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Vitamin D and Vascular Disease: The Current and Future Status of Vitamin D Therapy in Hypertension and Kidney Disease

Anand Vaidya, MD, MMSc¹ and John P. Forman, MD, MSc²

¹Division of Endocrinology, Diabetes, and Hypertension; Brigham and Women's Hospital; Harvard Medical School

²Channing Laboratory; Renal Division; Brigham and Women's Hospital; Harvard Medical School

Introduction

Vitamin D has long been known to be an important factor for normal calcium metabolism and skeletal health. In the past decade, resurging interest and new research has implicated vitamin D deficiency as a potential contributor to the pathophysiology of many extra-skeletal conditions, including vascular diseases such as high blood pressure and kidney disease (1). Recent experimental animal and observational human studies have repeatedly suggested that supplementation with vitamin D metabolites may lower the risk for hypertension and kidney injury, but definitive human trials favoring the adoption of vitamin D therapy for the primary or secondary prevention of these conditions are still pending.

One of the many challenges in evaluating the biologic role of vitamin D in influencing blood pressure and renal function is deciphering which circulating vitamin D metabolites to measure in cross-sectional studies (ie - 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D) and what forms of vitamin D therapy to use for interventional studies (oral vitamin D₂, oral vitamin D₃, oral vitamin D receptor agonist, or ultraviolet radiation to promote cutaneous synthesis). The typical clinical barometer of human vitamin D status is 25-hydroxyvitamin D₃ (25[OH]D), which is converted to the active vitamin D metabolite 1,25-dihydroxyvitamin D₃ (1,25[OH]₂D) in a tightly regulated manner by the 1- α -hydroxylase enzyme. Although 25(OH)D is a stable steroid metabolite in blood, and is easier to quantify and interpret than 1,25(OH)₂D, it is 1,25(OH)₂D and not 25(OH)D that activates the vitamin D receptor (VDR) at the end-organ level. Thus, observational studies that measure 25(OH)D as a marker of overall vitamin D status may not always represent the full scope of biologic action. Moreover, the inferences drawn from trials that provide conventional over-the-counter vitamin D₂ or D₃ supplements, might differ from those drawn from trials that bypass the tightly regulated 1- α -hydroxylase reaction and provide 1,25(OH)₂D (or other VDR agonists) to illicit end-organ effects.

Another challenge is designing an investigation to elucidate the potential mechanisms whereby vitamin D could impact blood pressure and kidney function. To date, the most

intensely investigated mechanism of action by which vitamin D could prevent or improve vascular diseases is the proposed negative regulation of the renin-angiotensin system (RAS). However, several other biologic pathways have been implicated by prior studies.

The following discussion will review mechanistic studies that have lead to human investigations, evaluate the human data with a specific focus on the limitations of their conclusions, and propose future directions that may definitively ascertain the role of vitamin D in the pathophysiology of hypertension and kidney disease.

Vitamin D and Hypertension

Mechanisms of Association

The association of vitamin D with blood pressure and hypertension has been described for over a quarter of a century (2). The most notable mechanism implicating vitamin D with hypertension is its role as a negative regulator of the RAS (3); inappropriately elevated RAS activity is known to contribute to human hypertension and cardiovascular risk (4–6).

The development of vitamin D receptor (VDR) null mice has facilitated numerous experiments that have shed light on the relationship between vitamin D, the RAS, and hypertension (7). Li et al. reported that VDR null mice had significant elevations in renin activity and circulating plasma angiotensin II concentrations (3), and exhibited increased activity of the local cardiac-tissue RAS (3, 8). These mice displayed a phenotype of hypertension and cardiac hypertrophy that was attenuated when RAS antagonists were administered. A distinct mouse model of 1-alpha-hydroxylase deficiency also exhibited a phenotype of enhanced RAS activity, hypertension, and cardiac hypertrophy, that was attenuated by treatment with 1,25(OH)₂D or RAS antagonists (9). The findings of these experiments were further consolidated with the demonstration that 1,25(OH)₂D acts to suppress the expression of renin (10, 11), suggesting that the vitamin D-VDR complex may function as a negative regulator of the RAS, and could thereby exert protective downstream effects on blood pressure and cardiac tissue.

