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Review Article

Vitamin D Receptor Activators and Clinical Outcomes in Chronic Kidney Disease

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Vitamin D deficiency appears to be an underestimated risk factor for cardiovascular disease in patients with chronic kidney disease. Evidence from both basic science and clinical studies supports the possible protective role of vitamin D beyond its effect on mineral metabolism. Toxicity of pharmacologic doses of active vitamin D metabolites, in particular calcitriol, is mainly due to the possibility of positive calcium and phosphorus balance. Therefore, vitamin D analogs have been developed, which suppress PTH secretion and synthesis with reduced calcemic and phosphatemic effects. Observational studies suggest that in hemodialysis patients the use of a vitamin D receptor (VDR) activator, such as calcitriol, doxercalciferol, paricalcitol, or alfacalcidol, is associated with a reduced mortality when compared with nonusers of any VDR activator. In this article the existing literature on the topic is reviewed, although a more robust answer to the question of whether or not VDR activators have beneficial effects in hemodialysis patients will hopefully come from a randomized controlled trial.

1. Introduction

Chronic kidney disease (CKD) is associated with increased cardiovascular events and mortality when the glomerular filtration rate declines below 60 mL/min [1–3]. One significant event in CKD patients is the development of calcitriol deficiency secondary to the reduction/absence of kidney α1-hydroxylase which mediates the final hydroxylation step of 25(OH)vitamin-D to 1,25-$(OH)_2$vitamin-D, or calcitriol [4, 5]. 1,25-$(OH)_2$vitamin-D deficiency causes parathyroid hyperplasia and increased parathyroid hormone [6]; the consequent hyperparathyroidism and hyperphosphatemia are important risk factors for mortality in CKD patients [4, 7]. Accordingly, vitamin D treatment is associated with a reduced rate of cardiovascular diseases and mortality [5, 8].

Several studies also underline the side effects of calcitriol treatment, such as hypercalcemia and hyperphosphatemia, which carry an increased risk of cardiovascular calcifications. Compared to calcitriol, vitamin D analogs, such as paricalcitol, cause less hypercalcemia and hyperphosphatemia because of less bone resorption and less intestinal absorption [9, 10]. Calcitriol and vitamin D analogs are better identified as Vitamin D receptor activators.

In addition to suppression of PTH, use of vitamin D receptor activators has been associated with other effects: reduced hospitalization and mortality, prevention of cardiovascular diseases, vascular calcification and atherosclerosis, inhibition of the rennin-angiotensin system, preservation form cellular senescence, improved endothelial function, reduced tubular interstitial fibrosis, and reduced inflammatory status.

Studies about vitamin D receptor activators and clinical outcomes (Table 1) in chronic kidney disease are reviewed in this article.

2. Materials and Methods

We researched on PubMed (US National Center for Biotechnology Information) all the articles about "paricalcitol and

Table 1: Vitamin D receptor activators: summary of clinical outcomes.

Suppression of PTH
Incidence of hypercalcemia and hyperphosphatemia
Mineral metabolism and bone disorder
Hospitalization
Mortality
Cardiovascular protection
Prevention of Atherosclerosis
Renal protection and reduction proteinuria
Renal protection and renin-angiotensin system
Renal protection and tubular interstitial fibrosis
Anti-inflammatory effect
Cellular senescence
Endothelial function

outcomes," "doxercalciferol and outcomes," and "maxacalcitol and outcomes" and we found 41 articles: 29 studies on paricalcitol (8 randomized controlled trial, 3 observational studies, 1 open label study, 5 retrospective studies, 1 review, and 10 experimental studies in animals), 4 studies on doxercalciferol (3 randomized controlled studies, 1 observational study), 7 studies on maxacalcitol (6 observational studies and 1 experimental study on mice), and 1 experimental study comparing two vitamin D analogs, paricalcitol and doxecalciferol.

3. Results and Discussion

3.1. Suppression of PTH: Effects on Calcium and Phosphate Levels

3.1.1. Comparing Paricalcitol and Placebo (Table 2). Coyne et al. [11] found that 91% of patients treated with paricalcitol reached two consecutive PTH level reductions of 30% or greater versus 13% of placebo patients ($P < .001$), while incidences of hypercalcemia, hyperphosphatemia were not significantly different between two groups. Martin et al. [12] demonstrated that 68% of patients treated with paricalcitol had a 30% decrease in serum PTH for 4 consecutive weeks—without evidence of hypercalcemia and hyperphosphatemia—versus 8% of patients treated with placebo ($P < .001$) (12). Lindberg et al. [13] showed, in an open-label study, that PTH levels fell into target range by month 5 without episodes of hypercalcemia and hyperphosphatemia.

3.1.2. Comparing Paricalcitol and Calcitriol (Table 2). A multicenter, double-blind RCT conducted by Sprague et al. [14] demonstrated that paricalcitol patients have ≥50% and faster reduction in baseline PTH versus calcitriol patients; they also showed that hypercalcemic episodes were 18% for paricalcitol versus 33% for calcitriol ($P < .01$). In a retrospective study, Mittman et al. [15] found that PTH levels were significantly lower for paricalcitol versus calcitriol (247 versus 190 pg/mL) while episodes of hypercalcemia and hyperphosphatemia were significantly fewer for paricalcitol versus calcitriol. A crossover study conducted by Coyne et al. [16] demonstrated that suppression of PTH at 36 hours was significantly greater after administration of 160 μg of paricalcitol (63.6% ± 2.3%) versus calcitriol (but similar after administration of 160 μg of paricalcitol), while the increase of serum calcium is greater in calcitriol group. Lund et al. [17] in a single-center, double-blind, active-controlled, randomized, crossover trial observed that fractional intestinal calcium absorption was significantly lower after paricalcitol versus calcitriol. Finally, Mittman et al. [18] in a 2-year, single-center crossover study demonstrated that conversion from calcitriol to paricalcitol resulted in lower serum calcium ($P < .001$), lower serum phosphorus ($P < .05$), reduced PTH ($P = .001$) and serum alkaline phosphatase ($P < .001$).

