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PERSPECTIVES IN RENAL MEDICINE

Vitamin D and its analogues: Do they protect against cardiovascular disease in patients with kidney disease?

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Background. Patients with chronic kidney disease (CKD) are at high risk for cardiovascular disease, and despite recent advances in hypertension control, anemia management, and dialysis adequacy, mortality remains high. Improved understanding of nontraditional risk factors, including those present at early phases in CKD, may lead to novel therapeutic strategies. CKD has been demonstrated to be an independent risk factor for cardiovascular disease in the general population, but data are lacking as to the associated potential abnormalities that occur in association with reduced glomerular filtration rate (GFR), which may contribute to this increased risk. Data are accumulating regarding the role of abnormalities of calcium, phosphorus, vitamin D, and parathyroid hormone (PTH) in cardiovascular disease. Vitamin D deficiency is present even in the early stages of CKD. Vitamin D plays a central role in calcium-phosphorus homeostasis, regulation of PTH, and formation and maintenance of bone. However, until recently, vitamin D has not been considered to have a biologic role in CKD beyond mineral regulation, or has been considered as a negative factor contributing to soft tissue and cardiovascular calcification. In light of recent observational studies showing an association of vitamin D therapy and survival benefit in hemodialysis patients, the effects of vitamin D on cardiovascular system have become a heavily debated issue.

Methods. A Medline search was performed to identify relevant literature describing the role of vitamin D in the pathogenesis of cardiovascular disease. Both the experimental and clinical literatures in English were reviewed.

Results. The accumulating published data demonstrate both associative relationships and mechanisms for biologic plausibility. The following three potential mechanisms may be important for the protective effects of vitamin D against cardiovascular disease mortality: vitamin D can inhibit various aspects of inflammation, which have been established as a key pathogenic mechanism in atherosclerosis; vitamin D exerts an antiproliferative effect on myocardial cell hypertrophy and proliferation, which underlies the pathogenesis of congestive heart failure; and vitamin D acts as a negative endocrine regulator for the renin-angiotensin system, which itself plays an important independent role in hypertension and cardiovascular health.

Conclusion. Vitamin D deficiency might be an underestimated nonclassical risk factor for cardiovascular disease in CKD. Based on a review of the evidence, from both basic science and clinical studies, this article supports the possible protective role of vitamin D beyond its effect on mineral metabolism, and suggests the need for ongoing evaluation of the role of vitamin D in cardiovascular health in the CKD population.

Key words: vitamin D, vitamin D analogues, chronic kidney disease, cardiovascular disease, dialysis, inflammation, cardiac hypertrophy, renin-angiotensin system, mechanisms.

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Vitamin D, in the form of 1,25-dihydroxyvitamin D_3 and vitamin D analogues, is given primarily to treat secondary hyperparathyroidism and the associated calcium and phosphate metabolic abnormalities of chronic kidney disease (CKD). Recent observational studies [1, 2] among patients on hemodialysis have indicated that vitamin D treatment was associated with a significant reduction in the risk of all-cause death and of cardiovascular death among these patients; while other studies have suggested that excess vitamin D contributes to risk of hypercalcemia and vascular calcification, which is associated with reduced survival and morbidity [3, 4]. Nonetheless, there is accumulating evidence that vitamin D may in fact be linked to cardiovascular processes in CKD populations. Thus, this review examines the literature that demonstrates the potential mechanisms of vitamin D in cardiovascular protection that outside its effect on calcium and phosphate metabolism.

CARDIOVASCULAR DISEASE IS ASSOCIATED WITH CKD

Cardiovascular disease is more prevalent in patients with CKD than in the general population [5], and is the leading cause of death in patients with end-stage renal disease (ESRD) [6]. Because of the high prevalence of patients with CKD and their high risk for death, the National Kidney Foundation Task Force on Cardiovascular Disease has targeted two cardiovascular disease

conditions, coronary artery disease and left ventricular hypertrophy (LVH), when considering strategies that can influence cardiovascular disease outcomes in CKD [6]. A substantial amount of data exists to support the large burden of cardiovascular disease in CKD populations. The United States Renal Data System annual report cites that 34% of ESRD patients have concomitant coronary artery disease or myocardial infarction. Other reports describe the high prevalence of LVH prior to and at dialysis initiation [7, 8]. Mortality due to cardiovascular disease has been estimated to be 10 to 20 times higher in dialysis patients than in the general population [9], and the National Kidney Foundation Task Force on Cardiovascular Disease recommends that CKD patients be considered among the highest risk group for developing cardiovascular disease [6].