Corollary human physiology studies have generally supported this evidence from animals. Nearly twenty-five years ago, Resnick et al. observed lower plasma renin activity with increasing 1,25(OH)₂D (12). More recently, human mechanistic studies have shown that lower levels of 1,25(OH)₂D and 25(OH)D are associated with higher plasma renin and angiotensin II concentrations (12–14), and that lower 25(OH)D levels are associated with higher systemic vascular-tissue RAS activity (15).

Alternatively, other investigators have proposed a non-genomic effect of vitamin D on the RAS and blood pressure. Resnick and colleagues hypothesized that vitamin D was involved in regulating the flux of calcium into vascular smooth-muscle cells, therefore influencing intra-cellular calcium concentrations, vascular tone, blood pressure (2, 12, 16, 17), and decreasing renin secretion from juxtaglomerular cells (18, 19).

Other vascular-protective pathways have also been implicated in the association of vitamin D with hypertension. *In vitro* experiments have shown that vitamin D reduces the deleterious effect of advanced glycation products on the endothelium, improves activity of

the nitric oxide system, reduces inflammatory parameters, and enhances prostacyclin production (20–23). In conjunction with these basic findings, human studies exploring mechanisms of vitamin D in the pathophysiology of hypertension reported that concentrations of vitamin D metabolites were associated with improved endothelial function and oxidative stress (24–28), and were associated with circulating concentrations of adipocytokines implicated with blood pressure control (29–33).

Summary of Human Clinical Data

Most human clinical studies evaluating the role of vitamin D on blood pressure have been cross-sectional analyses. The majority of these were consistent with the animal data in showing an inverse association between vitamin D and blood pressure (34–36) or the prevalence of hypertension (37, 38). In contrast, at least two large cross-sectional studies demonstrated no detectable association between vitamin D and blood pressure or the prevalence of hypertension (39, 40); however, in addition to the traditional limitations of cross-sectional analyses, these results may be biased by the fact that the study populations had relatively high 25(OH)D concentrations as well as prevalent use of anti-hypertensive drugs, both of which could obscure a potential association (39, 40).

Prospective studies have produced similarly mixed results. In a longitudinal analysis of men from the Health Professionals' Follow Up Study and women from the Nurses' Health Study followed for 4–8 years, Forman et al. observed a pooled adjusted relative risk for incident hypertension of 3.18 (95% C.I. 1.39 to 7.29) when comparing individuals with lower (<15 ng/mL) versus higher (30 ng/mL) concentrations of 25(OH)D (41). In a subsequent nested case-control analysis of normotensive women from the Nurses' Health Study II, they observed an adjusted odds ratio for incident hypertension of 1.66 (*P*-trend 0.01) when comparing those with 25(OH)D levels in the lowest versus highest quartiles (42). The longitudinal Michigan Bone Health and Metabolism Study evaluated the risk for systolic hypertension in over 500 Caucasian women who had 25(OH)D and blood pressure assessments in 1993, and again 14 years later in 2007 (43). Although they observed no cross-sectional association between 25(OH)D concentrations and concurrent blood pressure at baseline in 1993, 25(OH)D concentrations of < 32 ng/mL at baseline were associated with a significantly increased risk for systolic hypertension in 2007 (adjusted odds ratio 3.0 [95% C.I.: 1.01 to 8.7]). In contrast, Jorde et al. reported conflicting observations from the Tromsø study, which followed individuals naïve to anti-hypertensive therapy from 1994 to 2008 (44). They did note an inverse association between systolic blood pressure and quartiles of 25(OH)D at baseline in 1994, but these baseline 25(OH)D concentrations did not predict incident hypertension or future blood pressure. Regardless of whether the disparity in these findings was due to the narrow range of 25(OH)D concentrations within the study populations, or other unrecognized confounders, they underscored the need for definitive interventional studies.

