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Vitamin D in the Pathophysiology of Hypertension, Kidney Disease, and Diabetes: Examining the Relationship Between Vitamin D and the Renin-Angiotensin System in Human Diseases

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Abstract

Objective—Vitamin D has been implicated in the pathophysiology of extra-skeletal conditions such as hypertension, kidney disease, and diabetes, via its ability to negatively regulate the renin-angiotensin system (RAS). This article reviews the evidence supporting a link between vitamin D and the RAS in these conditions, with specific emphasis on translational observations and their limitations.

Methods—Literature review of animal and human studies evaluating the role of vitamin D in hypertension, kidney disease, and diabetes.

Results—Excess activity of the RAS has been implicated in the pathogenesis of hypertension, chronic kidney disease, decreased insulin secretion, and insulin resistance. Animal studies provide strong support for $1,25(OH)_2D$ mediated down-regulation of renin expression and RAS activity via its interaction with the vitamin D receptor. Furthermore, the activity of vitamin D metabolites in animals is associated with reductions in blood pressure, proteinuria and renal injury, and with improved β–cell function. Many observational, and a few interventional, studies in humans have supported these findings; however, there is a lack of well designed prospective human interventional studies to definitively assess clinical outcomes.

Conclusion—Animal studies implicate vitamin D receptor agonist therapy to lower RAS activity as a potential method to reduce the risk of hypertension, kidney disease, and diabetes. There is a need for more well designed prospective interventional studies to validate this hypothesis in human clinical outcomes.

Keywords

vitamin D; hypertension; kidney disease; diabetes; renin-angiotensin system

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Introduction

Vitamin D is an important mediator of calcium metabolism and skeletal health that is acquired and synthesized from dietary sources and ultraviolet radiation. It has also been implicated as a potential contributor to the pathophysiology of extra-skeletal conditions, including hypertension, kidney disease, and insulin resistance. The key clinical barometer of human vitamin D status 25-hydroxyvitamin D (25[OH]D), which is converted to the active vitamin D metabolite 1,25-dihydroxyvitamin D ($1,25[OH]_2D$) via sensitively regulated physiologic action by the 1-alpha-hydroxylase enzyme. Since 25(OH)D is a stable metabolite that is easier to quantify than $1,25(OH)_2D$, it is often evaluated in studies as a measure of vitamin D effect; however, it is $1,25(OH)_2D$ that is the active vitamin D receptor (VDR) agonist. When liganded with $1,25(OH)_2D$, the VDR can dimerize with the retinoid X receptor to become a transcription factor that may influence the expression of hundreds of genes. Additionally, the $1,25(OH)_2D$-VDR complex has been associated with several non-genomic cellular pathways.

The renin-angiotensin system (RAS) plays a crucial role in the physiology of sodium and volume homeostasis ; however, excess activity of the RAS is associated with cardio-metabolic diseases such as hypertension, kidney disease, and diabetes. In addition to the circulating RAS, the pathophysiology associated with the RAS is likely mediated by the many locally expressed tissue RAS's that have been identified in tissues such as the kidney, vascular endothelium, pancreas, cardiac tissue, and adipose tissue. To date, a strong body of evidence supports vitamin D as a negative regulator of the circulating and local tissue RAS. While other mechanisms implicating vitamin D in the pathogenesis of disease exist, this review will specifically examine the influence of the relationship between vitamin D and the RAS on: 1) blood pressure control and incident hypertension; 2) kidney function and chronic kidney disease; 3) and insulin sensitivity and incident diabetes. In particular, novel translational research that has provided basic science evidence for a relationship between vitamin D and the RAS will be highlighted, along with clinical observations from human investigations.

Vitamin D and Hypertension

Vitamin D metabolites have been associated with the regulation of blood pressure, and hormonal mechanisms regulating blood pressure, for decades. Observational reports have noted higher blood pressure trends in winter months and locations further from the equator, suggesting that low ultraviolet radiation, and thus decreased capacity for cutaneous vitamin D synthesis, are associated with hypertension. The most notable mechanism implicating vitamin D with hypertension is its role as a negative regulator of the RAS ; other notable hypotheses have suggested that vitamin D influences vascular endothelial function or vascular smooth muscle intra-cellular calcium concentrations. Because inappropriately elevated activity of the RAS contributes to hypertension and cardiovascular risk, many observational and interventional studies have focused on investigating the role of vitamin D metabolites in the development of hypertension.

