PostDoc Journal
Vol. 1, No. 4, April 2013

Journal of Postdoctoral Research
www.postdocjournal.com

Vitamin D Therapy and Cardiovascular Diseases

Ui Kyoung Kim[1] and Soochan Bae[1,2]

[1]Cardiovascular Institute, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

[2]Email: sbae1@bidmc.harvard.edu

Abstract

Vitamin D deficiency affects more than 1 billion people worldwide. Thirty to fifty percent of the U.S population has insufficient levels of vitamin D. Well-known for its major contribution to bone health, vitamin D has attracted the attention of science for its restorative role in cardiovascular diseases and cardiac injury, especially in chronic kidney disease (CKD) patients. Over the past few decades, research on vitamin D and its role in cardiovascular disease has been rapidly expanding, and now the direct association of vitamin D signaling and cardiovascular dysfunction and disease has been clearly recognized. Although a clear mechanism of how the restoration of vitamin D levels benefits cardiovascular health has yet to be identified, a number of clinical studies on vitamin D supplementation have shown its promise as a novel cure for cardiovascular diseases.

Introduction

Since the discovery of its role in curing rickets, vitamin D has been extensively studied by many researchers from a range of fields. Initially, it was mainly known for its crucial role in mineral metabolism and bone health. The population affected by vitamin D deficiency and insufficiency is estimated at more than 1 billion worldwide (Holick 2007). Also, between 30% and 50% of the U.S. population have inadequate levels of vitamin D and 8% are at risk of vitamin D deficiency (Looker et al. 2011). Beyond its chief role in bone health, vitamin D has drawn much attention for its effects in chronic kidney disease (CKD) patients and its association with cardiovascular risks. Patients with CKD are known to be strongly vitamin D deficient due to impaired 1α-hydroxylase enzyme activity in the kidney (Quarles 2008). In the same context, vitamin D levels are closely related to the risk of mortality and survival rates for end-stage renal disease patients. According to many observational cohort studies, 78% of hemodialysis patients are vitamin D deficient, and the 2-year mortality rate is more than doubled for patients who were not treated with injectable vitamin D therapy compared to treated patients (Teng et al. 2005; Wolf et al. 2007). Also, it is estimated that the rate of cardiac failure among patients undergoing hemodialysis is almost 40%, and that vitamin D deficiency is an independent indicator of early death in CKD patients (Foley et al. 1998; Gonzalez et al. 2004). Above all, growing evidence strongly suggests that vitamin D is associated with cardiovascular diseases such as congestive heart failure, thereby suggesting a clinically beneficial role in the treatment of these diseases. In this review, we investigate the relationship between vitamin D and cardiovascular risk factors, as well as potential preventive and restorative effects of vitamin D therapy on the initiation and progression of cardiovascular events.

Metabolism and function of vitamin D

Vitamin D is predominantly synthesized in the skin by the photochemical conversion of 7-dehydrocholesterol into vitamin D3 (cholecalciferol). This precursor compound exerts no significant biological effects. It is later hydroxylated in the liver to form 25-dihydroxyvitamin D3, which is a long-lived circulating storage form of the vitamin (Okano et al. 1977). It is further hydroxylated in the kidneys to form 1,25-dihydroxyvitamin D3, also known as calcitriol, which is the hormonally active form. This conversion is biologically critical, because calcitriol is the mediator of almost all biological pathways targeted by vitamin D. It exerts its effects on tissues by binding the nuclear membrane vitamin D receptor (VDR). Upon biding, VDR translocates to the nucleus and forms a heterodimer with

members of retinoid X receptor (RXR) family of receptors (Jones et al. 1998). In turn, the heterodimer of VDR and RXR binds to hormone response elements to regulate expression of targeted gene products (Demay 2006). The scope of VDR targeted genes is diverse, in terms of the types of tissues and the subsequent expected outcomes. Liganded VDR induces expression of the genes responsible for synthesizing the major apical Ca^{2+} channel proteins in intestinal epithelia cells, TRPV5 and TRPV 6, and also the basolateral ATPase-driven Ca^{2+} pump, PMCA-1 (Meyer et al. 2006; Pike and Meyer 2012). Binding of 1,25-dihydroxyvitamin D3 to VDR downregulates the expression of parathyroid hormone (PTH) genes, which exert effects on the regulation of Ca^{2+} level opposite to 1,25-dihydroxyvitamin D3. Furthermore, fibroblast growth factor (FGF23) is upregulated by 1,25-dihydroxyvitamin D3, and its expressed products have similar effects as PTH (Xu et al. 2002).