Observational studies have suggested higher blood pressures in winter months and latitudes further from the equator; thus implicating insufficient ultraviolet radiation exposure and decreased cutaneous synthesis of vitamin D₃ as potential culprits for vascular disease (45). Interventional studies to evaluate the effect of cutaneous vitamin D₃ synthesis with

ultraviolet radiation exposure have shed interesting but mixed results. Krause et al. randomized hypertensive subjects to receive total body ultraviolet radiation with either UVA or UVB, and observed that those receiving UVB had significant increases in 25(OH)D concentrations with concomitant decrements in 24-hour ambulatory systolic and diastolic blood pressures (−6 mmHg) (46). In a similar randomized study design, Scragg et al. evaluated normotensive individuals, but observed no changes in blood pressure despite significant rises in 25(OH)D concentrations (47). These findings of these studies may be limited by their relatively small sample sizes (n=18 and n=119, respectively), short durations of follow up (6 and 12 weeks, respectively), and focus on distinct study populations (hypertensive and normotensive, respectively).

To date, more than ten interventional studies have evaluated the effect of oral vitamin D therapy on blood pressure, although the majority of these trials were not designed specifically to evaluate blood pressure effects (48–61) (Table 1). The majority of these demonstrated no effect of oral vitamin D supplementation on blood pressure or incident hypertension. The largest of these studies was the Women's Health Initiative (n=36,282), designed to evaluate fracture and cancer risk in a population of largely 25(OH)D insufficient women receiving either a small dose of vitamin D₃ (400 IU/daily) with calcium supplementation, or placebo (55). After seven years of follow up, no change in blood pressure or incident hypertension were observed. The interpretation of these results was limited by the fact that the dose of vitamin D₃ was modest and not expected to significantly raise 25(OH)D levels (62–64), the rate of medication non-compliance was high (approximately 40%), and the majority of women in the placebo group also received supplemental vitamin D during the course of the study (approximately 60%). The second largest of these randomized studies (n=438) was designed to evaluate the effect of vitamin D₃ supplementation on weight loss, and included overweight and obese individuals, but did not exclude the use of anti-hypertensive medications (60). No change in blood pressure were observed after one year of therapy with either vitamin D₃ 40,000 IU/week, 20,000 IU/week, or placebo. Since 25(OH)D levels in this study rose from approximately 20 ng/mL to >50 ng/mL in the 40,000 IU/week group, these data argued that reasonable elevations in 25(OH)D did not influence blood pressure. On the other hand, whether a one year follow-up was sufficient to detect blood pressure outcomes, or whether a largely obese population with heterogeneous anti-hypertensive medication use was the ideal study population, is debatable.

Only two randomized trials to date have been designed to evaluate blood pressure as the primary end point in a population maintained free of anti-hypertensive therapy (50, 51). The first showed that, when compared with placebo, a single dose of vitamin D₃ 100,000 IU in a 25(OH)D deficient population (n=189) did not lower blood pressure after five weeks (50). The conclusions of this study are limited by its short duration of follow-up, relatively small sample size, and the modest 7 ng/mL rise in 25(OH)D levels (from a baseline of 13 ng/mL), all of which may have hampered the detection of a potential effect. In the second study, elderly 25(OH)D deficient women who received vitamin D₃ 800 IU/daily for 8 weeks exhibited a small but significant decline in systolic blood pressure (−7 mmHg) when compared with those who received placebo (51). Again, the conclusions of this positive study were limited by its short duration of follow-up, small sample size (n=148), and modest effect size.

