cre/VDRloxp/−, *ISO* isoproterenol (Reproduced from Chen et al. [72] with permission from Lippincott Williams and Wilkins/Wolters Kluwer Health; Copyright © American Heart Association, Inc. All rights reserved)

(mostly cardiovascular) [50]. Consistent with these findings, one smaller randomized Australian study that included 302 women with low 25(OH)D levels (<25 ng/mL) evaluated 1,000 IU daily of ergocalciferol or placebo and showed a non-significant reduction in cardiovascular events (2.0 % in ergocalciferol vs. 1.3 % placebo) [51].

The ongoing VITamin D and OmegA-3 TriaL (VITAL) aims to evaluate the role of cholecalciferol supplementation on cardiovascular diseases (primary outcome) [57]. VITAL has randomized 16,000 participants to either 2,000 IU of cholecalciferol daily or placebo with a median follow up of 5 years. Results of this well-designed trial are expected by 2016.

Biology

Cardiac tissue expresses the VDR gene, suggesting that vitamin D may have a direct effect on the heart [6, 7]. Furthermore, VDR expression is increased in hypertrophied hearts [58]. Cardiac tissue also expresses the 1-alpha hydroxylase and 24-hydroxylase genes, so in theory has the

potential to convert 25(OH)D into active $1,25(OH)_2D$ locally as well as convert $1,25(OH)_2D$ into inactive 1,24,25-tetrahydroxy vitamin D [59].

Animal models that are vitamin D deficient develop cardiac hypertrophy, fibrosis and hypertension [60, 61]. Other animal models such as Dahl salt-sensitive rats, which develop hypertension and proteinuria, also become profoundly vitamin D deficient [52, 62]. These rats develop LVH, high left ventricular end diastolic pressures and elevated levels of natriuretic peptides that can be reversed with administration of $1,25(OH)_2D$ analogs (such as paricalcitol) [52, 63] or doxercalciferol (a pro-hormone vitamin D2 analog) [63] . Similarly, vitamin D analogs prevent progression of LVH and heart failure [64] in animal models. One possible mechanism whereby hypertrophic changes occur is through a decrease in protein synthesis in cardiomyocytes, such as actin [54]. Treatment with paricalcitol has also been associated with higher VDR expression, reduction in Proliferating cell nuclear antigen (PCNA) [65], and inhibition of Protein kinase C alpha (PKCα) in the heart [51] Several other animal models including spontaneously hypertensive rats [66, 67], uremic rats [65], and even in swine [68] have shown similar associations. Among this abundance of positive data, one study utilizing a murine aortic constriction model failed to show that administration of a vitamin D analog could reverse cardiac hypertrophy, but reduced extracellular matrix proteins and natriuretic peptides [69]. Similarly, calcitriol reduced fibrosis and collagen synthesis in the hearts of rat models after partial nephrectomy, with no differences in heart weights [70].

VDR knockout mice models develop severe forms of hypertension and LVH that improve with vitamin D repletion [53, 71] Chen et al. developed a cardiomyocyte-specific VDR deletion mice, which had elevated natriuretic peptide genes and severe left ventricular hypertrophy similar to chronic hypertensive cardiomyopathy (Fig. 11.3). A similar animal model is the 1-alpha hydroxylase knockout mouse, which cannot convert 25(OH)D into the active form of the vitamin, $1,25(OH)_2D$, and therefore is functionally vitamin D deficient. These mice also develop LVH and can be rescued by administration of $1,25(OH)_2D$ analogs.

The exact mechanism by which vitamin D and its active analog predispose animals to develop LVH is not fully understood. VDR knockout mice have higher renin levels, which led to higher angiotensin activity and aldosterone levels [53]. Administration of $1,25(OH)_2D$ directly suppresses renin transcription by blocking the activity of the cyclic AMP responsive element in the renin promoter [73]. In mice that received an infusion of angiotensin II and developed LVH, the LVH was partially reversed by administration of an $1,25(OH)_2D$ analog [74]. Accordingly, the protective role of $1,25(OH)_2D$ in the heart of VDR-null mice is independent from its effects on calcium or phosphorus, and can be reproduced by repressing the renin-angiotensin system with captopril or losartan [75, 76].

Other possible pathways by which vitamin D may affect the heart include the regulation of extracellular matrix integrity through expression of matrix metalloproteinases (MMPs) as well as tissue inhibitors of metalloproteinases (TIMPs) [77], which can contribute to both systolic and diastolic dysfunction [78]. VDR knockout mice underexpress TIMP-1 and TIMP-2 and up regulate MMP-2 and MMP-9, which correlate with increases in fibrotic lesions [79]. These findings are consistent with data from a human trial that showed an inverse correlation of 25(OH)D and MMP-9 at baseline, and a reduction in levels of serum MMP-9 and TIMP-1 after 25(OH)D supplementation [80].

Another potential mechanism whereby vitamin D might influence heart structure, function, and cardiovascular events is via its association with atherosclerosis. Mice with 25(OH)D deficiency fed a high fat diet had ~2 to 8-fold greater aortic atherosclerotic lesions and increased macrophage infiltration and fat accumulation in atherosclerotic plaques compared to 25(OH)D sufficient controls [81]. A possible mechanism for this observation was suggested in ApoE −/− mice models in which calcitriol administration led to a decrease in atherosclerosis by augmenting T-reg cells (Foxp-3+ T cells), decreasing the number of macrophages, and decreasing dendritic cell maturation in atherosclerotic lesions [82]. In human ex-vivo experiments, macrophages from diabetic subjects showed a decrease in foam cell formation and LDL uptake after being cultured in $1,25(OH)_2D$ enriched media compared to $1,25(OH)_2D$ depleted media or after deletion of VDR. The underlying mechanism is thought to be decreased phosphorylation of c-Jun N-terminal kinase (JNK), a key player in the activation of transcription factors related to inflammation [83], with a consequent change in macrophage phenotype [84].

Conclusions

Extensive animal data using a variety of models suggest prominent effects of vitamin D in the heart (direct and indirect). Observational studies have shown mixed results, but overall appear to indicate that severe vitamin D deficiency is associated with LVH, ischemic heart disease and heart failure. However, these results have yet to be corroborated in the few randomized trials available. Well-designed randomized trials evaluating hard outcomes such as myocardial infarction, cardiovascular mortality, etc. are needed before vitamin D therapy can be recommended for prevention or treatment of cardiovascular diseases. Some of these trials will be coming within 3–4 years [40, 57]. Furthermore, the role of bioavailable 25(OH)D levels (compared to total 25(OH)D) is yet to be determined in future studies.

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