The most convincing mechanistic studies linking vitamin D with RAS activity and blood pressure regulation were conducted in animal models. Li et al. showed that VDR knock-out (KO) mice had significant elevations in renin activity and circulating plasma angiotensin II concentrations. These mice developed hypertension and cardiac hypertrophy that could be attenuated with the administration of RAS antagonist pharmacotherapy, and also exhibited increased activity of the local cardiac-tissue RAS. In parallel, a mouse model of 1-alpha-hydroxylase deficiency (inability to synthesize $1,25[OH]_2D$) also exhibited a phenotype of enhanced RAS activity, hypertension, and cardiac hypertrophy that was attenuated with the

administration of $1,25(OH)_2D$ or RAS antagonists. The collective work by these investigators has shown that $1,25(OH)_2D$-liganded VDR acts to suppress renin gene expression, suggesting that VDR agonists could exhibit protective effects on blood pressure and cardiac tissue. Corollary human physiology studies have shown that lower levels of $1,25(OH)_2D$ and 25(OH)D are associated with higher plasma renin activity, angiotensin II concentrations, and higher systemic vascular-tissue RAS activity.

Most human clinical studies evaluating the role of vitamin D on blood pressure have been cross-sectional analyses. The majority of these yielded results that were consistent with the animal data in showing an inverse association between vitamin D and blood pressure or prevalent hypertension. In contrast, at least two cross-sectional studies demonstrated no detectable association between vitamin D and blood pressure or the prevalence of hypertension ; however, in addition to the traditional limitations of cross-sectional analyses, these conflicting results may have been confounded by comparatively high 25(OH)D concentrations and prevalent use of anti-hypertensive medications that could obscure potential associations.

Longitudinal and prospective studies evaluating 25(OH)D levels have similarly shed mixed results. In a prospective longitudinal analysis of 613 men from the Health Professionals' Follow Up Study and 1198 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) in individuals with lower (<15 ng/mL) versus higher (30 ng/mL) concentrations of 25(OH)D. The same authors subsequently performed a nested case-control analysis with normotensive women from the Nurses' Health Study, and 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. In the longitudinal Michigan Bone Health and Metabolism Study, Griffin et al. evaluated the risk for systolic hypertension over 14 years in 559 Caucasian women who had 25(OH)D and blood pressure measures in 1993 and again in 2007. Although they observed no cross-sectional association between 25(OH)D concentrations and concurrent blood pressure in 1993, 25(OH)D concentrations of < 32 ng/mL in 1993 were significantly associated with an 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 Tromso study which followed individuals for 14 years (1994–2008) who were naïve to anti-hypertensive therapy. Although an inverse cross-sectional association between systolic blood pressure and quartiles of 25(OH)D was noted at baseline in 1994, 25(OH)D concentrations from 1994 did not predict incident hypertension or future blood pressure. Whether these inconsistent observations were due to the lack of sufficient range in 25(OH)D concentrations within the study populations, or other unrecognized confounding, they highlighted the need for definitive randomized controlled studies.

Interventional studies evaluating controlled ultraviolet exposure have also shown mixed results; Krause et al. observed mild blood pressure reductions in untreated hypertensives, whereas Scragg et al. observed no change in a largely normotensive population. Both of these studies were well designed with significant increases in 25(OH)D levels following ultraviolet therapy; however, they may have been limited by durations of follow up that were too short to detect pathological changes in arterial function (6 and 12 weeks respectively), and relatively small sample sizes.

To date, more than ten interventional studies involving vitamin D therapy in non-blood pressure primary outcomes have explored the effect of vitamin D therapy on blood pressure. The majority of these studies did not find a significant relationship between vitamin D supplementation and blood pressure or incident hypertension. The largest of these studies