Given the lack of well-designed, large-scale intervention studies evaluating the influence of oral vitamin D supplementation on blood pressure, several meta-analyses have attempted to aggregate prior study findings, but have produced inconclusive results (65–68). Witham et al. were able to detect a blood pressure lowering effect associated with vitamin D only when limiting their analyses to those few studies that focused on hypertensive individuals (65), whereas Pittas et al. were only able to detect this when limiting to studies that used higher doses of vitamin D supplementation (> 1000 IU/daily) (66). Burgaz and colleagues detected a reduced odds of hypertension when comparing the highest category of 25(OH)D concentration to the lowest (odds ratio 0.73, 95% C.I. 0.63 to 0.84) (67), but Elamin et al. detected no blood pressure lowering effect in a meta-analysis evaluating pooled cardiovascular outcomes (68).

Future Directions

To date, *in vitro* and animal experiments have provided convincing evidence to speculate the involvement of vitamin D in the pathophysiology of hypertension, possibly via its influence on the RAS, but human studies have not consistently supported this hypothesis. Because the majority of human clinical data stem from cross-sectional or interventional studies with notable design limitations, there is a need for definitive large-scale randomized controlled trials. To detect whether a true association between vitamin D and blood pressure control exists, future interventional studies should ideally be designed with sufficient sample size, long duration of follow-up, higher vitamin D supplementation doses, restriction of anti-hypertensive drug use, and potentially control for confounders of the RAS (such as dietary sodium intake). The VITAL study (NCT01169259) is a large randomized controlled trial ($n=20,000$) in the United States that opened for recruitment in late 2010, and aims to evaluate the impact of higher-dose vitamin D₃ supplementation (2,000 IU/daily) on cardiovascular and cancer outcomes over five years. The size, duration of follow-up, and higher doses in this study design may allow sufficient power to examine the effect of long-term oral vitamin D₃ supplementation on blood pressure. In addition, a subset of approximately 1,000 randomized participants in this trial will also have 24-hour ambulatory blood pressure assessments at baseline and after two years of study. There are potential limitations to this on-going trial: 1) participants will be older (>50 years of age), and therefore many may already have significant sub-clinical vascular disease that may not readily respond to a mild therapeutic; 2) the main trial of 20,000 participants may include those taking anti-hypertensive drugs (such as those that may influence the RAS), although the 1,000 participants who undergo 24-hour ambulatory blood pressure monitoring will not be taking anti-hypertensive medication; 3) the placebo group will be allowed to take up to 800 IU/daily of vitamin D₃ to reflect current standards of care (69) which could potentially attenuate the difference in effect between the intervention and control groups; and 4) whether an intervention that moderately raises concentrations of 25(OH)D (as opposed to direct treatment with a VDR-agonist) can provide therapeutic benefit over five years is unclear.

Vitamin D and Kidney Disease

Mechanisms of Association

A history of hypertension is frequent in those who develop kidney disease, yet vitamin D has been implicated as being reno-protective independent of its potential effects on blood pressure. The ensuing discussion will focus on the novel independent effects vitamin D metabolites may have on pathways that affect renal function and consequently progression of kidney disease.

As in the case of blood pressure, the most prominent mechanism explaining the role of vitamin D in kidney disease has been its negative regulation of the RAS in animal models. In addition to elevations in circulating RAS components, VDR-null mice also display increased expression of renal-vascular renin mRNA (3), supporting experiments that suggest vitamin D as an inhibitor of renin gene expression (11). When subjected to a model of renal injury consisting of unilateral ureteral obstruction, these animals demonstrated more severe kidney injury and fibrosis in the obstructed kidney, when compared with wild-type mice (70). The administration of an angiotensin-receptor antagonist attenuated the observed injury, suggesting that the deficiency of signaling through the VDR resulted in unfavorably high intra-renal RAS activity and obstructive renal injury. Similarly, mice that are deficient in the activity of the 1-alpha-hydroxylase enzyme have exhibited increased activity of the intra-renal RAS that can be ameliorated with 1,25(OH)₂D treatment (9). When diet induced obese mice were treated with doxercalciferol (1-alpha-hydroxyvitamin D₂), the expression of intra-renal renin and angiotensin II type 1 receptors was decreased, with concurrent decrements in proteinuria, podocyte injury, mesangial expansion, and inflammation (71).