3.1.3. Studies on other VDR Activators, Doxercalciferol, and Maxacalcitol (Tables 3 and 4). In a crossover study comparing paricalcitol and doxercalciferol, Joist et al. [19] observed a similar suppression of PTH, while serum phosphorus was significantly higher using doxercalciferol. In a double-blind randomized study, Frazão et al. [20], in an open-label doxercalciferol treatment (16 weeks), and randomized, double-blinded treatment with doxercalciferol or placebo (8 weeks), found that 80% of doxercalciferol patients showed a 70% reduction in PTH levels from baseline, although serum calcium and phosphate levels increased respectively from 9.2 to 9.7 mg/dL and from 5.4 to 5.9 mg/dL. Coburn et al. [21] in a randomized, double-blinded, placebo-controlled, multicenter trial in 55 patients with stage 3 or 4 CKD showed that iPTH levels decreased more in doxercalciferol treatment versus placebo ($P < .001$); no significant differences in mean serum calcium or phosphorus were observed between the two groups. In a randomized study, Zisman et al. [22] demonstrated that in patients on a maintenance dose of paricalcitol, dosing doxercalciferol at 55–60% of the paricalcitol dose results in comparable inhibition of PTH, with similar incidences of hypercalcemia and hyperphosphatemia. Comparing maxacalcitol and calcitriol, Hayashi et al. [23] found no significant differences between the two groups in serum iPTH and phosphorus concentration, while serum calcium was significantly higher in the maxacalcitol versus calcitriol group during early treatment, but not at the end of treatment. Shiizaki et al. [24], in a study conducted in 5/6 nephrectomized rats treated by a direct injection of maxacalcitol into the parathyroid gland, found a significant decrease of PTH versus rats treated by vehicle, along with upregulation of both VDR and CaSR in the parathyroid tissue; no differences in calcium and phosphorus levels were observed between two groups. Kazama et al. [25] found that both maxacalcitol and calcitriol significantly decreased plasma intact PTH levels and increased serum Ca levels, but PTH levels were significantly lower in the maxacalcitol group after 24 weeks of treatment. In addition, serum phosphate levels were significantly higher in the calcitriol group. Thus, these authors proposed maxacalcitol as a possible less phosphatemic active vitamin D agent which might reduce the risk

Table 2: Suppression of PTH and effects on calcium and phosphate levels: paricalcitol versus placebo and paricalcitol versus calcitriol.

Author	Year	Study	Outcome 1	Outcome 2
Coyne et al. [11]	2006	Three randomized, placebo-controlled, phase-3 trials were conducted in 220 patients with stage 3 and 4 CKD with secondary hyperparathyroidism. 24-week studies	Decreases in PTH levels of 30% or greater in 91% of paricalcitol versus 13% of placebo patients ($P < .001$)	Incidences of hypercalcemia, hyperphosphatemia, and elevated Ca × P were not significantly different between groups
Martin et al. [12]	1998	3 double-blind RCTs $n = 78$ dialysis patients 12-week study	27 of 40 patients receiving paricalcitol (68%) had a 30% decrease in serum PTH for 4 consecutive weeks, versus 3 of 38 patients (8%) receiving placebo ($P < .001$)	No evidence of hypercalcemia and hyperphosphatemia
Lindberg et al. [13]	2001	Open-label study $n = 164$ dialysis patients. 13-month study	Mean PTH levels fell into target range (100–300 pg/mL) by month 5	Serum calcium and phosphorus were in normal range
Sprague et al. [14]	2003	Multicenter, double-blind RCT; $n = 263$ dialysis patients. 32-week study	Paricalcitol patients had a ≥50% and faster reduction in baseline PTH versus calcitriol patients (87 versus 107 days). Paricalcitol patients reached a therapeutic PTH range in 18 weeks versus calcitriol patients who never reached the target range	Hypercalcemic episodes were 18% for paricalcitol versus 33% for calcitriol ($P = .008$)
Mittman et al. [15]	2004	Retrospective study $n = 101$ dialysis patients 24-month study	PTH levels were significantly lower for paricalcitol versus calcitriol (247 versus 190 pg/mL)	Number of hypercalcemic episodes were 111 for paricalcitol versus 69 for calcitriol; number of episodes of hyperphosphatemia were 225 for paricalcitol versus 186 for calcitriol
Coyne et al. [16]	2002	Crossover study $n = 10$ dialysis patients 36-hour study	Suppression of PTH at 36 hours was significantly greater after administration of 160 μg of paricalcitol (63.6% ± 2.3%) versus calcitriol	Ca × P product increased more after calcitriol administration than after a 6- or 8-fold greater dose of paricalcitol
Lund et al. [17]	2010	Single-center, double-blind, active-controlled, randomized, crossover trial. $n = 22$ hemodialysis patients	Fractional intestinal calcium absorption was significantly lower after paricalcitol (0.135 ± 0.006) versus calcitriol (0.158 ± 0.006, $P = .022$)	
Mittman et al. [18]	2010	2-year, single-center crossover study $n = 73$ hemodialysis patients converted from calcitriol to paricalcitol using a 1 : 3 conversion ratio	Conversion from calcitriol to paricalcitol resulted in lower serum calcium ($P < .001$), lower serum phosphorus ($P < .05$), reduced PTH ($P = .001$) and reduced serum alkaline phosphatase ($P < .001$)	

