The role of vitamin D in left ventricular hypertrophy and cardiac function

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The role of vitamin D in left ventricular hypertrophy and cardiac function. Cardiovascular disease is the leading cause of death among patients with end-stage renal disease (ESRD). Traditional cardiac risk factors, as well as other factors specific to the ESRD population such as hyperphosphatemia, elevated calcium and phosphate product, abnormal lipid metabolism, hyperhomocysteinemia, and chronic inflammation play a role in the excessive risk of cardiovascular death in this population. Left ventricular disorders are proven risk factors for cardiac mortality in hemodialysis patients. These disorders are present in incident ESRD patients at rates far above the general population. There is an accumulating body of evidence that suggests that vitamin D plays a role in cardiovascular disease. Abnormal vitamin metabolism, through deficiency of the active form of 1,25-dihydroxyvitamin D$_3$, and acquired vitamin D resistance through the uremic state, have been shown to be important in ESRD. Vitamin D deficiency has long been known to affect cardiac contractility, vascular tone, cardiac collagen content, and cardiac tissue maturation. Recent studies using vitamin D receptor deficient mice as a model demonstrate a crucial role of vitamin D in regulation of the renin-angiotensin system. Additionally, there is emerging evidence linking treatment with vitamin D to improved survival on hemodialysis and improvement in cardiac function. The emergence of this data is focusing attention on the previously underappreciated nonmineral homeostatic effects of vitamin D that very likely play an important role in the pathogenesis of cardiac disease in ESRD.

Cardiovascular disease is the leading cause of death among patients with end-stage renal disease (ESRD) [1]. The excessive risk of cardiovascular death in this population can be attributed to the presence of traditional cardiac risk factors, as well as other factors specific to the ESRD population such as hyperphosphatemia, elevated calcium and phosphate product, abnormal lipid metabolism, hyperhomocysteinemia, and chronic inflammation [2–8]. Left ventricular disorders play a prominent role in cardiac risk among hemodialysis patients, with congestive heart failure conferring an even higher risk of cardiac mortality than the presence of coronary artery disease [9]. Left ventricular hypertrophy (LVH) and left ventricular systolic function have both been shown to be independent risk factors for cardiovascular mortality in ESRD patients [10, 11], and are present in incident ESRD patients at rates far above the general population [9]. The pathophysiology of LVH in the ESRD population is not known exactly, but factors that have been implicated include hypertension, anemia, and chronic volume overload [12]. There is an accumulating body of evidence that suggests that vitamin D plays a role in cardiovascular disease. Abnormal vitamin metabolism has long been known to be important in the pathogenesis of secondary hyperparathyroidism through deficiency of the active form of 1,25-dihydroxyvitamin D$_3$ [13] and acquired vitamin D resistance through the uremic state [14, 15], but only recently has attention focused on vitamin D metabolism and cardiac disease in ESRD. Much of the evidence linking vitamin D to cardiac disease has been available for quite some time, but the importance of it is becoming clearer as the molecular mechanisms of vitamin D’s actions in the cardiovascular system are elucidated, and the results of recent studies in the area of treatment with vitamin D analogues become available.

LEFT VENTRICULAR HYPERTROPHY AND CONGESTIVE HEART FAILURE IN RENAL FAILURE

The burden of cardiovascular disease is well known in the ESRD population, with cardiovascular disease, including myocardial infarction (MI), congestive heart failure, and sudden cardiac death accounting for 50% of deaths among ESRD patients [1]. After stratification by age, gender, race, and presence of diabetes, the cardiovascular mortality of ESRD patients undergoing hemodialysis or peritoneal dialysis is 10 to 20 times higher than the general population [12]. The pathogenesis of cardiac disease in the ESRD population is complex, but involves the interplay of traditional risk factors along with risk factors that are specific to the dialysis population. The novel risk factors among dialysis patients include hyperphosphatemia, elevated calcium and phosphate

Key words: left ventricular hypertrophy, vitamin D, 1,25-dihydroxyvitamin D$_3$, cardiac function, end-stage renal disease, congestive heart failure.