Nearly identical reno-protective effects of vitamin D signaling were shown in three studies using mouse-models of diabetes (streptozocin induced [type 1 diabetes], and *db/db* or *KK-A^y/Ta* [type 2 diabetes]); these animals develop proteinuria and renal injury with elevated intra-renal RAS activity (72–74). Given alone, a VDR agonist (1,25[OH]₂D or paracalcitol) decreased RAS activity in these mice and attenuated the proteinuria and kidney injury. This effect was reproduced with angiotensin-receptor blocker therapy, but there was a synergistic effect on decreasing RAS activity and preventing further kidney injury when both the VDR agonist and angiotensin receptor blocker were used in combination (72–74). These experiments further support the RAS as a key mediator of the renal influence of VDR agonism, but implicated the involvement of two other pathways. VDR agonist treatment was also observed to inhibit the transforming growth factor beta (TGF-β) (72) and extracellular signal-regulated protein kinase (p-ERK1/2) (74) systems in these animals, suggesting a potential anti-proliferative or anti-inflammatory reno-protective function of VDR agonism in addition to its negative regulation of the RAS.

To date, the only corollary human mechanistic study showed that higher 25(OH)D concentrations were associated with significantly lower renal-vascular RAS activity in normotensive individuals with normal kidney function (75). Although this study was cross-sectional in nature, because it controlled for major modulators of the RAS (dietary sodium was fixed and no anti-hypertensive medications were included), the results strongly support the mechanism of vitamin D induced RAS inhibition in humans. The MODERATE study

(NCT01320722), currently enrolling subjects in the United States, will further characterize the biological relationship between vitamin D supplementation and the renal-vascular RAS in humans by evaluating renal-vascular RAS activity and renal plasma flow before and after randomization to eight weeks of oral vitamin D₂ 50,000 IU/week, or placebo. Future studies to evaluate the mechanism of VDR-agonists on the RAS, inflammatory pathways, and proteinuria in diabetes are still needed.

Summary of Human Clinical Data

Most human clinical studies in this area have investigated the role of vitamin D in patients with established chronic kidney disease (CKD) of varying stages, a condition usually marked by 1,25(OH)₂D insufficiency or deficiency, elevated parathyroid hormone levels, and often concurrent hypertension and/or diabetes. Observational studies have shown cross-sectional associations between lower 25(OH)D concentrations and the prevalence of CKD and proteinuria (76–78). In an analysis of over 15,000 individuals in the Third National Health and Nutrition Examination Survey (NHANES III), for example, de Boer et al. observed that those in the lowest compared with highest quartile of 25(OH)D levels had an adjusted odds for prevalent albuminuria of 1.37 ($P<0.01$) (78). Ravani et al. observed an inverse and independent longitudinal relationship between 25(OH)D concentrations and the two-year progression of kidney disease in 168 individuals with non-dialysis dependent CKD (stages 2–5) (79). Other studies have reached similar conclusions (80, 81).

High-quality, prospective observational and interventional studies evaluating the role of vitamin D₂ or D₃ in kidney disease are sparse. Kim et al. recently showed that, in patients with diabetes and CKD already treated with conventional RAS antagonists, vitamin D₃ supplementation reduced albuminuria and TGF- β , supporting similar observations in diabetic mice treated with paracalcitol (82). A meta-analysis of 22 low-to-moderate quality studies (17 observational and 5 randomized trials) suggested that vitamin D₂ or D₃ supplementation did not significantly affect serum creatinine or urine albumin excretion, even though supplementation was sufficient to raise 25(OH)D levels and suppress parathyroid hormone (83). However, most of the studies included in this aggregate analysis were not designed to evaluate outcomes of disease progression, and since CKD is a state of relative 1-alpha-hydroxylase insufficiency, the effectiveness of vitamin D₂ or D₃ supplementation on any outcome is unclear.