Effects of vitamin D on the cardiovascular system
Preclinical studies

Several laboratory studies have found a variety of evidence that may explain the link between vitamin D and cardiovascular health. It is now well-established that VDR and 1α-hydroxylase are expressed in the heart and blood vessels (Somjen et al. 2005; Chen et al. 2008). O'Connell and colleagues have found that vitamin D deficiency leads to abnormalities in cell proliferation and renin gene expression in cardiomyocytes (O'Connell et al. 1994; O'Connell et al. 1997). Moreover, recent studies have shown that VDR knockout mice are prone to increased cardiac renin gene expression and cardiac hypertrophy, and decisively, 1α-hydroxylase knockout mice develop cardiac hypertrophy (Xiang et al. 2005; Zhou et al. 2008). A notable study by Gardner and colleagues has strengthened the relationship between vitamin D and cardiac hypertrophy. That particular study found strong evidence that VDR expression is amplified, both in vivo and in vitro, during the event of cardiac hypertrophy (Chen et al. 2008)

Beyond recognizing its targeting of the heart, there have been many efforts to confirm the efficacy of vitamin D treatment to alleviate symptoms of cardiovascular dysfunction and disease. Further investigation has shown the beneficial effects of exogenous administration of calcitriol, the active form of vitamin D, and its analog, paricalcitol, in in vivo models of cardiac hypertrophy, with treated animals showing improved left ventricular structure and function and cardiac output (Bodyak et al. 2007; Mancuso et al. 2008). Recently, it was demonstrated that treatment with paricalcitol effectively prevents pre-existing cardiac hypertrophy from becoming further aggravated and developing into heart failure in rats fed with high-salt diet. This particular study presented remarkable evidence that PKC-α activation in the heart is attenuated by paricalcitol treatment, thus possibly pointing to an important mechanism that regulates cardiac function (Bae et al. 2011). Another study that examined doxercalciferol, or 1α-hydroxyvitamin D2 (vitamin D2 pro-hormone) has substantiated this association. The study found that administration of doxercalciferol reduced cardiac hypertrophy due to a high-salt diet in rats (Choi et al. 2011). VDR activation also improves diastolic function, as it alters calcium flux and consequently encourages the relaxation of cardiomyocytes (Green et al. 2006). Moreover, it has been found that VDR has direct anti-hypertrophic activity on cardiomyocytes, apart from the suppressed renin effect (Chen and Gardner 2012). Overall, the direct association of vitamin D signaling and cardiovascular dysfunction and disease has been clearly recognized, and vitamin D therapy thus promises to be novel approach that might complement currently available therapies for heart failure.

Clinical and epidemiological studies

Numerous clinical and epidemiological studies have suggested a strong association between vitamin D deficiency and cardiovascular disease in the general population. The results found that vitamin D levels are highly associated with the incidence of arterial disease, myocardial infarction, heart failure, stroke, and other cardiovascular diseases (Wang et al. 2008; Anderson et al. 2010).

According to data from the NHANES III (National Health and Nutrition Examination Survey), the

odds of having increased blood pressure is twice as great in adolescents with the lowest serum 25-hydroxyvitamin D levels (less than 15ng/mL) than in groups of adolescents with higher levels (Thacher and Clarke 2011). Moreover, low 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D3 levels are strongly and independently associated with increased risk of cardiovascular mortality, by approximately 83%, when compared to higher serum vitamin D levels (Dobnig et al. 2008; Grandi et al. 2010). It was also observed that low vitamin D levels are significantly associated with increased risk of sudden cardiac death in diabetic dialysis patients and in patients with coronary disease risk factors (Pilz et al. 2008; Drechsler et al. 2010). Furthermore, insufficient vitamin D levels were found to be inversely associated with increased arterial stiffness and endothelial dysfunction (Al Mheid et al. 2011).