was the Women's Health Initiative (n=36,282), designed to evaluate whether 400 IU of daily vitamin D_3 with calcium supplementation reduced fracture and cancer risk when compared to placebo in a population of largely vitamin D insufficient women. After seven years of follow up, no change in blood pressure or incident hypertension was observed. The interpretation of these results was limited by modest vitamin D_3 supplementation in the intervention arm, and a high rate of non-study related vitamin D supplementation in the placebo group. The second largest of these studies (n=438) was designed to evaluate the effect of vitamin D_3 supplementation on weight loss, and included overweight and obese individuals, but did not exclude the use of anti-hypertensive medications. After one year of randomization to either vitamin D_3 40,000 IU/week or 20,000 IU/week or placebo, no change in blood pressure was observed. Since 25(OH)D levels in this study rose from a baseline of <30 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 prospective 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, and have revealed mixed results. The first showed that a single dose of vitamin D_3 100,000 IU in a vitamin D deficient population did not lower blood pressure after five weeks, when compared to placebo ; but, the short duration and modest 7 ng/mL rise in 25(OH)D levels (from a baseline of 13 ng/mL) limit the convincibility of a negative result. In the second study, elderly 25(OH)D deficient women who received vitamin D_3 800 IU/daily for 8 weeks had a significant, but modest, decline in systolic blood pressure (−7 mmHg), when compared to those who received placebo ; however, the short duration of follow-up and small sample size (n=148) limit the strength and interpretation of these positive results as well.

As 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 designed to optimally evaluate the influence of vitamin D therapy on blood pressure. Ideally, future interventional studies should have sufficient sample size, longer duration of follow-up, higher vitamin D metabolite supplementation doses, restriction of anti-hypertensive drug use, while controlling for confounders of the RAS. Meta-analyses have attempted to aggregate prior trial findings, including many of the aforementioned. Witham et al. were able to detect a blood pressure lowering effect associated only when limiting their analyses to those few studies that focused on hypertensive individuals, whereas Pittas et al. were only able to detect effects using studies with higher doses of vitamin D_3 supplementation (> 1000 IU/daily). The meta-analysis by Burgaz et al. 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). In contrast, Elamin et al. detected no blood pressure lowering effect in a meta-analysis evaluating cardiovascular outcomes. 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 vitamin D_3 supplementation (2,000 IU/daily) on cardiovascular and cancer outcomes over five years. The size, duration of follow-up, and higher vitamin D_3 doses in this study design may allow sufficient power and effect size to examine the influence of long-term vitamin D_3 supplementation on blood pressure.

Vitamin D and Kidney Disease

The development of hypertension and kidney disease is often inter-related, yet vitamin D has been implicated as reno-protective independent of its potential effect on blood pressure. In normal physiology, $1,25(OH)_2D$ acts to lower parathyroid hormone; the standard use of

VDR agonists in chronic kidney disease to lower parathyroid hormone levels for the management of the calcium-phosphate product and renal osteodystrophy is well established. While prior hypotheses have suggested that parathyroid hormone may directly influence vascular function and blood pressure, this discussion will focus specifically on the novel independent effects vitamin D metabolites may have on the RAS, and consequently renal function and progression of kidney disease.

As in the case of hypertension, 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-KO mice also display increased expression of renal-vascular renin mRNA. 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 to wild-type. The administration of an angiotensin-receptor antagonist attenuated the observed injury, suggesting that reduced signaling through the VDR resulted in unfavorably high intra-renal RAS activity and obstructive renal injury. Additionally, 1-alpha-hydroxylase deficient mice exhibit increased activity of the intra-renal RAS that is down-regulated with the administration of $1,25(OH)_2D$. In support of prior hypotheses that VDR agonists negatively regulate renin expression, treatment of diet induced obese mice with doxercalciferol (1-alpha-hydroxyvitamin D_2) lowered the expression of intra-renal renin and angiotensin II type 1 receptors, with concurrent decrements in proteinuria, podocyte injury, mesangial expansion, and inflammation. Three different mouse models of diabetes (streptozocin induced [type 1], and *db/db or* KK-A^y/Ta [type 2]) have been observed to develop proteinuria and renal injury with elevated intra-renal RAS activity in untreated animals. These mice exhibited lowering of RAS activity and attenuation of proteinuria and kidney injury when treated with a VDR agonist alone ($1,25(OH)_2D$ or paracalcitol), or an angiotensin-receptor blocker alone, but synergistically improved outcomes when the combination of the two was used. In addition to reducing intra-renal renin and RAS activity in these experiments, VDR agonist treatment was observed to inhibit the TGF-β and p-ERK1/2 systems, implicating other potential pathways by which VDR agonists induce reno-protection. Corollary human mechanistic studies have reported that lower 25(OH)D concentrations are associated with impairments in glomerular filtration rate and higher renal-vascular RAS activity. The MODERATE study (NCT01320722), currently enrolling subjects in the United States, aims to further characterize the biological relationship between vitamin D and the renal-vascular RAS in humans by evaluating renal RAS activity and renal plasma flow before and after randomization to eight weeks of vitamin D_2 50,000 IU/week, or placebo.