In contrast to investigations that have evaluated the influence of vitamin D₂ or D₃ in kidney disease, those that have studied the effect of direct VDR agonism have shown more conclusive and consistent findings. To date, there have been at least five notable interventional studies evaluating the reno-protective benefits of VDR agonist therapy in patients with CKD (84–88) (Table 2). These five studies have provided human clinical evidence to support the aforementioned animal data demonstrating a reduction in surrogate biochemical measures of renal failure (such as proteinuria) (72–74), but were not designed to examine whether VDR agonist therapy delayed the progression of CKD, or whether it may have a role in the primary prevention of kidney disease. Agarwal et al. synthesized the results of 220 patients with CKD (stages 3 or 4) from three randomized placebo-controlled studies treated with paracalcitol or placebo for up to six months (84). Paracalcitol therapy

reduced automated dipstick proteinuria in 50% of subjects ($P<0.01$); in comparison, proteinuria was reduced by only 25% of subjects who received placebo. Although this study took into account the use of specific anti-RAS hypertensive medications, it may have been limited by the quantification of proteinuria via an automated dipstick assay. In a smaller interventional study, Alborzi et al. randomized 24 individuals with CKD stage 3 to either placebo, paracalcitol 1 µg/daily, or paracalcitol 2 µg/daily, for one month and observed reductions in C-reactive protein and albuminuria in the higher paracalcitol dose group (85). Szeto et al. evaluated only ten patients with IgA nephropathy who had proteinuria despite using RAS antagonist pharmacotherapy, and observed a 25% decrease in urine protein-to-creatinine ratio ($P<0.01$) within six weeks of receiving calcitriol 0.5 µg twice weekly (86). Individuals who experienced lowering of proteinuria in this study also exhibited a proportional reduction in serum TGF-β, thus providing further support for vitamin D induced inhibition of the TGF pathway (72). In support of the Agarwal and Alborzi studies, Fishbane et al. also observed a 17% ($P<0.05$) reduction in proteinuria among 61 patients with CKD who were randomized to either paracalcitol or placebo for six months (87).

The largest, and most recent, interventional study by de Zeeuw et al. provides the strongest translation of animal to human evidence to date. In a multinational double-blind placebo-controlled trial, de Zeeuw and colleagues randomly assigned 281 patients with type 2 diabetes with albuminuria, who were all on pharmacologic RAS antagonist therapy, to six months of either placebo, paracalcitol 1 µg/daily, or paracalcitol 2 µg/daily (88). Patients treated with paracalcitol 2 µg/daily experienced a steady 18–28% decrease in the urinary albumin-to-creatinine ratio when compared with placebo (the primary end point).

Future Directions

In parallel with studies in diabetic mice showing reductions in albuminuria and renal injury with combined VDR agonists and RAS-antagonist therapy (72–74), the results by de Zeeuw et al. consolidate prior human data reported by Agarwal, Alborzi, Szeto, Fishbane et al., and strongly support the use of VDR-agonists to lower proteinuria in diabetic nephropathy that is already being treated with conventional RAS-antagonism. While these studies evaluated strong surrogate measures of progressive CKD (proteinuria), they are limited in that they: 1) did not evaluate long-term outcomes (such as the time to progression of disease or dialysis), and 2) were not designed to investigate whether the mechanism of the beneficial effects of VDR agonists were due to incremental RAS antagonism, synergistic inhibition of the TGF pathway, or other biological mechanisms. A better understanding of these queries could have significant implications for the potential use of vitamin D analogues in the primary prevention of kidney disease, or continued use in CKD in combination with other pharmacotherapies. Furthermore, studies have associated the use of VDR agonists among non-dialysis and dialysis-dependent CKD patients with an improved survival benefit; however, these studies were not designed to evaluate the underlying mechanism for improved survival (89–94). Future studies are needed to ascertain whether vitamin D therapy is effective for the primary prevention of CKD, to delay the progression of CKD stages, to reduce the need for dialysis in CKD, and to improve overall survival in CKD. Mechanistic studies in humans that further identify the biologic pathways by which vitamin D influences renal function may help shape efficient trial designs.