of extraskeletal calcification [25]. Oyama et al. [26] treated patients with maxacalcitol intravenously and found that lower pretreatment plasma iPTH and calcium levels, but not phosphorus levels, were predictor of the response to treatment with maxacalcitol. On the other hand, serum levels of phosphorus did not significantly increase during treatment.

3.1.4. Parathyroid Hyperplasia (Table 5). Several studies addressed the issue of parathyroid hyperplasia (Table 5). Okuno et al. [27] demonstrated that the responsiveness to maxacalcitol therapy of secondary hyperparathyroidism is dependent on parathyroid gland size and that the simple measurement of maximum parathyroid gland diameter by ultrasonography may be useful for predicting responsiveness to maxacalcitol treatment. They suggest that glands larger than 11 mm do not adequately respond to treatment. Shiizaki et al. [28] also studied 20 patients with SHPT and enlarged parathyroid glands treated by percutaneous maxacalcitol

Table 3: Suppression of PTH and effects on calcium and phosphate levels: doxercalciferol versus placebo and doxercalciferol versus paricalcitol.

Author	Year	Study	Outcome 1	Outcome 2
Joist et al. [19]	2006	Crossover study $n = 13$ dialysis patients 36-hour study paricalcitol versus doxercalciferol	Clinical suppression of PTH at 36 hours was comparable between treatment arms (63% following paricalcitol therapy and 65% following doxercalciferol therapy).	Serum phosphorus was significantly higher during administration of doxercalciferol (2.12 ± 0.11 mmol/L versus 1.85 ± 0.07 mmol/L).
Frazão et al. [20]	2000	Double-blind, RCT $n = 99$ dialysis patients 8-week study	80% of doxercalciferol patients showed a 70% reduction in PTH levels from baseline, and 83% of the doxercalciferol patients met the study PTH targets.	During double-blinded treatment, 3.26% and 0.46% of [Ca] measurements exceeded 11.2 mg/dl with doxercalciferol and placebo, respectively.
Coburn et al. [21]	2004	RCT, $n = 55$ patients with stage 3 or 4 CKD treated with doxercalciferol versus placebo.	Mean plasma iPTH level decreased by 46% from baseline after 24 weeks of doxercalciferol treatment ($P < .001$), versus placebo. After 6 weeks, iPTH level decreased with doxercalciferol versus placebo ($P < .001$).	No significant differences in mean serum calcium or phosphorus between the groups.
Zisman et al. [22]	2005	RCT, $n = 27$ hemodialysis patients randomized to receive doxercalciferol at either 35, 50, or 65% of the paricalcitol dose for 6 weeks	A conversion factor of 0.57 for the dose of doxercalciferol relative to paricalcitol resulted in equivalent suppression of iPTH	Incidences of hypercalcemia and hyperphosphatemia were similar for all groups

Table 4: Suppression of PTH and effects on calcium and phosphate levels: maxacalcitol versus placebo and maxacalcitol versus calcitriol.

Author	Year	Study	Outcome 1	Outcome 2
Hayashi et al. [23]	2004	$n = 91$ patients 47 patients treated with calcitriol versus 44 patients treated with maxacalcitol for 12 months	There were no significant differences between the two groups in serum iPTH	No significant differences between the two groups in phosphorus concentration. Serum calcium was significantly higher in the maxacalcitol versus calcitriol group during early treatment, but not at the end of treatment
Shiizaki et al. [24]	2005	Uremic (5/6 NX) rats fed a high-phosphate diet and treated by a direct injection of maxacalcitol-OCT (DI-OCT) or vehicle (DI-vehicle)	DI-OCT decreased PTH levels with a significant difference DI-OCT versus DI-vehicle. Upregulations of both VDR and CaSR after DI-OCT were observed versus DI-vehicle-treated rats.	Serum calcium and phosphorus levels did not changed markedly in both groups
Kazama et al. [25]	2005	$n = 126$ nondiabetic hemodialysis patients with PTH levels greater than 300 pg/mL treated with either maxacalcitol ($n = 80$) or calcitriol ($n = 46$) for 24 weeks.	Both treatments decreased plasma intact PTH levels ($P < .0001$) and increased serum Ca levels ($P < .0001$). PTH levels were significantly lower in the maxacalcitol group after 24 weeks ($P < .01$).	Serum phosphate was significantly greater in the calcitriol group ($P < .05$)
Oyama et al. [26]	2005	Nondiabetic dialysis patients ($n = 146$) with iPTH levels >300 pg/mL were treated with i.v. maxacalcitol injected 3/week for 48 weeks.	96 patients were successfully treated (iPTH levels < 300 pg/ml within 48 weeks). Pretreatment PTH and Ca levels were lower in patients successfully treated with maxacalcitol.	Serum phosphorus levels did not significantly increase. Phosphorus levels were not predictive of the response to treatment with maxacalcitol.