The majority of human clinical studies have investigated the role of vitamin D in patients with established chronic kidney disease (CKD) of varying stages, a condition usually confounded by $1,25(OH)_2D$ insufficiency or deficiency, elevated parathyroid hormone levels, and concurrent hypertension. Observational studies have shown cross-sectional associations between lower 25(OH)D concentrations and the prevalence of CKD and proteinuria. These cross-sectional findings are limited by their inability to predict direction of change or causality of these relationships. In contrast, a recent systematic review and meta-analysis of 22 studies (17 observational and 5 randomized trials) of vitamin D_2 or D_3 supplementation suggested that while these interventions expectedly raised 25(OH)D and lowered parathyroid hormone levels in CKD, they did not significantly affect other biochemical markers of kidney disease progression. 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 insufficient 1-alpha-hydroxylase activity, the effectiveness of vitamin D_2 or D_3 supplementation on any outcome is debatable. On the other hand, Ravani et al. observed an inverse and independent longitudinal relationship between 25(OH)D

concentrations and the progression of kidney disease in 168 individuals with non-dialysis dependent CKD (stages 2–5) over two years. The use of VDR agonists among non-dialysis and dialysis-dependent CKD patients has also been associated with an improved survival benefit in several studies, but these studies were not designed to evaluate whether the underlying mechanism for improved survival was due to intra-renal RAS regulation, parathyroid and calcium metabolism, or other reasons.

To date, there have been several interventional studies evaluating the reno-protective benefits of VDR agonist therapy in patients with CKD. These studies have provided strong evidence to support the aforementioned animal data demonstrating a reduction in surrogate biochemical measures of fulminate renal failure (such as proteinuria) with vitamin D therapy. However, they were not designed to examine whether vitamin D therapy delays the progression of CKD, or whether it may have a role in the primary prevention of kidney disease. Agarwal et al. aggregately evaluated 220 patients with CKD (stages 3 or 4) from three randomized placebo-controlled studies evaluating the effect of paracalcitol therapy versus placebo for up to six months. Half of the proteinuric subjects receiving paracalcitol experienced reductions in automated dipstick proteinuria, in comparison to only a quarter of those receiving placebo ($P<0.01$). This finding was independent of many confounding factors, including the use of RAS-specific anti-hypertensive agents, but may have been limited by the quantification of proteinuria via an automated dipstick assay. Similarly, in two smaller studies, Alborzi et al. and Szeto et al. reported reductions in proteinuria with short duration VDR agonist administration. The former randomized 24 individuals with CKD stage 3 to placebo, or 1 μg/daily or 2 μg/daily of paracalcitol, for one month and observed reductions in C-reactive protein and albuminuria in the higher paracalcitol dose group. The latter study evaluated ten patients with IgA nephropathy who had proteinuria despite using RAS antagonist pharmacotherapy; within six weeks of receiving calcitriol 0.5 μg twice weekly, a 25% decrease in urine protein-to-creatinine ratio was observed ($P<0.01$). These investigators, along with Kim et al. who observed reduced albuminuria with vitamin D_3 supplementation in diabetes, also observed a proportional reduction in TGF-β in individuals with reduced proteinuria, mimicking the aforementioned findings in mice that received paracalcitol. The findings by Fishbane et al. largely supported these studies when they observed a 17% ($P<0.05$) reduction in proteinuria among 61 patients with CKD randomized to either paracalcitol or placebo for six months.