CKD, AN INDEPENDENT RISK FACTOR FOR CARDIOVASCULAR DISEASE

Patients with CKD often have many traditional cardiovascular risk factors defined in the Framingham Heart Study, such as older age, hypertension, diabetes, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol [10]. However, cross-sectional studies of CKD patients demonstrate that the Framingham risk equation, which predicts cardiovascular disease risk based on traditional risk factors, cannot explain all of the cardiovascular disease risk in patients with CKD [9–11]. Recent studies have suggested that the presence of reduced glomerular filtration rate (GFR) itself is a risk factor for cardiovascular disease [12]. While some systematic reviews have concluded that the findings from observational studies were equivocal [13], other long-term, observational studies in different age groups [14–17] have provided evidence that reduced GFR is an independent predictor of death and cardiovascular disease. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure Seventh Report has even stated that estimated GFR < 60 mL/min is a major risk factor for cardiovascular disease [15, 18]. The specific abnormalities associated with decreased GFR that contribute to increased cardiovascular disease risk remain to be defined.

ABNORMAL CALCIUM AND PHOSPHATE METABOLISM IS ASSOCIATED WITH WORSE OUTCOMES

Several nontraditional factors have been implicated as risk factors for cardiovascular disease in CKD patients [9], but are beyond the scope of this review. Increased vascular and visceral calcifications, which are associated with hyperphosphatemia and both hyperparathyroidism and hypoparathyroidism, have been correlated with increased risk of cardiovascular disease [19]. Atherosclerotic plaques of ESRD patients have been found to be more heavily calcified than nonuremic patients, with thickening of the media layer but not of the intima [20, 21]. In comparison with nonuremic patients, ESRD patients have greater calcified transformation of plaques but do not have greater extension of the plaque or a greater number of early lesions [20]. London et al [22], evaluating the common carotid artery and blood vessels of the pelvis and thigh in ESRD patients, found calcification in both the media and the intima, and subsequently related this to abnormalities in serum phosphorus, calcium and bone morphometry. Their work suggests that intimal calcification occurs predominantly in older patients with traditional cardiovascular risk factors, while medial calcifications are found largely in younger patients with longer duration of dialysis. In another study, Chertow et al [23] used electron beam tomography to determine potential factors in the development of progressive coronary and aortic artery calcification. The result showed that calcium may directly or indirectly [through parathyroid hormone (PTH)] influence the balance of skeletal and extraskeletal calcification, but there was no association between vitamin D use (or measured levels) and progressive calcification. In their study, both types of calcification were significantly associated with all-cause mortality and cardiovascular mortality compared to patients with no increased evidence of calcification [21]. Medial calcifications were more strongly associated with these endpoints, although patients with intimal calcification had the worse prognosis for all-cause mortality.

Observational clinical studies support hyperphosphatemia, abnormalities of parathyroid hormone and increased vascular calcification as risk factors for cardiovascular disease among CKD patients [24]. Longitudinal data reveal an increased risk of death for ESRD patients with serum phosphorus above 6.5 mg/dL and for patients with calcium $\times$ phosphorus (Ca $\times$ P) product above 72 mg^2/dL^2 [25]. An increased risk of death from coronary artery disease has also been reported for patients with similarly elevated serum phosphorus levels, and an increased risk of sudden death has been associated with elevated levels of serum phosphorus, Ca $\times$ P, and PTH [25]. However, these data are based on administrative databases and are observational in nature, thus describing an association that requires further exploration.