Table 5: Parathyroid hyperplasia.

Author	Year	Study	Outcome
Okuno et al. [27]	2003	$n = 25$ patients treated with maxacalcitol (PTH >300 pg/ml; mean maximal diameter of parathyroid glands 11.0 ± 0.7 mm before treatment), divided in two groups: group S gland diameter <11.0 mm versus group L with gland diameter >11.0 mm. Parathyroid volume was measured by ultrasonography.	At 4–24 weeks after administration of maxacalcitol, intact PTH concentrations decreased significantly in group S ($P < .01$), versus group L. Serum calcium increased significantly in group L ($P < .05$), versus group S. Glands larger than 11 mm do not adequately respond to treatment.
Shiizaki et al. [28]	2003	$n = 20$ patients with SHPT and enlarged parathyroid glands were treated by percutaneous maxacalcitol injection therapy (PMIT) under ultrasonographic guidance consecutively 6 times, followed by i.v. maxacalcitol.	PMIT and subsequent i.v. maxacalcitol administration significantly decreased PTH levels and parathyroid gland volume for at least 12 weeks.
Akizawa and Kurokawa [29]	2002	A trial on the long-term administration of maxacalcitol (3 times weekly for 26 weeks subsequent to a 26-week pretrial) in 124 dialysis patients with secondary hyperparathyroidism.	PTH levels fell promptly and significantly and were well controlled for one year. Serum calcium levels rose significantly, but within a physiological range. Hypercalcemia (33.1%) was resolved or ameliorated after the withdrawal or dose reduction of maxacalcitol.
Saito et al. [30]	2010	An outpatient treatment regimen using percutaneous maxacalcitol injection therapy (PMIT) on a weekly basis for 4–6 weeks following dialysis.	Intact PTH decreased from 797 to 253 pg/mL. Ultrasonographic examination detected a gradual reduction in parathyroid gland volume from 1.27 to 0.24 cm^3.

Table 6: Mineral metabolism and bone disorder.

Author	Year	Study	Outcome
Slatopolsky et al. [31]	2003	A study in uremic rats to assess the efficacy of paricalcitol in prevention (protocol I) and treatment (protocol II) of hyperparathyroidism and renal osteodystrophy.	Paricalcitol was effective in preventing (protocol I) and suppressing (protocol II) the significant hyperparathyroidism induced by uremia and enhanced by a high phosphorus diet; it improved bone histology in uremic rats affected by severe secondary hyperparathyroidism.
Kazama et al. [32]	2005	$N = 50$ chronic dialysis patients with PTH levels >300 pg/mL treated with 10 μg of i.v. maxacalcitol thrice a week.	PTH, bone-specific alkaline phosphatase and osteocalcin levels were significantly lowered; serum calcium levels increased. Osteoprotegerin levels significantly decreased ($P < .0001$).

injection therapy, which significantly decreased the serum intact-PTH level and parathyroid gland volume for at least 12 weeks. Akizawa and Kurokawa [29], in a trial on the long-term administration of maxacalcitol, found that PTH levels fell promptly and were well controlled for one year, with doses ranging from 2.5 to 20 mg per dialysis. Serum calcium levels rose significantly, but within a physiological range; episodes of hypercalcemia were present in 33% of patients. Saito et al. [30] proposed an outpatient treatment regimen using percutaneous maxacalcitol injection therapy on a weekly basis for 4–6 weeks following dialysis. They found no major complications and intact parathyroid hormone decreased from 797 ± 178 pg/mL to 253 ± 25 pg/mL, while the parathyroid gland volume gradually decreased from 1.27 ± 1.06 cm^3 to 0.24 ± 0.15 cm^3.

3.2. Vitamin D Receptor Activators, Mineral Metabolism, and Bone Disorders (Table 6). Activation of the vitamin D receptor plays a role in bone metabolism and treatment with VDR activators may favorably affect bone disease. Slatopolsky et al. [31] studied uremic rats to assess the efficacy of paricalcitol in prevention and treatment of renal osteodystrophy. Paricalcitol resulted effective in preventing and suppressing hyperparathyroidism induced by uremia and enhanced by

Table 7: Hospitalization and mortality.

Author	Year	Study	Outcome
Dobrez et al. [33]	2004	Data from January 1999 to November 2001; $n = 11443$ hemodialysis patients who received at least 10 doses of vitamin D therapy	The paricalcitol group had a lower risk of first all-cause hospitalization (14% less, $P < .0001$), fewer hospitalizations per year (0.642 fewer, $P < .001$) and fewer hospital days per year (6.84 fewer, $P < .001$) versus calcitriol
Vervloet et al. [34]	2009	A review of observational studies that examined the association between the use of VDRA and mortality	Hospitalization is less frequent in patients treated with paricalcitol versus patients treated with calcitriol
Teng et al. [35]	2003	A historical cohort study to compare the 36-month survival rate among dialysis patients receiving treatment with paricalcitol (29,021 patients) versus calcitriol (38,378 patients).	The mortality rate among patients receiving paricalcitol was 0.180 per person-year versus 0.223 per person-year among those receiving calcitriol ($P < .001$). The difference in survival was significant at 12 months and increased with time. In the adjusted analysis, the mortality rate was 16 percent lower (95% CI, 10 to 21 percent) among paricalcitol-treated patients than among calcitriol-treated patients. At 12 months, calcium and phosphorus levels had increased by 6.7 and 11.9 percent, respectively, in the paricalcitol group, as compared with 8.2 and 13.9 percent, respectively, in the calcitriol group ($P < .001$).
Tentori et al. [36]	2006	$n = 7731$ patients (calcitriol: $n = 3212$; paricalcitol: $n = 2087$; doxercalciferol: $n = 2432$) in the years 1999–2004. Median follow-up was 37 weeks.	Mortality rates (deaths/100 patient-years) were identical in patients treated with doxercalciferol (15.4, 95% CI 13.6–17.1) and paricalcitol (15.3, 13.6–16.9) and higher in patients on calcitriol (19.6, 18.2–21.1) ($P < .0001$). Overall, mortality was higher for patients who did not receive vitamin D versus those who did.