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Table 1. Summary of human studies linking vitamin D with hypertension and cardiovascular disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Findings</th>
<th>Model</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baksi</td>
<td>Increased contractility of cardiac tissue in response to increased extracellular calcium</td>
<td>Vitamin D–deficient rats</td>
<td>[48]</td>
</tr>
<tr>
<td>Weishaar</td>
<td>Increased plasma renin activity</td>
<td>Cultured myocytes</td>
<td>[32]</td>
</tr>
<tr>
<td>O’Connell</td>
<td>Shift in myosin side chain favoring V1 isotype</td>
<td>Cultured myocytes</td>
<td>[56]</td>
</tr>
<tr>
<td>Walters</td>
<td>Increased contractility of isolated aortic rings in response to norepinephrine</td>
<td>Cultured myocytes</td>
<td>[52]</td>
</tr>
<tr>
<td>O’Connell</td>
<td>1,25-dihydroxyvitamin D3 reduces cellular proliferation of cultured myocytes by decreasing entry into S-phase</td>
<td>Vitamin D receptor deficient mice</td>
<td>[31]</td>
</tr>
<tr>
<td>Li</td>
<td>Elevated angiotensin II, aldosterone, hypertension, and increased heart mass</td>
<td>Vitamin D receptor deficient mice</td>
<td>[58]</td>
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</table>

product, lipoprotein(a), hyperhomocysteinemia, and chronic inflammation [2–8]. These risk factors are most closely associated with atherogenesis, though the presence of LV dysfunction is another important predictor of cardiac death on dialysis [10, 11].

The impact of congestive heart failure on survival in ESRD patients on dialysis is striking. The presence of congestive heart failure (CHF) confers a higher adjusted relative risk of death (1.26 vs. 1.11) than does the presence of coronary artery disease in new ESRD patients [9]. Harnett et al reported an unadjusted 5-year survival of 20% among patients who initiate hemodialysis with congestive heart failure compared with a 50% survival among those without heart failure [16]. Similar findings were reported by Silberberg from a cohort of 91 patients who had an echocardiogram within 2 months of starting hemodialysis. In patients with a left ventricular mass index (LVMI) >125, 5-year survival was slightly above 20% and, among those with an LVMI <125, 5-year survival was 50%. Interestingly, Foley et al [17] found that the presence of coronary artery disease was not predictive of mortality on hemodialysis when age, diabetes, angina pectoris, cardiac failure, and serum albumin were analyzed as covariates. However, the presence of clinical heart failure and the presence of systolic dysfunction were predictive of poor long-term survival, with no patients with either of these abnormalities surviving to 5 years [18]. This could be reflective of the 6-month survival requirement of study entry as early mortality has been shown to be predicted by the presence of coronary artery disease [19]. However, it also suggests that much of the mortality of coronary artery disease in dialysis patients is manifest through cardiac failure [20].

The presence of left ventricular hypertrophy is an important risk factor in the development of congestive heart failure in hemodialysis. Left ventricular disorders are very common on hemodialysis. Parfrey et al reported that only 15.6% of patients begin dialysis therapy with a normal echocardiogram, with concentric LVH, LV dilatation, and systolic dysfunction occurring in 40.7%, 28%, and 15.6%, respectively [10]. In a cross-sectional study of chronic kidney disease and dialysis patients, Greaves et al found a high prevalence of echocardiographic LVH or LV dilatation to occur in 50% of patients [21]. The presence of these individual LV disorders was significantly associated with the subsequent development of clinical CHF while on dialysis. In Harnett’s study, higher LV mass index and increased LV end diastolic diameter were associated with subsequent development of CHF [16]. Thus, addressing left ventricular disorders should be taken on with the same urgency in ESRD patients as atherosclerosis risk factor reduction. Modalities that have been shown to reduce LVH in renal failure include treatment with angiotensin-converting enzyme (ACE) inhibitors [22], control of anemia [23], and daily dialysis [24]. Now, recent evidence is emerging that vitamin D therapy plays an independent role in treatment of increased LV mass. The evidence for an emerging role of vitamin D in left ventricular disorders in renal disease is the topic of the remainder of this review.

VITAMIN D IN CARDIOVASCULAR DISEASE

There is ample clinical evidence, outside of renal failure, that vitamin D may play a role in cardiovascular disease. Vitamin D deficiency is a common clinical entity [25], and the association of vitamin D deficiency and hypertension has been studied on an epidemiologic level. Serum calcitriol levels are inversely related to blood pressure in normo- and hypertensive subjects [26, 27]. Additionally, there are earlier interventional studies, looking at the effects of vitamin D supplementation and blood pressure in normotensives and hypertensives. In 7 studies reviewed by Zitterman, 3 found no effect, and 4 found lower blood pressures in healthy individuals treated with 25-hydroxyvitamin D3 supplementation [28]. Hypocalcemia is a potential explanation for these findings [29, 30], although another plausible mechanism for the association of vitamin D deficiency and hypertension is hyper-reninemic hyperaldosteronism, as has been
demonstrated in vitamin D receptor knockout mice [31] and vitamin D–deficient animals [32]. Additionally, vitamin D deficiency has also been implicated in the pathogenesis of CHF in patients without renal failure. Low levels of calcitriol, lower serum calcium, and higher phosphorus levels are associated with clinical congestive heart failure and elevated pro-ANP levels in patients with a serum creatinine <2 mg/dL [33]. However, the most direct evidence for the role of vitamin D in cardiac disease comes from studies in ESRD patients receiving vitamin D analogues for the control of hyperparathyroidism. Preliminary data from our group show short daily hemodialysis reduces left ventricular mass, and that treatment with paricalcitol may have an additive effect [34]. This is consistent with the results of Park et al, who showed regression of LV hypertrophy in hemodialysis patients treated with vitamin D [35]. There is also emerging evidence that treatment with vitamin D analogues reduces mortality in hemodialysis patients [36–38]. It is too early to know if the beneficial effect of vitamin D treatment is mediated by effects on cardiac function; there is, however, literature to support the notion that vitamin D has a beneficial effect on cardiac tissue.