A recent article by Stevens et al [26] further demonstrates the increased probability of mortality associated with different combinations of calcium, phosphorus, and PTH, and suggests that different dialysis vintages and different constellations of these variables portend risk of mortality, thus underscoring the complexity of the area. Interestingly, serum calcium levels have been inconsistently correlated with mortality risk; however, this may be due to the lack of attention to vitamin D therapy as

a possible confounder. A recent cohort study, presented in preliminary form, analyzed the baseline distribution of serum intact PTH (iPTH) and Ca × P levels by quintiles in hemodialysis patients receiving paricalcitol, calcitriol, or no vitamin D therapy in regard to their relationship with hospitalization outcomes. The results showed no or a weak association between serum iPTH and Ca × P with morbidity among those treated with vitamin D analogues, but a strong association among those not receiving vitamin D treatment [27]. Thus, vitamin D therapy may be a confounder for the association between morbidity and PTH or Ca × P product: the benefit of vitamin D may be unrelated to its effects on PTH or mineral control.

CLINICAL OUTCOMES WITH VITAMIN D THERAPY, A POSSIBLE PROTECTIVE EFFECT

A number of recently published observational studies provide further support for a possible protective role for vitamin D in the CKD population. These studies described the effect of calcitriol and vitamin D analogues on all-cause mortality and cardiovascular mortality in patients on hemodialysis, and suggest an association between vitamin D analogues and lower risk of death and cardiovascular death. Using administrative data, Teng et al [1] retrospectively analyzed the 3-year survival rate of 67,399 patients on hemodialysis between 1999 and 2001. The analysis compared patients treated with calcitriol to those treated with the vitamin D analogue paricalcitol with the objective to determine whether paricalcitol treatment, which results in less elevation in serum calcium and phosphorus levels than calcitriol (previously studied by Sprague et al [28]), resulted in a lower mortality rate. A Cox regression analysis described an association of paricalcitol treatment with both significantly less increase in serum calcium and phosphorus at 12 months, and a significantly higher survival over the 36 months as compared to calcitriol. Caution in interpretation of this nonrandomized, observational data is important. However, the underlying protective mechanism may extend beyond the impact on calcium and phosphate metabolism, as the results showed that the risk of death was significantly lower at all levels of serum calcium, phosphorus, and PTH in the presence of paricalcitol.

Importantly, Teng et al [1] did not include a nonvitamin D–treated comparative group to evaluate the effects of calcitriol on outcome. Two other studies have addressed this question. Tentori and associates have presented, in abstract form, an analysis of a large cohort of approximately 8000 hemodialysis patients treated during a similar time period and reported the comparative survival rates of patients treated with calcitriol, paricalcitol, doxercalciferol (another vitamin D analogue), or no treatment [29]. There were no major differences in survival between those receiving any vitamin D supplements; however, the hazard ratio (HR) for mortality was significantly higher (1.2) in the no treatment group. No significant differences in serum calcium levels among the treatment groups were found, although the mean PTH was higher in patients receiving paricalcitol and doxercalciferol than those treated with calcitriol. In another observational study of 242 patients on chronic hemodialysis, those treated with alfacalcidol, another vitamin D analogue, were found to have a significantly lower risk of death from cardiovascular causes than those with no vitamin D treatment [2]. There were no significant differences in noncardiovascular mortality. A step-wise multivariate Cox analysis indicated that cardiovascular mortality was significantly associated with age, presence of diabetes, and inversely related to treatment with alfacalcidol.

Overall, the results of these observational studies provide support for the hypothesis that there may be a protective benefit of vitamin D therapy relative to no vitamin D treatment in dialysis patients, which appears to be separate from the direct impact of vitamin D on mineral metabolism parameters.

HOW COULD VITAMIN D REDUCE CARDIOVASCULAR MORTALITY? A CASE FOR BIOLOGIC PLAUSIBILITY

The last decades have demonstrated that improving dialysis quality by increasing Kt/V and management of anemia leads to an improved survival benefit in hemodialysis patients, and that CKD patients may benefit from control of hypertension, anemia, and other factors. Nonetheless, survival still remains poor for the majority of dialysis patients, and those with CKD remain more likely to die of cardiovascular disease causes than to survive to dialysis. Interestingly, either relative or absolute deficiency of vitamin D is present even in the early stages of CKD [30]. Thus, it is possible, that vitamin D deficiency may be one of the underrecognized, nonclassic risk factors for cardiovascular disease in CKD patients. Previous work has viewed vitamin D primarily in terms of its role in bone and calcium-phosphate metabolism; however, more recent information has shown potentially unique actions of vitamin D beyond these classic effects.