The most recent interventional study demonstrates perhaps the strongest correlation of human to animal data. In a multinational double-blind placebo-controlled trial, de Zeeuw and colleagues randomized 281 patients with type 2 diabetes and albuminuria, who were on pharmacologic RAS antagonist therapy, to placebo, paracalcitol 1 μg/daily, or paracalcitol 2 μg/daily, for six months. Participants treated with paracalcitol 2 μg/daily (in addition to RAS-antagonist therapy) experienced a steady 18% to 28% decrease in the urinary albumin-to-creatinine ratio when compared to placebo (the primary end point). In concert with the reductions in albuminuria and renal injury seen with combined VDR agonists and RAS-antagonist therapy in diabetic mice, the results by de Zeeuw et al. strongly support the use of VDR-agonists in combination with anti-RAS pharmacotherpy to lower proteinuria in diabetic nephropathy. Notably, while this study evaluated a strong surrogate of progressive CKD (proteinuria), it did not evaluate long-term outcomes such as the time to progression of disease or dialysis, nor was it designed to investigate whether the mechanism of the beneficial effects of paracalcitol 2 μg/daily 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 in diabetes, or continued use in CKD in combination with other pharmacotherapies.

Vitamin D and Diabetes

Vitamin D has been associated with β–cell function, peripheral insulin sensitivity, incident diabetes, and mortality in diabetes. However, definitive human clinical trial evidence to support vitamin D supplementation in improving glycemic control or delaying the onset of diabetes is lacking, and is further hampered by inconsistent findings in human studies with limited study designs. As in the case of hypertension and kidney disease, one of the main putative mechanisms linking vitamin D to glucose control is its regulation of the RAS. The intra-pancreatic and circulating RAS are known to negatively affect β–cell function and peripheral insulin sensitivity. Thus, it is speculated that the down-regulation of the RAS by vitamin D may mediate its beneficial effects on glycemic control and diabetes.

Animal studies, and *in vitro* experiments, have provided evidence supporting the deleterious activation of the pancreatic islet cell RAS by hyperglycemia, and resultant islet cell dysfunction and diminished β–cell mass consequent to higher local RAS activity. Activity of the pancreatic islet cell RAS is enhanced in animal models of diabetes, whereas the administration of RAS antagonists improves β-cell function, decrease oxidative stress, and prevents islet fibrosis and apoptosis. These basic research experiments may in part explain the improved glycemic control or reduced incidence of diabetes associated with RAS antagonists in some human clinical trials and meta-analyses. Li et al. observed increased pancreatic islet RAS expression in VDR-KO mice. Furthermore, two separate investigations have shown that in the presence of $1,25(OH)_2D$, islet cells from wild-type mice demonstrate attenuated local islet RAS production and improved insulin secretion. Together, these findings suggest that antagonism of pancreatic islet RAS may improve β-cell function and mass, and that VDR agonists may improve insulin secretion via negative regulation of renin expression.

There is an abundance of human clinical studies examining the potential link between levels of vitamin D metabolites (or vitamin D intake) with glycemic control and the incidence of diabetes. Unfortunately, the majority are either inconclusive cross-sectional associations, or not designed to specifically assess these end points. Furthermore, the study of type 1 and type 2 diabetes may not be immediately comparable since the pathophysiology of the two conditions are distinct. In type 1 diabetes, the EURODIAB case-control study found that vitamin D supplementation in infancy (by historical questionnaire) reduced the odds of developing type 1 diabetes (adjusted OR 0.67, 95% C.I.: 0.53 to 0.86). Similarly, in a Finnish birth cohort (n=12,231) that was followed until age 30, infants who received the recommended vitamin D_3 2,000 IU/daily during the first year of life, had a relative risk of 0.22 (95% C.I. 0.05 to 0.89) for developing type 1 diabetes when compared to those who received less. While both studies support the potential immuno-modulatory effect of vitamin D, they were limited by their retrospective study designs and small number of cases developing type 1 diabetes during follow up. In contrast, longitudinal analyses in the DAISY study found no association between 25(OH)D levels or vitamin D intake with islet autoimmunity or progression to type 1 diabetes in 2,644 children. To date, large scale prospective studies evaluating the effect of vitamin D therapy on the incidence of type 1 diabetes have not been performed.

Cross-sectional studies evaluating type 2 diabetes have also provided inconclusive results. Scragg et al. evaluated over 6,000 individuals from the NHANES, and found that lowest-quartile 25(OH)D levels were associated with a diagnosis of diabetes by fasting blood glucose, when compared to those in the highest quartile; however, this observation was only seen when excluding non-Hispanic blacks (n=1,736). Other analyses of large cohorts have demonstrated significant inverse associations between vitamin D metabolites and glycated hemoglobin, the prevalence of diabetes, and the 5-year incidence of developing diabetes.