a high phosphorus diet. In addition paricalcitol ameliorated the histomorphometric changes induced by uremia and high phosphorus diet, improving bone histology in uremic rats affected by severe secondary hyperparathyroidism. Kazama et al. [32] treated 50 patients with hyperparathyroidism (serum PTH > 300 pg/mL) with $10\,\mu$g of maxacalcitol intravenously injected thrice a week. They observed, along with a reduction of PTH levels, a significant decrease of bone-specific alkaline phosphatase and osteoprotegerin levels. Osteoprotegerin is a natural glycoprotein which plays a critical role in osteoclast physiology. Elevated levels of circulating osteoprotegerin may account for the development of bone and mineral metabolic abnormalities in uremia.

3.3. Hospitalization and Mortality (Table 7). There are studies which demonstrate that VDR activators are able to reduce hospitalization and mortality. Dobrez et al. [33] observed in 11 443 hemodialysis patients receiving at least 10 doses of vitamin D therapy that paricalcitol group had a lower risk of first all-cause hospitalization (14% less, $P < .0001$), fewer hospitalizations per year (0.642 fewer, $P < .001$), and fewer hospital days per year (6.84 fewer, $P < .001$) versus calcitriol. Vervloet and Twisk [34] analyzed the observational studies on the association between use of VDR activators and mortality. They underscored the absence of randomized controlled trials but considered the available observational studies "quite robust and consistent". The hypothesis of a positive, clinically significant effect of treatment with VDR activators is supported by the presence of plausible mechanisms that might explain their observed benefit in patients on dialysis, beyond their classic role in bone and mineral metabolism. Specifically, these include inhibition of renin biosynthesis, modulation of arterial function, positive effects on left ventricular hypertrophy, attenuation of insulin resistance, potential positive impact on immune function, reduced incidence of cancer, and other potential mechanisms [34]. A seminal study on the possible relationship between paricalcitol treatment and reduced mortality was published by Teng et al. [35]. They designed a historical cohort study to compare the 36-month survival rate among hemodialysis patients receiving treatment with paricalcitol versus calcitriol: mortality rate among patients receiving paricalcitol was significantly lower versus patients receiving calcitriol ($P < .001$). Tentori et al. [36], conduced on 7731 patients to compare calcitriol, paracaclcitol and doxercalciferol. They demonstrated that mortality rates were similar in patients treated with doxercalciferol and paricalcitol, while higher in patients treated with calcitriol ($P < .001$). Thus, the survival benefit in chronic kidney disease patients, independent of the effects on parathyroid hormone and calcium levels, appears to be better with the use of vitamin D analogs (paricalcitol and doxercalciferol), followed by the use of calcitriol, and the worst survival is associated with no VDR activation therapy. The mechanisms underlying the cardiovascular and survival benefit of VDR activators are still under active investigation. Several different potential factors could play a role, as VDR has been identified in more than 30 different tissues in the human body, including the vasculature [8].

Table 8: Cardiovascular protection.

Author	Year	Study	Outcome
Bodyak et al. [37]	2007	Study in Dahl salt-sensitive (DSS) rats to evaluate if paricalcitol is able to attenuate the development of left ventricular abnormalities	Compared with DSS rats fed a high-salt (HS) diet (6% NaCl for 6 weeks), DSS rats fed a high-salt HS receiving paricalcitol showed lower heart and lung weights, reduced LV mass, posterior wall thickness and end diastolic pressures, and increased fractional shortening. Blood pressures did not significantly differ between the groups
Xiang et al. [38]	2005	VDR knockout (KO) mice were compared with wild-type (WT) mice	In VDRKO mice, the cardiac renin mRNA level was significantly increased, suggesting that the cardiac hypertrophy in VDRKO mice is a consequence of activation of both the systemic and cardiac RAS and that 1,25-dihydroxyvitamin D_3 regulates cardiac functions
Zhou et al. [39]	2008	25(OH)D 1alpha-hydroxylase KO mice were compared with WT mice to determine whether the cardiovascular effect of 1,25vitD is dependent on calcium or phosphorus.	Ablation of the 1alpha-hydroxylase gene in mice led to hypertension, cardiac hypertrophy, and systolic dysfunction, and this cardiac phenotype was rescued with exogenous 1,25vitD administration. 1,25vitD plays a protective role in the cardiovascular system by repressing the renin-angiotensin system independent of extracellular calcium or phosphorus.
PRIMO study (Paricalcitol Benefits in Renal Disease Induced Cardiac Morbidity Study) [40]	Ongoing	RCT, oral paricalcitol compared to placebo in 220 predialysis patients (GFR 15–45 ml/min) affected by mild-to-moderate LVH and an LV ejection fraction >50%	Study ongoing
Mizobuchi et al. [41]	2007	Uremic rats (5/6 NX rats) were given calcitriol, paricalcitol, or doxercalciferol 3/week for 1 month	Calcitriol and doxercalciferol, but not paricalcitol, increased vascular calcification in uremic rats. The different effects of VDRA on vascular calcification are independent of an effect on Ca and P. Doxercalciferol significantly increased the Ca × P product and the aortic calcium content. A lower doxercalciferol did not increase the calcium-phosphate product but increased the aortic calcium content.