In particular, the vitamin D receptor, which mediates the actions of vitamin D, has been found in almost every organ, including the heart, the vascular wall, the kidney, and immune cells [31–33]. As a ligand-activated transcriptional factor, the vitamin D receptor regulates a large number of genes involved not only in calcium and phosphate metabolism but also in other physiologic processes. Therefore, it will be important to explore possible mechanisms which support the influence of vitamin D on cardiovascular disease, independent of its effects on PTH and calcium-phosphate homeostasis.

Table 1. Potential mechanisms involved in vitamin D protection of the cardiovascular system

Potential mechanisms	Key evidence	Key references	Limitations
Anti-inflammation, antiatherogenesis, and protection against blood vessel injury	Inhibition of antigen presenting cell maturation, and functions; inhibition of smooth muscle cell proliferation; down-regulation of nuclear factor-κ B (NF-κB) activity, stimulation of anti-inflammatory cytokine production; and modulation of matrix metalloproteinase-9 (MMP-9) and C-reactive protein status	[38, 40–42]	Experimental data of vitamin D suppression of atherosclerosis has yet to be established
Inhibition of cardiac hypertrophy and myocyte proliferation	Inverse relationship between vitamin D levels and congestive heart failure; vitamin D treatment reduces left ventricular hypertrophy (LVH); vitamin D deficiency or vitamin D receptor deficiency leads to increase in blood pressure and myocardial hypertrophyin rats and mice; and suppression of endothelin-induced cardiomyocyte hypertrophy and atrial natriuretic peptide expression	[45, 46, 48, 49, 51, 58, 60]	Direct experimental evidence for vitamin D suppression of cardiac hypertrophy in animal models is still lacking
Regulation of the renin-angiotensin system	Inverse relationship between vitamin D levels and plasma renin activity; vitamin D treatment reduces blood pressure, cardiac hypertrophy and plasma renin activity; disruption of the vitamin D receptor gene leads to elevated renin production, cardiac hypertrophy, and high blood pressure in mice; and transcriptional repression of renin gene expression by vitamin D	[46, 54, 57–61]	More studies are needed to demonstrate the ability of vitamin D or vitamin D analogues to suppress plasma renin activity and blood pressure in hypertensive animals and clinical trials

As shown in Table 1, three major potential mechanisms may be important to explain the protective effects of vitamin D against cardiovascular mortality: the regulation of inflammation, the effect on myocardial cell hypertrophy and proliferation, and the regulation of the renin-angiotensin system. Accumulating data from basic and clinical studies do suggest a potential role for vitamin D in cardiovascular health.

VITAMIN D AND INFLAMMATION UNDERLYING ATHEROSCLEROSIS

Inflammation is now regarded as a key pathogenic mechanism in atherosclerosis:the propagation of atherogenic placques as a result of inflammatory processes is well described, and beyond the scope of this review [34–36]. Macrophages and T cells play a central role in the inflammation process, the formation of foam cells and atherosclerotic lesions on the arterial wall. The inflammatory response consists of release of cytokines, such as interleukin (IL)-1, IL-4, IL-6, interferon (INF)-γ and tumor necrosis factor (TNF)-α, by macrophages and T cells. These factors contribute to smooth muscle cell proliferation and plaque formation, and increase the synthesis and release of positive acute-phase proteins, such as C-reactive protein (CRP) and amyloid A, and reduce negative acute-phase proteins, such as albumin and transferrin. CRP has been demonstrated in numerous studies to be predictive of cardiovascular disease and its long-term outcomes [34]. Interestingly, high phosphate concentrations in the presence of high levels of PTH, which are often associated with vitamin D deficiency, can also induce smooth muscle cell proliferation and transformation to bone-forming cells [37].

VITAMIN D AND THE INFLAMMATORY PROCESS

Vitamin D has long been known to possess immunoregulatory activities [38]. The immunomodulatory effects of vitamin D are mediated by the vitamin D receptor, which is present in most immune cells. Vitamin D appears to inhibit antigen-presenting cell maturation [39, 40], as well as angiogenesis and vascular smooth muscle cell proliferation [41]. Vitamin D also down-regulates nuclear factor-κB (NF-κB) activity, increases IL-10 production and decreases IL-6, IL-12, IFN-γ, and TNF-α production, leading to a cytokine profile which favors less inflammation [38].