Studies evaluating vitamin D in the mechanism of type 2 diabetes have observed that 25(OH)D concentrations are positively associated with adiponectin (a circulating peptide that promotes insulin sensitivity), but these studies were not designed to evaluate whether insulin sensitivity was consequently affected. Muscogiori et al. reported perhaps the strongest negative human mechanistic evidence to date. In 39 non-diabetic individuals who underwent hyperinsulinemic euglycemic clamp, 25(OH)D concentrations were not associated with peripheral insulin sensitivity after adjustment for notable confounders, such as body-mass index. This study highlights one of the two major confounders when evaluating for a true causal relationship between vitamin D and diabetes. The first is that body-mass index is a critical predictor of both 25(OH)D and diabetes ; thus, it may bias analyses towards rejecting the null hypothesis. The second is that dietary sodium intake acutely modifies insulin sensitivity and activity of the RAS (a putative mediator of the relationship between vitamin D and diabetes). Therefore, prospective interventional studies with randomization, and controlled dietary sodium conditions, are needed to thoroughly evaluate for a causal relationship between vitamin D and insulin sensitivity or incident diabetes.

Prospective and longitudinal studies have shed mixed results. In a Finnish cohort study following over 4,000 non-diabetics for 17 years, Mattila et al. encountered 187 new cases of type 2 diabetes. Although the relative risk for developing diabetes between the highest and lowest quartile of 25(OH)D after multivariate adjustment was suggestive of a protective effect (relative risk=0.70), the result was not statistically significant (*P*-trend 0.07). In contrast, at least six other longitudinal assessments have reported a significant inverse association between 25(OH)D concentrations and future severity of insulin resistance and/or incidence of diabetes.

To date, interventional studies have largely refuted the theory that vitamin D may benefit insulin sensitivity, however, it is important to note that they were not designed to specifically examine this question. In the Women's Health Initiative, post-menopausal women were randomized to receive a low dose of vitamin D_3 (400 IU/daily) or placebo. After a mean follow-up time of seven years, the hazard for incident type 2 diabetes was 1.01 (95% C.I.: 0.94–1.10), suggesting a null effect. In two distinct randomized placebo-controlled intervention studies, Jorde et al. used significantly higher doses of vitamin D_3 40,000 IU/weekly and found 1), no improvement in glycemic control in 32 type 2 diabetes patients already prescribed metformin and insulin, treated for 6 months and 2), no improvement in glucose tolerance in 330 non-diabetic individuals treated for one year. In contrast, two smaller placebo-controlled interventional studies recently reported significant improvements in homeostatic model assessment for insulin resistance (HOMA-IR) in 42 South Asian women receiving vitamin D_3 4,000 IU/daily for 6 months, and fasting blood glucose and glycated hemoglobin in type 2 diabetics receiving vitamin D fortified yogurt drinks for 3 months. The results of each of these interventional studies (whether positive or negative in outcome) are limited in part by a combination of short duration of follow-up, inadequate power and study design to detect the outcome of interest, insufficient dose of vitamin D, and potentially uncontrolled dietary sodium intake during assessments of insulin sensitivity. Systematic reviews and meta-analyses have attempted to address these limitations with aggregate pooled evaluations, but have concluded that there is currently insufficient human data to strongly support a link between vitamin D and diabetes.

Summary and Future Directions

Recent translational research has implicated $1,25(OH)_2D$, via its interaction with the VDR, in the pathophysiology of hypertension, progressive kidney disease, and diabetes. While the contribution of the RAS in the development of these conditions is known, novel basic

animal experiments have provided evidence to support the negative regulation of the RAS by VDR agonism in mediating these associations. While some human mechanistic studies have supported these animal data, many have provided inconsistent conclusions. Future intervention studies designed to definitively evaluate the clinical utility of vitamin D therapy will need to identify whether the focus of investigation should be on primary prevention or attenuated progression of disease. In addition, future trials must consider study designs with adequate power and sample size, the optimal vitamin D metabolite for intervention, and potentially dietary sodium control (for baseline and endpoint assessments) to avoid confounding by the RAS.

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ABBREVIATIONS

25(OH)D	25-hydroxyvitamin D_3
1,25(OH)$_2$D	1,25-dihydroxyvitamin D_3
VDR	vitamin D receptor
RAS	renin-angiotensin system
C.I	confidence interval
KO	knock-out
CKD	chronic kidney disease

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