**MOLECULAR BASIS OF VITAMIN D PHYSIOLOGY IN CARDIAC FUNCTION**

The vitamin D receptor has a wide tissue distribution, including cardiac tissue [39], and clearly, vitamin D plays important roles beyond its effects on calcium and phosphorus homeostasis. Vitamin D exerts its effects on tissues through interaction with the vitamin D receptor (VDR). The VDR is a member of the nuclear receptor family that activates gene transcription once bound by ligand [40]. Like other members of this family, VDR forms a heterodimer with the RXR (retinoic acid) receptor in order to bind DNA. The active form of vitamin D, 1,25-dihydroxyvitamin D₃, binds to the VDR with much higher affinity than 25-hydroxyvitamin D₃ [41]. There are many novel activities of vitamin D that are beginning to be recognized. These include effects on immune function, cellular proliferation, and neuroprotection [42–45]. Thus, it is clear that in the uremic state, which is associated with vitamin D deficiency [13] and vitamin D resistance [14, 15], many tissues can be affected by abnormal vitamin D physiology, including cardiac tissue.

Vitamin D has been shown to have several biological effects on the heart in animal studies. It plays a role in cardiac cell contraction, proliferation, maturation, protein expression, and collagen expression. The VDR was first identified in cultured cardiac cells by Sampson et al [46], and in rat normal hearts by Walters et al [47]. Baksi et al showed increased contractility in response to increasing concentration of the extracellular calcium bath in atria from rats maintained on a vitamin D–deficient diet [48]. Additionally, there is increased contractile response to norepinephrine in isolated aortic rings from vitamin D–deficient mice, as well as increased plasma renin activity [32]. These results suggest that vitamin D may play a role in maintenance of vascular tone and cardiac output; given the association of hypertension and hypocalcemia in humans [49], these could not be attributed to vitamin D depletion alone. To address this, the rats were maintained on a diet containing 2.5% calcium and 1.0% phosphate, a change in diet that normalizes PTH, calcium, and phosphorus in the vitamin D–deficient animals. With normalization of these parameters, the contractile response of isolated atria and increased renin levels remained; however, the vascular smooth muscle response to norepinephrine was abolished. The implication is that there are indirect and direct effects of vitamin D on cardiovascular function, and that the one mechanism of indirect action is through calcium concentration. Additionally, Weishaar has shown that rats fed a vitamin D–deficient diet have increased amounts of collagen by measuring hydroxyproline per gram of heart tissue and collagen deposition in the extracellular space of the myocardium. This effect could not be suppressed by normalcalcemia when the animals were fed a 2.5% calcium diet [50], suggesting that this is a direct effect of vitamin D.

**Table 2. Summary of animal studies demonstrating cardiovascular effects of vitamin D**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Finding</th>
<th>Study population</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kristal-Boneh/Young</td>
<td>Serum calcitriol levels are inversely related to blood pressure</td>
<td>Normal and hypertensive, population-based study</td>
<td>[26, 27]</td>
</tr>
<tr>
<td>Zitterman</td>
<td>Possible lower BP in healthy individuals taking Vitamin D supplementation</td>
<td>Review of 7 intervention studies</td>
<td>[28]</td>
</tr>
<tr>
<td></td>
<td>Low calcitriol, lower calcium, and higher phosphorus levels are associated with congestive heart failure</td>
<td>CHF population with creat &lt;2.0 mg/dL</td>
<td>[33]</td>
</tr>
<tr>
<td>Park</td>
<td>Regression of LV hypertrophy in patients treated with vitamin D</td>
<td>Hemodialysis patients, small study</td>
<td>[35]</td>
</tr>
<tr>
<td>Mizani</td>
<td>Normalization of LV hypertrophy in patients treated with high doses of paricalcitol</td>
<td>Hemodialysis patients, small study</td>
<td>[34]</td>
</tr>
<tr>
<td>Teng</td>
<td>Decreased cardiovascular mortality in patients treated with paricalcitol</td>
<td>Large studies, epidemiologic, cross-sectional</td>
<td>[37, 38]</td>
</tr>
</tbody>
</table>
deficiency. Thus, vitamin D deficiency appears to favor a hyperreninemic, hypertensive state with impairment of cardiac contractile function and an increase in myocardial collagen content, a series of abnormalities that could predispose to LVH and CHF.