Chronic kidney disease (CKD) patients, especially those with end-stage renal disease, are known to be more susceptible to vitamin D insufficiency and deficiency. Nearly half of pediatric CKD patients are vitamin D deficient and the risk of deficiency increases as the stage of CKD advances; the prevalence of vitamin D deficiency for adult hemodialysis patients was found to be almost 66% (Kalkwarf et al. 2012; Bansal et al. 2013). Corroborating the link between cardiovascular risk and low vitamin D levels is that CKD patients with a higher risk of vitamin D deficiency frequently suffer from cardiovascular dysfunctions and ultimately heart failure. Risks of diastolic dysfunction, myocardial calcification and increased left ventricular mass are increased among CKD patients (Patange et al. 2012). For CKD patients, as the disease progresses, renal mass and function are severely compromised, resulting in decreases in the availability of 1α-hydroxylase enzyme. Consequently, the level of calcitriol in the serum declines, which leads to compensatory overshooting of parathyroid hormones, often called secondary hyperparathyroidism (Dusso et al. 2011). Moreover, it appears that secondary hyperparathyroidism is associated with increased risk of cardiovascular events, such as elevated arterial pressure and myocardial contractility (Zittermann 2006)

A recent epidemiological study conducted over a 29-year period found that stepwise increases in the risk of ischemic heart disease, myocardial infarction (MI) and early death occur with stepwise decreases of plasma 25-hydroxyvitamin D levels. Those with the lowest levels of vitamin D had a 40% increased risk of ischemic heart disease, a 64% higher chance of an MI, a 57% increased risk of early death, and an 81% higher likelihood of fatal ischemic heart disease/MI (Brondum-Jacobsen et al. 2012). Another interesting study to note is the MONICA/KORA Augsburg case-cohort study, which examined the cases of coronary disease in healthy middle-aged men and women over a follow-up period of 11 years. The results captured a novel gender-specific relationship between higher vitamin D serum levels and decreased coronary disease cases: that vitamin D level was more strongly associated with cardiovascular risks in women than men. The authors speculated possible explanations for a stronger inverse relationship in women. Hormonal activity differences, especially in estrogen, might contribute to the discrepancy in responses to vitamin D (Karakas et al. 2013).

While the results from interventional studies have not been consistent, there have been continuing efforts to prove the efficacy of vitamin D supplementation as a treatment for cardiovascular diseases. A randomized controlled trial in which the subjects took daily doses of vitamin D and calcium together or a placebo showed no difference in coronary or cerebrovascular risk between the two groups (Hsia et al. 2007). Similarly, daily vitamin D supplementation (400IU or 1000IU) for 1 year did not alter levels of cardiovascular risk biomarkers such as HDL or LDL cholesterol or inflammatory markers. Yet, the level of TNF-α was reduced in participants who received 2000 IU of vitamin D supplements for 1 year, suggesting to some extent the possibility of a therapeutic role of vitamin D (Wood et al. 2012). In addition, there have been a number of convincing studies to support a possible curative effect of vitamin D therapy for a wide range of diseases. A moderate to high dose of vitamin D supplementation slightly decreases cardiovascular risks (Wang et al. 2010). Further, upon treatment with vitamin D for 16 weeks,

the level of BNP (B-type natriuretic peptide), a molecule considered to be a powerful indicator for cardiovascular risk, decreases significantly (Witham et al. 2010). Recently, paricalcitol has been approved by the FDA for the treatment of secondary hyperparathyroidism associated with severe chronic kidney disease.

In addition, clinical trials, such as the Paricalcitol Injection Benefits in Renal Failure Induced Cardiac Morbidity in Subjects with Chronic Kidney Disease (PRIMO) trial, have been investigating the potential benefits of daily supplementation with oral paricalcitol. The previous PRIMO study found that paricalcitol therapy over 48 weeks did not change the left ventricular mass index or show any positive effects on diastolic dysfunction in CKD patients when compared to the placebo group. Nevertheless, the subsequent PRIMO post hoc analysis suggests the contrary. A paricalcitol therapy of 48 weeks prevented the rise of plasma BNP levels and reduced left ventricular mass index, a result that is encouraging for further investigations (Tamez et al. 2012; Thadhani et al. 2012). All things considered, there has been much meaningful evidence collected that implies the potential of vitamin D supplementation as both a preventive and curative measure for cardiovascular diseases.

Possible cardioprotective mechanisms by vitamin D signaling

Years of research with different experimental models and cells have provided important insights into the possible mechanisms underlying the cardiovascular effects and regulation of vitamin D. Here, we summarize mechanistic evidence on the increased risk of cardiovascular risk related to vitamin D deficiency.

