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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.

Key words: left ventricular hypertrophy, vitamin D, 1,25-dihydroxyvitamin D3, cardiac function, end-stage renal disease, congestive heart failure.

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

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

Author	Findings	Model	Reference
Baksi	Increased contractility of cardiac tissue in response to increased extracellular calcium		[48]
Weishaar	Increased plasma renin activity		[32]
	Increased contractility of isolated aortic rings in response to norepinephrine		[32]
	Increased collagen in cardiac tissue	Vitamin D–deficient rats	[50]
O'Connell	Shift in myosin side chain favoring V1 isotype		[53]
Walters	Vitamin D_3 stimulates uptake of calcium by cardiac tissue		[51]
O'Connell	1,25-dihydroxyvitamin D_3 reduces cellular proliferation of cultured myocytes by decreasing entry into S-phase	Cultured myocytes	[52]
O'Connell	1,25-dihydroxyvitamin D_3 inhibits cardiac myocyte differentiation through protein kinase C dependent mechanism		[56]
Li	Elevated angiotensin II, aldosterone, hypertension, and increased heart mass	Vitamin D receptor deficient mice	[31]
	Elevated intracardiac renin		[58]

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 a 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 D_3 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