Consistent with a possible protective role against atherosclerosis, vitamin D has been shown to modulate the expression of tissue matrix metalloproteinases (MMPs) [42]. MMPs are connective tissue enzymes secreted by activated macrophages during inflammatory responses, and are involved in remodeling of the vascular wall and myocardium. MMPs break down collagen within the atherosclerotic lesion and cause lesion rupture, leading to thrombosis [34–36]. Timms et al [42] have analyzed the relationship between plasma levels of CRP, MMP-9, tissue inhibitor of metalloproteinase

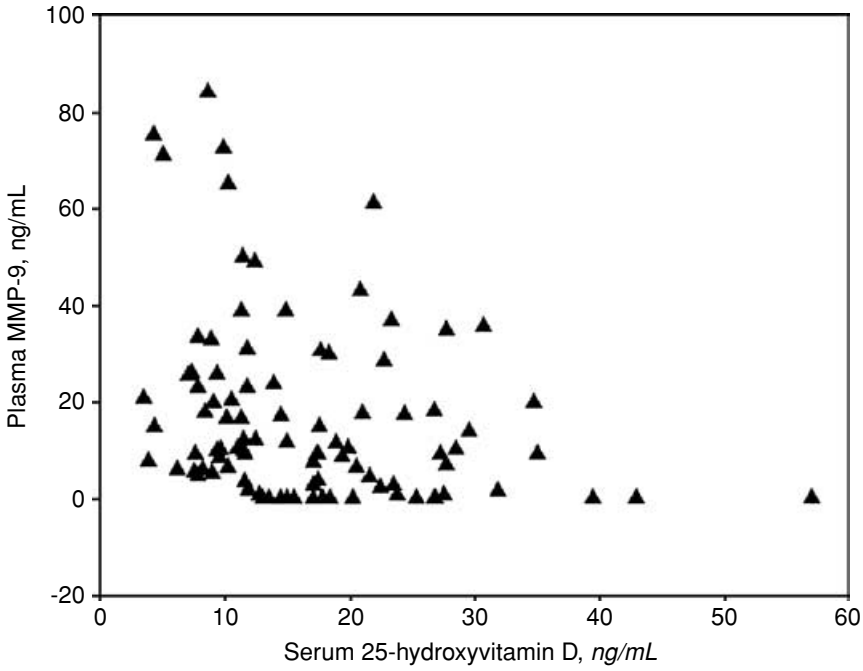

Fig. 1. Inverse relationship between plasma matrix metalloproteinase 9 (MMP-9) levels and vitamin D status (25-hydroxyvitamin D). These data were obtained from apparently healthy subjects of Bangladeshi origin living in London, United Kingdom (from Timms et al, *Q J Med* 95:787–796, 2002, with permission).

(TIMP-1) (a specific inhibitor of MMP), and serum levels of vitamin D among an apparently healthy population prone to vitamin D deficiency (Indo-Asian population), and found that plasma MMP-9 levels inversely related to vitamin D status (Fig. 1). Multiple linear regression analysis indicated that vitamin D status was the only independent determinant of CRP and MMP-9 levels. When patients with vitamin D deficiency were treated with three monthly cholecalciferol injections and evaluated 1 year later, mean MMP-9, TIMP-1, and CRP levels were decreased significantly from the pretreatment baseline [42]. These results suggest that vitamin D may inhibit various aspects of the inflammatory response to cardiovascular injury, and that in the presence of vitamin D deficiency vitamin D administration may reduce atherosclerotic plaque progression and plaque rupture. Consistent with these findings, Watson et al [43] have reported an inverse correlation between serum vitamin D levels and coronary calcification, which also suggests a protective role of vitamin D in atherogenesis.

Additional avenues of research that may further link vitamin D to cardiovascular disease outcomes relate to endothelial progenitor cells (EPCs). It is becoming evident that EPCs are associated with cardiovascular health [44]. Interestingly, MMP-9 activation is one of the factors required for recruitment and mobilization of bone marrow–derived EPCs, while CRP has been shown to have a detrimental effect on EPC differentiation and survival. Thus, vitamin D may be important in both the prevention of inflammation and the stimulation of EPCs from the bone marrow, thus affecting a number of key biologic processes that have an impact on cardiovascular health.