Renin-Angiotensin System

The renin-angiotensin system (RAS) regulates blood pressure, intravascular volume, and electrolyte homeostasis via renin released from juxtaglomerular cells. It promotes the conversion of angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin converting enzyme (ACE). Vitamin D has a function as a negative regulator of the RAS by inhibiting the expression of renin (Li et al. 2002; Yuan et al. 2007). Thus, vitamin D deficiency, as expected, leads to upregulation of the RAS. This upregulation inevitably increases the risk of cardiac hypertrophy, mainly due to pressure overload, but it has been also shown than angiotensin II can directly and independently increase blood (Baker et al. 1990; Dostal and Baker 1992). It was also found that the ACE inhibitor, captopril, reversed cardiac hypertrophy and stabilized the levels of atrial natriuretic peptide. This result suggests that cardiac hypertrophy results from the activation of both the systemic and cardiac RAS, and vitamin D indeed plays a central role in cardiac function (Xiang et al. 2005).

Several experimental studies have definitively demonstrated the effectiveness of vitamin D in reducing renin expression levels and plasma renin activity in mice (Li et al. 2002; Fryer et al. 2007). The results suggest that liganded VDR exerts a direct negative regulation on renin gene expression by interacting with CREB (Cyclic AMP Response Element Binding Protein) and preventing its association with CRE on the renin gene promoter (Yuan et al. 2007). Furthermore, in rats with 5/6 nephrectromy, the treatment of paricalcitol downregulates several components of the RAS: angiotensiogen, renin, renin receptor, angiotensinogen and angiotensin II type I receptor in the kidney remnant, which leads to hypertension, cardiac enlargement and elevation of natiruretic peptides (Freundlich et al. 2008)

Fibrosis

Fibrosis is a fundamental biological process for the replacement or repair of damaged and dead cells due to injury, and this critical survival mechanism is another important factor that contributes to morbidity and mortality from cardiovascular diseases (Wynn 2007; Artaza et al. 2011). The association between fibrosis and vitamin D has been elucidated by mounting evidence. Artaza et al. revealed that 1,25-dihydroxyvitamin D3 exposure reduced the expression of different collagen isoforms, which are powerful markers of fibrosis, in multipotent mesenchymal cells (Artaza and Norris 2009). Moreover, these findings have been corroborated, as the administration of paricalcitol

reverses the significant downregulation of VDR in the fibrotic kidney, and therefore increases VDR expression, which suggests a greater impact of vitamin D signaling and vitamin D deficiency in a dysfunctioning kidney (Tan et al. 2006). Also, administration of paricalcitol reduces cardiac fibrogenesis and expression of pro-fibrotic genes in the heart. Likewise, there is a small reduction of left ventricular hypertrophy accompanied by a substantial reduction in cardiac fibrosis, thereby protecting from diastolic dysfunction to some extent (Meems et al. 2012). Yet, there has been some contradicting evidence. In a rat model of 5/6 nephrectomy, the administration of paricalcitol did not reduce, but rather exacerbated, myocardial fibrosis and pro-fibrotic gene expression (Rahman et al. 2007; Repo et al. 2007).

Inflammation

Recently, vitamin D has attracted much attention, as it has been suggested to play a critical regulatory role in inflammation, which is one of the factors leading to cardiovascular risks. A low 25-hydroxyvitamin D level increases the levels of C-reactive protein and IL-10, thus leading to a higher risk of inflammation (Zittermann 2006). This association has been further supported by the finding that vitamin D supplementation promotes the serum concentration of anti-inflammatory cytokine IL-10, and suppresses the increase in serum levels of the pro-inflammatory cytokine TNF-α in congestive heart failure patients. These results suggest downregulatory effects of vitamin D on inflammatory biomarkers (Schleithoff et al. 2006). In addition, it was found that vitamin D inhibits pro-inflammatory cytokines including IL-6 and IL-12 (Mathieu and Adorini 2002). Interestingly enough, the negative regulatory mechanism of vitamin D on the production of IL-12 has been shown to involve downregulation of NF-κB gene expression (D'Ambrosio et al. 1999). It is well-known that the post-MI (myocardial infarction) healing process is controlled by inflammatory cytokines such as TNF-a, IL-6, IL-8 and IL-10. Through a certain phase of post-MI, the cytokines act as cardioprotective molecules, as they appear to reduce apoptosis (Maggio et al. 2006). However, when increased levels of cytokines are sustained, they eventually worsen the situation for myocardial remodeling, as cytokines self-amplify through positive feedback targeting NF-κB (Puhakka et al. 2003; Arnson et al. 2013). Another important finding demonstrated that high TNF-α levels hinder the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D3 by endothelial cells, causing a vicious loop of promoting inflammation and suppressing vitamin D activation (Witham et al. 2010). Therefore, the pro-inflammatory state is thought to be closely involved in the pathophysiology of cardiac and endothelial dysfunction.