3.4. Cardiovascular Protection (Table 8). One hypothesis derived from the available observational studies suggests that systemic activation of VDRs may have direct effects on the cardiovascular system to decrease mortality in patients with chronic kidney disease [8]. Vitamin D and its analogs may play a role in preserving the cardiovascular system and reducing vascular calcification. In accordance with this concept, Levin and Li [54] suggested that Vitamin D deficiency might be an underestimated risk factor for cardiovascular disease in chronic kidney disease. They also underscore that evidence from both basic science and clinical studies supports the possible protective role of vitamin D beyond its effect on mineral metabolism. Bodyak et al. [37] studied Dahl salt-sensitive rats fed a high-salt diet (6% NaCl for 6 weeks) and receiving paricalcitol, showing lower heart and lung weights, reduced left ventricular mass, posterior wall thickness and end diastolic pressures, and increased fractional shortening. Xiang et al. [38] studied VDR knockout mice and they showed that cardiac renin mRNA levels were significantly increased, suggesting that the cardiac hypertrophy in VDR knock-out mice is a consequence of the activation of both the systemic and cardiac rennin angiotensin system and that 1,25-dihydroxyvitamin D_3 regulates cardiac functions. In another gene knock-out study by Zhou et al. [39], ablation of the 1alpha-hydroxylase gene in mice led to hypertension, cardiac hypertrophy, and systolic dysfunction, and this cardiac phenotype was rescued with exogenous 1,25-dihydroxyvitamin D administration. The authors concluded that calcitriol plays a protective role in the cardiovascular system by repressing the renin-angiotensin system independent of extracellular calcium or phosphorus. In humans, the PRIMO study (*P*aricalcitol Capsules Benefits in *R*enal Failure *I*nduced Cardiac *MO*rbidity Study), a multinational, randomized, double-blinded trial with oral paricalcitol compared to placebo, is ongoing [40]: its primary outcome measure is to investigate the effects of paricalcitol on progression or regression of left ventricular hypertrophy in Stage 3B/4 chronic kidney disease subjects,

Table 9: Prevention of atherosclerosis.

Author	Year	Study	Outcome
Husain et al. [42]	2010	A study in atherosclerotic mice to investigate the protective effect of paricalcitol combined with angiotensin-converting enzyme inhibitor (enalapril) on aortic oxidative injury	ApoE-deficient mice developed hypertension which was prevented by enalapril or enalapril + paricalcitol treatment (not by paricalcitol alone). Atherosclerotic plaque in the aorta of ApoE-deficient mice was prevented by paricalcitol, enalapril, and paricalcitol + enalapril treatments

through the evaluation of changes in left ventricular mass index, in a time frame of 48 weeks.

Mizobuchi et al. [41] studied uremic rats treated with calcitriol, paricalcitol, or doxercalciferol and found that calcitriol and doxercalciferol, but not paricalcitol, increase vascular calcification in uremic rats; in particular the different effects of VDR activators on vascular calcification appear to be independent of serum calcium and phosphate levels.

3.5. Prevention of Atherosclerosis (Table 9). Husain et al. [42] conducted a study in atherosclerotic mice to investigate the protective effect of paricalcitol combined with angiotensin-converting enzyme inhibition (by enalapril) on aortic oxidative injury. They found that ApoE-deficient mice developed hypertension, which was prevented by enalapril or by the combined enalapril and paricalcitol treatment, but not by paricalcitol alone. On the other hand, atherosclerotic plaque in the aorta of ApoE-deficient mice was prevented by paricalcitol, enalapril, and paricalcitol + enalapril treatments. Combination therapy afforded greater protection against aortic inflammatory and oxidative injury in atherosclerosis than monotherapy. This observation underscores the role of VCR activators not only as PTH suppressors but also as an essential treatment in patients with chronic kidney diseases, which are notoriously more exposed to cardiovascular diseases and atherosclerosis.

3.6. Renal Protection and Reduction of Proteinuria (Table 10). Agarwal et al. [43] in three double-blind, randomized, placebo controlled studies in patients with chronic kidney disease stage 3 and 4, found a reduction in proteinuria in 51% of paricalcitol patients versus 25% of placebo patients ($P < .01$). The demonstration of a reduction in proteinuria associated with paricalcitol treatment, independent of concomitant use of agents that block the renin angiotensin system RAA, suggests that paricalcitol is a potential pharmacologic means of reducing proteinuria in chronic kidney disease. As a consequence, de Zeeuw et al. [44] designed a multinational, placebo-controlled, double-blind trial (VITAL study): patients affected by type 2 diabetes and albuminuria receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were randomized to receive placebo, 1 μg/day paricalcitol, or 2 μg/day paricalcitol. They demonstrated that patients treated with 2 μg of paricalcitol showed an early and sustained reduction in urinary albumin-to-creatinine ratio versus placebo ($P < .05$). In another, smaller double-blind randomized study, Fishbane et al. [45] randomized 61 patients with estimated glomerular filtration rate from 15 to 90 mL/min/1.73 m^2 and protein excretion greater than 400 mg/24 h to receive paricalcitol, 1 mcg/day, or placebo: changes in protein excretion from baseline to last evaluation were +2.9% for controls and −17.6% for the paricalcitol group ($P < .05$). Zhang et al. [46] studied streptozotocin- (STZ-) induced diabetic mice and discovered that treatment with losartan and paricalcitol completely prevented albuminuria, restored glomerular filtration barrier structure, and markedly reduced glomerulosclerosis, preventing renal injury in diabetic nephropathy. Thus, evidence is available suggesting that inhibition of the rennin angiotensin system with combination of vitamin D analogs and rennin angiotensin system inhibitors effectively prevents renal injury in diabetic nephropathy and it may be associated with improved renal protection.