CARDIAC HYPERTROPHY AND EFFECTS OF VITAMIN D

Vitamin D may also play a role indirectly in the pathogenesis of congestive heart failure. Zitterman et al [45] have evaluated 54 patients (20 patients <50 years old and 34 patients ≥50 years old) with congestive heart failure (New York Heart Association classes ≥2) and compared them with 34 normal subjects (≥50 years old). In this study, levels of N-terminal proatrial natriuretic peptide (NT-proANP), a predictor of congestive heart failure and LVH severity, vitamin D metabolites, and parameters of calcium metabolism were measured in fasting blood samples. Both groups of congestive heart failure patients had markedly increased serum levels of NT-proANP and reduced circulating levels of 25-hydroxyvitamin D and calcitriol, indicating an inverse relationship between vitamin D levels and congestive heart failure. Moreover, several small studies have demonstrated an impact of vitamin D treatment on reduction of LVH among patients on chronic hemodialysis. Although most of these studies were of short duration and small sample size, Park et al [46] demonstrated that 15 weeks of intravenous calcitriol treatment of patients with ESRD and secondary hyperparathyroidism with LVH resulted in a marked reduction in LVH (Fig. 2).

McGonigle et al [47] demonstrated that the baseline serum 25-hydroxycholecalciferol was significantly

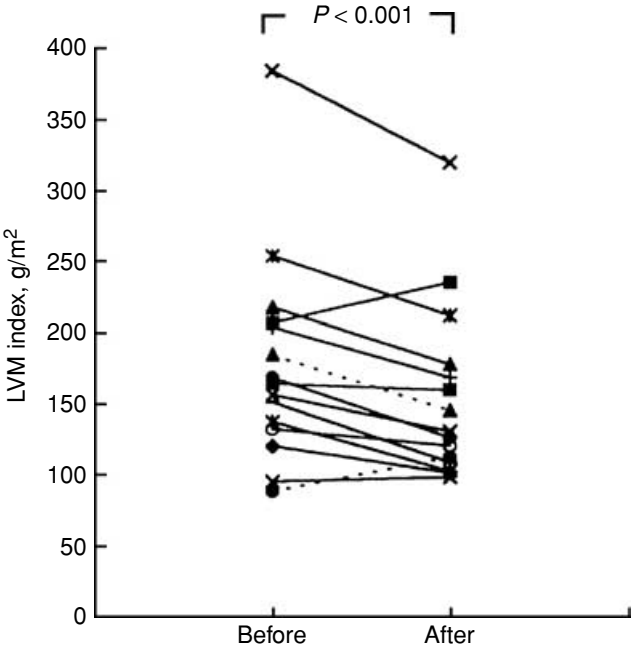

Fig. 2. Changes of left ventricular mass (LVM) index before and after calcitriol therapy in hemodialysis patients with secondary hyperparathyroidism. The patients received intravenous injection of calcitriol for 15 weeks (from Park et al, *Am J Kidney Dis* 33:73–81, 1999, with permission).

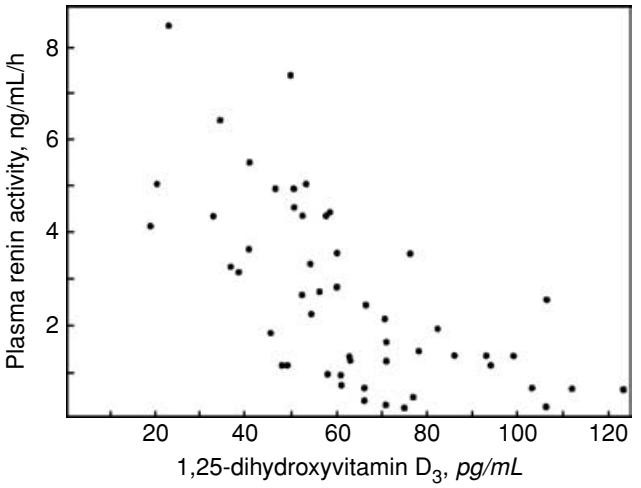

Fig. 3. Inverse relationship between plasma renin activity and 1,25-dihydroxyvitmain D levels in patients with essential hypertension (from Resnick et al, *Ann Intern Med* 105:649–654, 1986, with permission).

and inversely correlated with left ventricular function, and that after 6 weeks of intravenous treatment with 1α-hydroxycholecalciferol, there were small but significant improvements in indices of left ventricular function. Taken together, these small clinical studies support the hypothesis that vitamin D may be protective for myocardial structure and function.