Future aspects of Vitamin D treatment on the cardiovascular disease

In animal models, paricalcitol and doxercalciferol have a demonstrated beneficial effect on preventing cardiac dysfunction (Choi et al. 2011). However, calcitriol has caused non-desired hypercalcemic actions and has a narrow therapeutic window. Therefore, treatment may be better accomplished by analogs of calcitriol with a wider safety margin (Wu-Wong 2009). Currently, researchers are focused on developing other selective VDR agonist drug candidates with high selectivity and efficacy to treat the heart failure phenotype and high renin-associated dysfunctions (Simpson 2011).

Nevertheless, despite the significant potential for vitamin D therapy in cardiac hypertrophy and heart failure, its clinical utility has thus far been limited by the fact that vitamin D also elevates serum Ca^{2+}. In trying to circumvent some of the pharmacodynamic limitations inherent to this class of compounds, several groups have attempted to synthesize structural analogs that retain the selectivity profile of the parent compound, 1,25-dihydroxyvitamin D3, but are devoid of the classic calcification issues (Bouillon, et al. 1995; Boehm et al. 1999; Swann et al. 2002; Ma et al. 2006; Norman 2006). To date, more than 3000 calcitriol analogues have been synthesized, but few are of clinical interest.

Furthermore, there has been building evidence pointing to omega-3 fatty acids as a potential means of treatment for cardiovascular events. In the GISSI-P study launched in 2004, daily

supplementation with omega-3 fatty acids, in addition to regular medical treatment, had the effect of reducing cardiac and all-cause mortality for post-myocardial infarction patients (Guttler et al. 2012) Likewise, there has been an ongoing trial, called VITAL, which involves vitamin D and omega-3 fatty acids and their efficacy in the primary prevention of cardiovascular diseases and cancer. Although no affirming clinical evidence is yet available, the role omega-3 fatty acids in cardiovascular diseases is another area of interest from which the vitamin D research field could find inspiration for future research.

Conclusion

Extensive evidence collected over the past decade clearly suggests a strong association between low serum vitamin D levels and the risk of cardiovascular diseases and dysfunctions. Also, several potential mechanisms whereby vitamin D may affect the pathophysiology of cardiovascular disease events have been recognized, through many laboratory studies in animal models and at a molecular level. However, a clear mechanism as to how vitamin D restoration benefits cardiac health and restores heart function has yet to be clearly identified. Currently, insufficient interventional data from randomized controlled trials (RCT) is available make any conclusions on the effects of vitamin D intake on cardiovascular disease, especially in humans. To further solidify the relationship between vitamin D and cardiovascular risk factors, more RCTs with larger groups are still needed to determine whether vitamin D therapy will alleviate clinically meaningful cardiovascular events such as myocardial infarction, heart failure and hypertrophy.

References

1. Al Mheid, I., R. Patel, et al. (2011). Vitamin D status is associated with arterial stiffness and vascular dysfunction in healthy humans. J Am Coll Cardiol 58(2): 186-192.

2. Anderson, J. L., H. T. May, et al. (2010). Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol 106(7): 963-968.

3. Arnson, Y., D. Itzhaky, et al. (2013). Vitamin D Inflammatory Cytokines and Coronary Events: A Comprehensive Review. Clin Rev Allergy Immunol.

4. Artaza, J. N., S. Contreras, et al. (2011). Vitamin D and cardiovascular disease: potential role in health disparities. J Health Care Poor Underserved 22(4 Suppl): 23-38.

5. Artaza, J. N. and K. C. Norris (2009). Vitamin D reduces the expression of collagen and key profibrotic factors by inducing an antifibrotic phenotype in mesenchymal multipotent cells. J Endocrinol 200(2): 207-221.

6. Bae, S., B. Yalamarti, et al. (2011). Preventing progression of cardiac hypertrophy and development of heart failure by paricalcitol therapy in rats. Cardiovasc Res 91(4): 632-639.

7. Baker, K. M., M. I. Chernin, et al. (1990). Renin-angiotensin system involvement in pressure-overload cardiac hypertrophy in rats. Am J Physiol 259(2 Pt 2): H324-332.