Summary

Translational research has shed novel insights into the role of vitamin D in vascular diseases such as hypertension and kidney disease. The role of 1,25(OH)₂D as a negative inhibitor of the RAS has been supported by mechanistic animal and human studies, but other potential biologic mechanisms to explain the role of vitamin D on vascular function are also emerging. To date, human clinical studies have ascribed a modest, but inconsistent blood pressure lowering effect to oral vitamin D therapy and ultraviolet radiation exposure. On the other hand, they have demonstrated a consistent decrement in surrogate measures of CKD progression, such as proteinuria, with VDR agonists. Future interventional studies with higher vitamin D doses, larger sample sizes, longer durations of follow-up, and study designs that are suited to measure and recognize the mechanism of action, may provide more conclusive data on whether vitamin D therapy may be beneficial in the primary prevention, or treatment, of hypertension and kidney disease.

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Table 1

Summary of interventional studies evaluating the effect of vitamin D₂ or D₃ supplementation on blood pressure.

Study	N	Dose	Duration	Baseline 25(OH)D	Change in 25(OH)D	Result	Blood Pressure as Primary Endpoint
Orwoll (1990) ⁴⁸	65	1000 IU/day	3 yr	Not given	Not given	Null	No
Pan (1993) ⁴⁹	58	200 IU/day	11 wk	24 ng/mL	Not given	Null	No
Scragg (1995) ⁵⁰	189	100,000 IU x 1	5 wk	13 ng/mL	7 ng/mL	Null	Yes
Pfeifer (2001) ⁵¹	148	800 IU/day	8 wk	10 ng/mL	12 ng/mL	Positive	Yes
Schleithoff (2006) ⁵²	93	10,000 IU/day	15 mo	15 ng/mL	27 ng/mL	Null	No
Major (2007) ⁵³	63	400 IU/day	15 wk	Not given	Not given	Null	No
Sugden (2008) ⁵⁴	34	100,000 IU x 1	8 wk	15 ng/mL	9 ng/mL	Positive	No
Margolis (2008) ⁵⁵	36,282	400 IU/day	7 yr	19 ng/mL	Not given	Null	No
Zittermann (2009) ⁵⁶	165	16,600 IU/day	1 yr	12 ng/mL	22 ng/mL	Null	No
Daly (2009) ⁵⁷	140	800 IU/day	2 yr	Not given	Not given	Null	No
Jorde (2009) ⁵⁸	32	40,000 IU/week	6 mo	24 ng/mL	23 ng/mL	Null	No
Nagpal (2009) ⁵⁹	71	120,000 IU x 3 doses	6 wk	13 ng/mL	14 ng/mL	Null	No
Jorde (2010) ⁶⁰	438	40,000 IU/week or 20,000 IU/week	1 yr	23 ng/mL	17–33 ng/dL	Null	No

Table 2

Summary of interventional studies evaluating the effect of vitamin D receptor agonist therapy on proteinuria.

Study	N	Intervention	Duration	Significant decrease in proteinuria
Agarwal (2008) ⁸⁴	220 (CKD stages 3–4)	paracalcitol	Up to 6 months	Yes
Alborzi (2008) ⁸⁵	24 (CKD stages 2–3)	paracalcitol	1 month	Yes
Szeto (2008) ⁸⁶	10 (IgA nephropathy)	calcitriol	12 weeks	Yes
Fishbane (2009) ⁸⁷	61 (CKD stages 2–4)	paracalcitol	6 months	Yes
de Zeeuw (2010) ⁸⁸	281 (CKD stages 2–4)	paracalcitol	6 months	Yes