Vitamin D also has many effects on cardiac tissue growth and development. Walters et al demonstrated that the uptake of calcium by cardiac muscles cells is in part regulated by vitamin D3, an effect that is receptor mediated, requiring transcription and protein synthesis [51]. Vitamin D has also been shown to affect the growth of cardiac cells in culture. O’Connell et al showed that 1,25-dihydroxyvitamin D3 reduces proliferation rate, PCNA levels, and c-myc levels of myocytes in culture through decreased entry into S-phase [52]. Vitamin D deficiency also results in a shift in the tissue distribution of V1 and V3 myosin chains, favoring the V1 isotype [53]. Shifts in myosin isotypes have been shown to alter myocyte contractility [54, 55]. Interestingly, this shift was seen only if the animals were maintained with normocalcemia (2.5% calcium and 1.0% phosphorus diet); thus, increased cardiac contractility cannot be completely explained by shift in myosin distribution [53]. Cardiac myocyte differentiation is also inhibited by 1,25-dihydroxyvitamin D3. This is evidenced by inhibition of the increase in MM (cardiac specific) creatinine kinase (CK) isotype from the predominant BB (brain specific) CK isotype found in immature myocytes. This effect of vitamin D on cardiac myocyte differentiation can be inhibited by staurosporine, and mimicked by PMA (phorbol 12-myrsitate 13-acetate), demonstrating that this effect of vitamin D is mediated by protein kinase C activation [56]. It is clear that vitamin D plays a crucial role in cardiac tissue through regulation of intracellular calcium levels, proliferation, cell differentiation, and maturation.

Li et al have recently characterized the VDR-deficient mice, and have demonstrated the effects of vitamin D on the renin-angiotensin system [31]. They showed that VDR-deficient mice have elevated levels of circulating angiotensin II (Ang II), increased production of renin with hypertension (readily reversed by captopril), and increased heart mass. They also showed that administration of vitamin D suppressed renin expression in normal mice. The effects on renin secretion and Ang II levels were not abrogated by dietary normalization of the serum calcium. This is consistent with the alterations in the renin-angiotensin axis described by Weishaar 12 years earlier in vitamin D–deficient animals [32]. The increased renin expression in VDR receptor mice was suppressible by salt loading, but renin levels remained much higher than in the control mice, suggesting that 1,25-dihydroxyvitamin D3 has an independent, but additive, effect with distal salt delivery on regulation of renin secretion and blood pressure regulation. The direct applicability of this animal data to the human situation is unclear at the present time, but the VDR has been identified in human heart tissue as a 55 kD protein [57]. Given the clinical literature that is increasingly implicating vitamin D in the pathogenesis of cardiac disease, especially in dialysis patients, it is likely that many of the effects of vitamin D on cardiac function in the rodent models apply to humans. Thus, functional or absolute vitamin D deficiency may predispose to
development of LVH by impairing cardiac contractility, increasing myocardial collagen content, altering myosin protein expression, and activating the renin-angiotensin axis.

CONCLUSION

Vitamin D has long been part of the nephrologist’s armamentarium in treating secondary hyperparathyroidism. There is now increasing evidence that vitamin D treatment has more far-reaching consequences in the dialysis population than just treatment of secondary hyperparathyroidism and prevention of renal osteodystrophy. Vitamin D plays a role in cardiovascular disorders such as hypertension and CHF in the general population, and there is ample evidence that vitamin D is important in the development and physiology of cardiac tissue. Clinical studies have begun to demonstrate some of the beneficial effects of vitamin D on left ventricular hypertrophy in patients with ESRD, as well as improved survival of hemodialysis patients treated with vitamin D. Given the overwhelming burden of cardiovascular mortality in the ESRD population, and the important role that left ventricular hypertrophy plays in this mortality, it is likely that abnormal vitamin D metabolism in renal failure contributes to cardiovascular disease. This can occur through deficiency of the 1,25-dihydroxyvitamin D₃; or through resistance to its actions in the uremic state. Regardless of the mechanism, further study in this area is needed through a prospective, randomized trial specifically looking at cardiovascular and mortality outcomes in a hemodialysis and CKD populations. Design of such studies will have to carefully account for differences in calcium phosphate product, hyperparathyroidism, and phosphate control between study and control groups in order to determine the direct effects of vitamin D.

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