8. Bansal, N., D. Fan, et al. (2013). Incident atrial fibrillation and risk of end-stage renal disease in adults with chronic kidney disease. Circulation 127(5): 569-574.

9. Bodyak, N., J. C. Ayus, et al. (2007). Activated vitamin D attenuates left ventricular abnormalities induced by dietary sodium in Dahl salt-sensitive animals. Proc Natl Acad Sci U S A 104(43): 16810-16815.

10. Boehm, M. F., P. Fitzgerald, et al. (1999). Novel nonsecosteroidal vitamin D mimics exert VDR-modulating activities with less calcium mobilization than 1,25-dihydroxyvitamin D3. Chem Biol 6(5): 265-275.

11. Bouillon, R., W. H. Okamura, et al. (1995). Structure-function relationships in the vitamin D endocrine system. Endocr Rev 16(2): 200-257.

12. Brondum-Jacobsen, P., M. Benn, et al. (2012). 25-hydroxyvitamin d levels and risk of ischemic heart disease, myocardial infarction, and early death: population-based study and meta-analyses of 18 and 17 studies. Arterioscler Thromb Vasc Biol 32(11): 2794-2802.

13. Chen, S. and D. G. Gardner (2012). Liganded vitamin D receptor displays anti-hypertrophic activity in the murine heart. J Steroid Biochem Mol Biol.

14. Chen, S., D. J. Glenn, et al. (2008). Expression of the vitamin d receptor is increased in the hypertrophic heart. Hypertension 52(6): 1106-1112.

15. Choi, J. H., Q. Ke, et al. (2011). Doxercalciferol, a pro-hormone of vitamin D, prevents the development of cardiac hypertrophy in rats. J Card Fail 17(12): 1051-1058.

16. D'Ambrosio, D., P. Panina-Bordignon, et al. (1999). Molecular mechanisms of T helper cell differentiation and tissue-specific migration. Curr Top Microbiol Immunol 246: 117-122.

17. Demay, M. B. (2006). Mechanism of vitamin D receptor action. Ann N Y Acad Sci 1068: 204-213.

18. Dobnig, H., S. Pilz, et al. (2008). Independent association of low serum 25-hydroxyvitamin d and 1,25-dihydroxyvitamin d levels with all-cause and cardiovascular mortality. Arch Intern Med 168(12): 1340-1349.

19. Dostal, D. E. and K. M. Baker (1992). Angiotensin II stimulation of left ventricular hypertrophy in adult rat heart. Mediation by the AT1 receptor. Am J Hypertens 5(5 Pt 1): 276-280.

20. Drechsler, C., S. Pilz, et al. (2010). Vitamin D deficiency is associated with sudden cardiac death, combined cardiovascular events, and mortality in haemodialysis patients. Eur Heart J 31(18): 2253-2261.

21. Dusso, A., E. A. Gonzalez, et al. (2011). Vitamin D in chronic kidney disease. Best Pract Res Clin Endocrinol Metab 25(4): 647-655.

22. Foley, R. N., P. S. Parfrey, et al. (1998). Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 32(5 Suppl 3): S112-119.

23. Freundlich, M., Y. Quiroz, et al. (2008). Suppression of renin-angiotensin gene expression in the kidney by paricalcitol. Kidney Int 74(11): 1394-1402.

24. Fryer, R. M., P. A. Rakestraw, et al. (2007). Differential inhibition of renin mRNA expression by paricalcitol and calcitriol in C57/BL6 mice. Nephron Physiol 106(4): p76-81.

25. Gonzalez, E. A., A. Sachdeva, et al. (2004). Vitamin D insufficiency and deficiency in chronic kidney disease. A single center observational study. Am J Nephrol 24(5): 503-510.

26. Grandi, N. C., L. P. Breitling, et al. (2010). Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. Prev Med 51(3-4): 228-233.

27. Green, J. J., D. A. Robinson, et al. (2006). Calcitriol modulation of cardiac contractile performance via protein kinase C. J Mol Cell Cardiol 41(2): 350-359.

28. Guttler, N., K. Zheleva, et al. (2012). Omega-3 Fatty acids and vitamin d in cardiology. Cardiol Res Pract 2012: 729670.

29. Holick, M. F. (2007). Vitamin D deficiency. N Engl J Med 357(3): 266-281.

30. Hsia, J., G. Heiss, et al. (2007). Calcium/vitamin D supplementation and cardiovascular events. Circulation 115(7): 846-854.