3.7. Renal Protection and Inhibition of the Renin-Angiotensin System (Table 11). Paricalcitol inhibits the rennin-angiotensin system. Freundlich et al. [47], in a study in remnant kidney model of chronic renal failure (5/6 nephrectomy) mice, administrated paricalcitol and found that paricalcitol decreases angiotensinogen, renin, renin receptor, and vascular endothelial growth factor mRNA levels in the remnant kidney by 30–50 percent versus untreated animals. Bodyak et al. [37] also found that paricalcitol significantly reduced cardiac renin expression in Dahl salt-sensitive rats.

3.8. Renal Protection and Tubular Interstitial Fibrosis (Table 12). Tan et al. [48], using a mouse model of obstructive nephropathy, found that paricalcitol attenuates renal tubulo-interstitial fibrosis. Paricalcitol reduced infiltration of T cells and macrophages in the obstructed kidney and this inhibition of inflammatory cell infiltration was accompanied by a decreased expression of RANTES and TNF-alpha. Their results suggest that paricalcitol inhibits renal inflammatory infiltration and RANTES expression by promoting VDR-mediated sequestration of NF-kappaB signaling. Wang et al. [49] treated with the VDR agonist doxercalciferol diet-induced obese mice, presenting proteinuria, renal mesangial expansion, accumulation of extracellular matrix proteins, and activation of oxidative stress. Treatment with doxercalciferol decreased proteinuria, podocyte injury, mesangial expansion, and extracellular matrix protein accumulation. The VDR agonist also decreased macrophage infiltration, oxidative stress, proinflammatory cytokines, and profibrotic growth factor. In addition, it prevented the activation of the renin-angiotensin-aldosterone system including the angiotensin II type 1 receptor and the mineralocorticoid

Table 10: Renal protection and reduction of proteinuria.

Author	Year	Study	Outcome
Agarwal et al. [43]	2005	Three RCTs in 220 CKD stage 3 and 4 patients randomized to oral paricalcitol ($N = 107$) or placebo ($N = 113$), followed for up to 24 weeks	Decreased proteinuria in 29/57 (51%) of paricalcitol patients versus 15/61 (25%) placebo patients, $P = .004$ (odds for reduction in proteinuria 3.2 times greater for paricalcitol patients)
de Zeeuw et al. (VITAL study) [44]	2010	Multinational RCT in 281 patients with type 2 diabetes and albuminuria receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were randomized to receive 24-week treatment with placebo, 1 μg/day paricalcitol, or 2 μg/day paricalcitol	Patients on 2 μg paricalcitol had an early, sustained reduction in UACR (urinary albumin-to-creatinine ratio), ranging from –18% to −28% ($P = .014$) versus placebo
Fishbane et al. [45]	2009	RCT of 61 patients with estimated glomerular filtration rate from 15 to 90 mL/min/1.73 m^2 and protein excretion greater than 400 mg/24 h to receive paricalcitol, 1 mcg/day, or placebo.	Changes in protein excretion from baseline to last evaluation were +2.9% for controls and −17.6% for the paricalcitol group ($P < .05$).
Zhang et al. [46]	2008	Study in streptozotocin- (STZ-) induced diabetes model mice	Treatment with losartan and paricalcitol completely prevented albuminuria, restored glomerular filtration barrier structure, and markedly reduced glomerulosclerosis, effectively preventing renal injury in diabetic nephropathy

Table 11: Renal protection and inhibition of the rennin-angiotensin system.

Author	Year	Study	Outcome
Freundlich et al. [47]	2008	Study in remnant kidney model of chronic renal failure (5/6 nephrectomy) mice, administrating two different doses of paricalcitol thrice weekly for 8 weeks.	Paricalcitol was found to decrease angiotensinogen, renin, renin receptor, and vascular endothelial growth factor mRNA levels in the remnant kidney by 30–50% compared to untreated animals.
Bodyak et al. [37]	2007	Study in Dahl salt-sensitive (DSS) rats. Evaluation of the ability of paricalcitol to attenuate the development of LV abnormalities.	Paricalcitol significantly reduced cardiac renin expression in DSS rats

receptor. An additional novel finding of this study is that the VDR activator decreased the accumulation of neutral lipids (triglycerides and cholesterol) and the expression of enzymes that mediate fatty acid and cholesterol synthesis.