The clinical findings have been corroborated by animal and in vitro studies, which provide a potential mechanism for explanation of these observations.

Weishaar and Simpson [48] and Weishaar et al [49] described a series of experiments exploring the role of vitamin D in myocyte proliferation and hypertrophy. They demonstrated that vitamin D deficiency induced myocardial hypertrophy, increased heart weight/body weight ratio and extracellular matrix production in myocardial tissue in rats. Moreover, 1,25-dihydroxyvitamin D_3 treatment inhibited cell proliferation of primary ventricular myocytes isolated from neonatal rat hearts, which was accompanied by down-regulation of c-myc and proliferating cell nuclear antigens (PCNAs) [50]. Using a similar in vitro ventricular myocyte culture, Wu et al [51] found that 1,25-dihydroxyvitamin D_3 inhibited myocyte hypertrophy induced by endothelin and the expression of α-skeletal actin and ANP gene, which were associated with myocardial hypertrophy and heart failure. These findings suggest that vitamin D plays an important role in cardiac homeostasis and that its deficiency may increase the risk of cardiac hypertrophy through biologically plausible mechanisms.

VITAMIN D REGULATION OF THE RENIN-ANGIOTENSIN SYSTEM

Clinical and epidemiologic studies over the past decades have demonstrated an inverse relationship between serum levels of 1,25-dihydroxyvitamin D_3 and blood pressure [52, 53] and/or plasma renin activity [54, 55] in normotensive and hypertensive subjects (Fig. 3). It has been reported that 4-week treatment with vitamin D and calcium reduced systolic blood pressure in nonhypertensive elderly women who were vitamin D deficient [56], and that 18-week vitamin D treatment reduced blood pressure in hypertensive subjects [57]. While these are relatively short-term studies without cardiovascular events, they do describe important intermediate outcomes in the development of cardiovascular disease. In chronic hemodialysis patients with secondary hyperparathyroidism, the previously mentioned study by Park et al [46] reported that 15 weeks of intravenous calcitriol treatment regressed LVH, which was accompanied by a significant reduction in plasma renin activity and plasma angiotensin II levels. Taken together, accumulating clinical data have provided evidence for a possible mechanism whereby vitamin D suppresses plasma renin activity and blood pressure. Therefore, either relative or absolute vitamin D deficiency may be a contributing risk factor to cardiovascular disease among CKD patients, and that vitamin D may protect cardiovascular health through modulation of the renin-angiotensin system.

Li et al [58, 59] have recently explored the mechanism underlying the relationship between vitamin D and the renin-angiotensin system using genetic animal