31. Jones, G., S. A. Strugnell, et al. (1998). Current understanding of the molecular actions of vitamin D. Physiol Rev 78(4): 1193-1231.

32. Kalkwarf, H. J., M. R. Denburg, et al. (2012). Vitamin D deficiency is common in children and adolescents with chronic kidney disease. Kidney Int 81(7): 690-697.

33. Karakas, M., B. Thorand, et al. (2013). Low Levels of Serum 25-Hydroxyvitamin D Are Associated with Increased Risk of Myocardial Infarction, Especially in Women: Results from the MONICA/KORA Augsburg Case-Cohort Study. J Clin Endocrinol Metab 98(1): 272-280.

34. Li, Y. C., J. Kong, et al. (2002). 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin-angiotensin system. J Clin Invest 110(2): 229-238.

35. Looker, A. C., C. L. Johnson, et al. (2011). Vitamin D status: United States, 2001-2006. NCHS Data Brief(59): 1-8.

36. Ma, Y., B. Khalifa, et al. (2006). Identification and characterization of noncalcemic, tissue-selective, nonsecosteroidal vitamin D receptor modulators. J Clin Invest 116(4): 892-904.

37. Maggio, M., J. M. Guralnik, et al. (2006). Interleukin-6 in aging and chronic disease: a magnificent pathway. J Gerontol A Biol Sci Med Sci 61(6): 575-584.

38. Mancuso, P., A. Rahman, et al. (2008).

1,25-Dihydroxyvitamin-D3 treatment reduces cardiac hypertrophy and left ventricular diameter in spontaneously hypertensive heart failure-prone (cp/+) rats independent of changes in serum leptin. J Cardiovasc Pharmacol 51(6): 559-564.

39. Mathieu, C. and L. Adorini (2002). The coming of age of 1,25-dihydroxyvitamin D(3) analogs as immunomodulatory agents. Trends Mol Med 8(4): 174-179.

40. Meems, L. M., M. V. Cannon, et al. (2012). The vitamin D receptor activator paricalcitol prevents fibrosis and diastolic dysfunction in a murine model of pressure overload. J Steroid Biochem Mol Biol 132(3-5): 282-289.

41. Meyer, M. B., M. Watanuki, et al. (2006). The human transient receptor potential vanilloid type 6 distal promoter contains multiple vitamin D receptor binding sites that mediate activation by 1,25-dihydroxyvitamin D3 in intestinal cells. Mol Endocrinol 20(6): 1447-1461.

42. Norman, A. W. (2006). Minireview: vitamin D receptor: new assignments for an already busy receptor. Endocrinology 147(12): 5542-5548.

43. O'Connell, T. D., J. E. Berry, et al. (1997). 1,25-Dihydroxyvitamin D3 regulation of cardiac myocyte proliferation and hypertrophy. Am J Physiol 272(4 Pt 2): H1751-1758.

44. O'Connell, T. D., R. E. Weishaar, et al. (1994). Regulation of myosin isozyme expression by vitamin D3 deficiency and 1,25-dihydroxyvitamin D3 in the rat heart. Endocrinology 134(2): 899-905.

45. Okano, T., M. Yasumura, et al. (1977). Photochemical conversion of 7-dehydrocholesterol into vitamin D3 in rat skins. J Nutr Sci Vitaminol (Tokyo) 23(2): 165-168.

46. Patange, A. R., R. P. Valentini, et al. (2012). Vitamin D Deficiency Is Associated With Increased Left Ventricular Mass and Diastolic Dysfunction in Children With Chronic Kidney Disease. Pediatr Cardiol.

47. Pike, J. W. and M. B. Meyer (2012). Regulation of mouse Cyp24a1 expression via promoter-proximal and downstream-distal enhancers highlights new concepts of 1,25-dihydroxyvitamin D(3) action. Arch Biochem Biophys 523(1): 2-8.

48. Pilz, S., W. Marz, et al. (2008). Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J Clin Endocrinol Metab 93(10): 3927-3935.

49. Puhakka, M., J. Magga, et al. (2003). Interleukin-6 and tumor necrosis factor alpha in relation to myocardial infarct size and collagen formation. J Card Fail 9(4): 325-332.

50. Quarles, L. D. (2008). Endocrine functions of bone in mineral metabolism regulation. J Clin Invest 118(12): 3820-3828.

51. Rahman, A., S. Hershey, et al. (2007). Heart extracellular matrix gene expression profile in the vitamin D receptor knockout mice. J Steroid Biochem Mol Biol 103(3-5): 416-419.