3.9. Anti-Inflammatory Action (Table 13). In a pilot trial, Alborzi et al. [50] randomized patients in 3 groups receiving oral paricalcitol 0, 1, or 2 mcg/day. They observed a reduction of high sensitivity C-reactive protein and of albuminuria in patients treated with paricalcitol, with a mechanism independent of its effects on hemodynamics or PTH suppression, as no differences were observed in iothalamate clearance, 24-hour ambulatory blood pressure, or PTH levels. Eleftheriadis et al. [51] also found that basal TNF-alpha concentration and basal IL-8 concentration were reduced by paricalcitol. These studies therefore suggest that paricalcitol also has immunomodulatory properties, another reason for administration of paricalcitol in patients with chronic renal failure. Indeed, patients with chronic kidney disease have chronic inflammation in the cardiovascular system and a reduced immunity to infections.

3.10. Endothelial Function (Table 14). VDR activators have been shown to modulate inflammation, thrombosis, and vasolidation, which are associated with endothelial dysfunction [55], and they have a potential for treatment of cardiovascular disease, including the improvement of endothelial dysfunction, which increases cardiovascular disease risk in chronic kidney disease [56]. Wu-Wong et al. [52] suggest that VDR activation improves endothelial function. They studied uremic rats (5/6 nephrectomized rat) and demonstrated that the uremia-impaired aortic relaxation was improved by paricalcitol (with a short duration of treatment, 2 weeks), in a dose-dependent manner, independent of serum PTH levels or blood pressure. PTH suppression alone did not improve endothelial function since in a separate experiment cinacalcet suppressed PTH without affecting endothelial-dependent vasorelaxation. The role of phosphate in uremic

Table 12: Renal protection and reduction of tubular interstitial fibrosis.

Author	Year	Study	Outcome
Tan et al. [48]	2006	Study of the effects of paricalcitol in a mouse model of obstructive nephropathy	Paricalcitol reduced infiltration of T cells and macrophages in the obstructed kidney and this inhibition of inflammatory cell infiltration was accompanied by a decreased expression of inflammatory cytokines. Paricalcitol attenuates renal tubulo-interstitial fibrosis in this animal model of renal obstructive damage.
Wang et al. [49]	2011	Study in mice with diet-induced obesity, treated with doxercalciferol.	Doxercalciferol decreased proteinuria, podocyte injury, mesangial expansion, extracellular matrix protein accumulation, macrophage infiltration, oxidative stress, proinflammatory cytokines, and profibrotic growth factor. In addition, it prevented the activation of the renin-angiotensin-aldosterone system. VDR activation also decreased the accumulation of neutral lipids (triglycerides and cholesterol) and the expression of enzymes that mediate fatty acid and cholesterol synthesis.

Table 13: Anti-inflammatory action.

Author	Year	Study	Outcome
Alborzi et al. [50]	2008	A pilot trial in 24 patients randomized to 3 groups to receive 0, 1, or 2 mcg of paricalcitol orally for 1 month.	At 1 month, the treatment/baseline ratio of high sensitivity C-reactive protein was 1.5 (95% CI: 1.1 to 2.1; $P < .05$) with placebo, 0.8 (95% CI: 0.3 to 1.9; $P = .62$) with the 1 mcg dose, and 0.5 (95% CI: 0.3 to 0.9; $P < .05$) with a 2 mcg dose of paricalcitol. The treatment/baseline ratio of 24-hour albumin excretion rate was 1.35 (95% CI: 1.08 to 1.69; $P = .01$) with placebo, 0.52 (95% CI: 0.40 to 0.69; $P < .001$) with a 1-mcg dose, and 0.54 (95% CI: 0.35 to 0.83; $P = .01$) with a 2 mcg dose ($P < .001$ between group changes).
Eleftheriadis et al. [51]	2010	A study in 10 healthy volunteers; peripheral blood mononuclear cells (PBMC) were cultured for 48 hours in presence or not of lipopolysaccharide (LPS) and in the presence or not of paricalcitol. TNF-alpha and IL-8 produced by PBMC were measured.	Basal TNF-alpha concentration and IL-8 concentrations were reduced by paricalcitol. Paricalcitol also blunted the TNF-alpha concentration increase induced by LPS. Paricalcitol reduced to its basal level the IL-8 concentration increase by LPS. The in vitro inhibition of TGF-alpha and IL-8 by paricalcitol confirms the immunomodulatory properties of this vitamin D analogue.

Table 14: Endothelial function.

Author	Year	Study	Outcome
Wu-Wong et al. [52]	2010	Study in uremic rats (5/6 NX rats), treated for two weeks with paricalcitol.	Uremia impaired aortic relaxation was improved by paricalcitol in a dose-dependent manner, independent of serum PTH levels or blood pressure. PTH suppression alone did not improve endothelial function since in a separate experiment cinacalcet suppressed PTH without affecting endothelial-dependent vasorelaxation.
Karavalakis et al. [53]	2008	Uremic (5/6 NX) rats treated with paricalcitol (0.2 mcg/kg, thrice weekly) for 12 weeks. Aortic histology was studied	Paricalcitol treatment showed both benefits and harmful effects: vasoconstriction was reduced but calcification increased. Plasma phosphate was increased, 2.1- to 2.5-fold higher than normal.

subjects is important to consider. In the study by Wu-Wong et al. [52] uremic rats had normal serum phosphate levels. In a previous study, Karavalakis et al. [53] reported that, in the 5/6 nephrectomized rats fed a special diet that induced severe hyperphosphatemia, paricalcitol at 0.2 μg/kg reduced vasoconstriction but increased vascular calcification.

The improvement of endothelial function by VDR activators may be one of the mechanisms responsible for the cardiovascular benefit associated with these agents in chronic kidney disease.

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