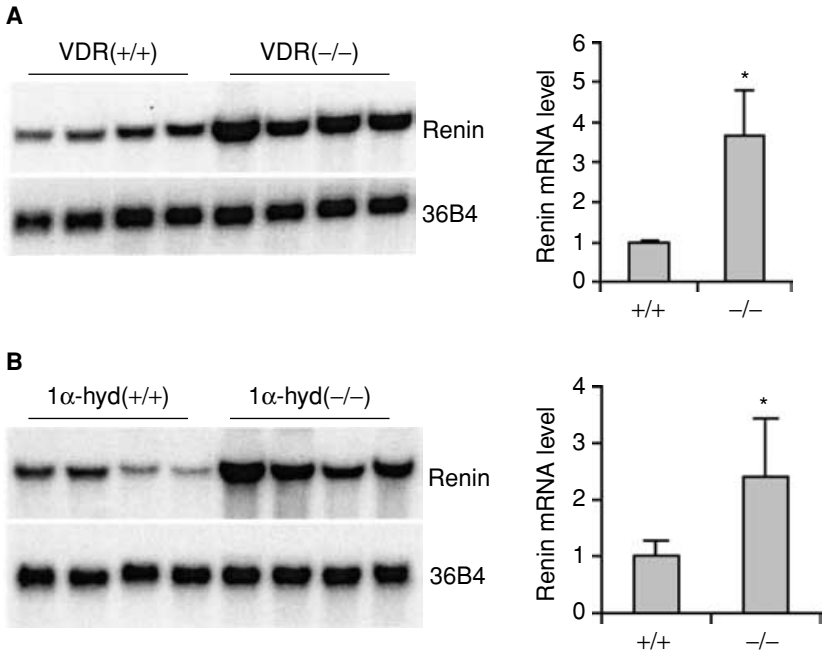

Fig. 4. Stimulation of the renin-angiotensin system in mutant mice lacking either the vitamin D receptor (VDR) gene or the 25-hydroxyvitamin D 1α-hydroxylase (1α-hyd) gene. A marked increase in renin mRNA transcript was seen in both vitamin D receptor knockout mice (*A*) and 1α-hydroxylase knockout mice (*B*). Left panels are Northern blot, and right panels are PhosphorImager quantitative results of renin mRNA levels detected by Northern blot analysis. $^*P < 0.01$ vs. wild-type mice.

models. Based on previous clinical and epidemiologic findings, they hypothesized that vitamin D is a negative endocrine regulator of renin biosynthesis in vivo. Consistent with this hypothesis, they found that renin mRNA and protein levels in the kidney were markedly increased in both vitamin D receptor knockout mice and 25-hydroxyvitamin D 1α-hydroxylase knockout mice (Fig. 4), indicating that intact vitamin D signaling is required for maintaining a proper level of renin production. They showed that plasma angiotensin II levels were markedly elevated in vitamin D receptor knockout mice, while angiotensinogen expression in the liver was not different from normal mice, indicating that the plasma angiotensin II elevation was due to increased renin activity. The vitamin D receptor knockout mice developed hypertension and cardiac hypertrophy due to the dysregulation of the renin-angiotensin system [58, 60, 61]. Further studies demonstrated that normal mice rendered vitamin D deficient also had increased renin production, whereas 1,25-dihydroxyvitamin D_3 treatment of normal mice resulted in renin suppression [58]. These studies clearly support the observation that 1,25-dihydroxyvitamin D_3 directly suppresses renin gene expression, and this suppression is independent of the effect of vitamin D on calcium metabolism. Thus, vitamin D appears to play a key role in renocardiovascular homeostasis by functioning as a negative endocrine regulator of the renin-angiotensin system. These studies also provide a molecular basis to explore the potential of vitamin D analogues as therapeutic renin inhibitors to control the renin-angiotensin system and blood pressure [62].

FUTURE DIRECTIONS

Data from both experimental and clinical studies appear to support the concept that vitamin D deficiency is associated with an increased risk for cardiovascular disease in CKD populations. Although this role may be, to some extent, mediated through elevated PTH and calcium-phosphate metabolism, recent scientific evidence suggests additional, possibly more relevant, biological mechanisms. Vitamin D may well modulate and suppress the inflammatory response to blood vessel injury, inhibit cardiomyocyte hypertrophy and proliferation, and negatively regulate the renin-angiotensin system. All of these effects may be equally or more important than the effect of vitamin D on PTH and calcium-phosphorus levels in the control of cardiovascular disease. However, there are limitations to these speculated mechanisms, as some aspects of our analyses rely on indirect evidence. Obviously, more direct experimental data are needed to confirm these mechanisms (Table 1).

Given the biologic effects of vitamin D and the results of observational studies that demonstrate an association of vitamin D therapy and improved cardiovascular outcomes in hemodialysis patients independent of calcium, phosphate and PTH levels, further studies are now necessary. Both observational and randomized controlled clinical trials are necessary to confirm the beneficial effect of vitamin D and analogues and to determine the impact of vitamin D deficiency and supplementation on clinical outcomes. Studies of biologic markers are also needed to better understand the mechanisms and the relationship of vitamin D therapy to clinical outcomes in all stages

of CKD. In addition, it would be important to compare the efficacy of different preparations of vitamin D analogues to understand whether there are class effects or differential effects of different preparations.

At the current time, it is not known at which level of vitamin D deficiency to start treatment and whether the effect is completely independent or partially related to the presence of hyperparathyroidism. Given the substantial number of patients with cardiovascular disease who have compromised kidney function, the importance of vitamin D in that population should be explored. Carefully designed trials which are able to address these complex questions will be able to determine the relative value of vitamin D therapy on the modulation of cardiovascular disease risk in CKD patients.

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