52. Repo, J. M., I. S. Rantala, et al. (2007). Paricalcitol aggravates perivascular fibrosis in rats with renal insufficiency and low calcitriol. Kidney Int 72(8): 977-984.

53. Schleithoff, S. S., A. Zittermann, et al. (2006). Vitamin D supplementation improves cytokine profiles in patients with congestive heart failure: a double-blind, randomized, placebo-controlled trial. Am J Clin Nutr 83(4): 754-759.

54. Simpson, R. U. (2011). Selective knockout of the vitamin d receptor in the heart results in cardiac hypertrophy: is the heart a drugable target for vitamin D receptor agonists? Circulation 124(17): 1808-1810.

55. Somjen, D., Y. Weisman, et al. (2005). 25-hydroxyvitamin D3-1alpha-hydroxylase is expressed in human vascular smooth muscle cells and is upregulated by parathyroid hormone and estrogenic compounds. Circulation 111(13): 1666-1671.

56. Swann, S. L., J. J. Bergh, et al. (2002). Rational design of vitamin D3 analogues which selectively restore activity to a vitamin D receptor mutant associated with rickets. Org Lett 4(22): 3863-3866.

57. Tamez, H., C. Zoccali, et al. (2012). Vitamin D reduces left atrial volume in patients with left ventricular hypertrophy and chronic kidney disease. Am Heart J 164(6): 902-909 e902.

58. Tan, X., Y. Li, et al. (2006). Paricalcitol attenuates renal interstitial fibrosis in obstructive nephropathy. J Am Soc Nephrol 17(12): 3382-3393.

59. Teng, M., M. Wolf, et al. (2005). Activated injectable vitamin D and hemodialysis survival: a historical cohort study. J Am Soc Nephrol 16(4): 1115-1125.

60. Thacher, T. D. and B. L. Clarke (2011). Vitamin D insufficiency. Mayo Clin Proc 86(1): 50-60.

61. Thadhani, R., E. Appelbaum, et al. (2012). Vitamin D therapy and cardiac structure and function in patients with chronic kidney disease: the PRIMO randomized controlled trial. JAMA 307(7): 674-684.

62. Wang, L., J. E. Manson, et al. (2010). Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Intern Med 152(5): 315-323.

63. Wang, T. J., M. J. Pencina, et al. (2008). Vitamin D deficiency and risk of cardiovascular disease. Circulation 117(4): 503-511.

64. Witham, M. D., F. J. Dove, et al. (2010). The effect of different doses of vitamin D(3) on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. Diabetologia 53(10): 2112-2119.

65. Wolf, M., A. Shah, et al. (2007). Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int 72(8): 1004-1013.

66. Wood, A. D., K. R. Secombes, et al. (2012). Vitamin D3 supplementation has no effect on conventional cardiovascular risk factors: a parallel-group, double-blind, placebo-controlled RCT. J Clin Endocrinol Metab 97(10): 3557-3568.

67. Wu-Wong, J. R. (2009). Potential for vitamin D receptor agonists in the treatment of cardiovascular disease. Br J Pharmacol 158(2): 395-412.

68. Wynn, T. A. (2007). Common and unique mechanisms regulate fibrosis in various fibroproliferative diseases. J Clin Invest 117(3): 524-529.

69. Xiang, W., J. Kong, et al. (2005). Cardiac hypertrophy in vitamin D receptor knockout mice: role of the systemic and cardiac renin-angiotensin systems. Am J Physiol Endocrinol Metab 288(1): E125-132.

70. Xu, H., L. Bai, et al. (2002). Age-dependent regulation of rat intestinal type IIb sodium-phosphate cotransporter by 1,25-(OH)(2) vitamin D(3). Am J Physiol Cell Physiol 282(3): C487-493.

71. Yuan, W., W. Pan, et al. (2007). 1,25-dihydroxyvitamin D3 suppresses renin gene transcription by blocking the activity of the cyclic AMP response element in the renin gene promoter. J Biol Chem 282(41): 29821-29830.

72. Zhou, C., F. Lu, et al. (2008). Calcium-independent and 1,25(OH)2D3-dependent regulation of the renin-angiotensin system in 1alpha-hydroxylase knockout mice. Kidney Int 74(2): 170-179.

73. Zittermann, A. (2006). Vitamin D and disease prevention with special reference to cardiovascular disease. Prog Biophys Mol Biol 92(1): 39-48.