Use of Paricalcitol as Adjunctive Therapy to Renin-Angiotensin-Aldosterone System Inhibition for Diabetic Nephropathy: A Systematic Review of the Literature

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ABSTRACT

Purpose: Diabetic nephropathy (DN) is a major complication of diabetes. Paricalcitol is a vitamin D analog that is typically used for secondary hyperparathyroidism in patients with chronic kidney disease but may have some beneficial effect on DN. This review evaluates the effect of paricalcitol in combination with renin-angiotensin-aldosterone system inhibitor therapy in managing DN.

Methods: A literature search was conducted of PubMed and ClinicalTrials.gov. Limits were set to include only clinical trials in humans written in English. The search terms used were *paricalcitol* and *diabetic nephropathy*. The following outcomes of kidney function and damage as well as adverse drug events were assessed and included: 24-h urine albumin excretion, serum phosphorus and calcium concentrations, urinary albumin excretion rates, estimated glomerular filtration rate, and markers of inflammation and endothelial function.

Findings: Four studies with a total of 389 patients were identified for review through the process described above. Two of the 6 studies provide evidence of the effect of paricalcitol on DN by way of reduction in urine albumin to creatinine ratio and urinary albumin excretion rate when compared with placebo. One study reported an increase in serum phosphorous, 1 study observed a decrease in estimated glomerular filtration rate, and 1 study reported no effect on inflammatory markers or endothelial function.

Implications: The number of clinical trials examining the effect of paricalcitol in DN is small. The studies that have been completed enrolled <300 patients. Paricalcitol can reduce protein in the urine, but there is no compelling evidence that it preserves kidney function.

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Keywords: Diabetic kidney disease, diabetic nephropathy, paricalcitol, renin-angiotensin-aldosterone system.

INTRODUCTION

Diabetic nephropathy (DN) is the most common renal complication of diabetes mellitus.[1] It is a microvascular complication of uncontrolled type 2 diabetes mellitus (T2D) and is a leading cause of end-stage renal disease (ESRD).[2] The current pharmacotherapeutic treatment and prevention of DN involve management of T2D through careful control of blood glucose using oral antidiabetic agents, such as sulfonylureas, metformin, dipeptidyl peptidase 4 inhibitors, and injectable glucagon-like protein receptor agonists and insulin.[3] Sodium-glucose cotransporter 2 inhibitors are also used in the treatment of T2D and have recently been found to preserve renal function.[4,5] Another mainstay of treatment for patients with diabetes and renal involvement has been the renin-angiotensin-aldosterone system (RAAS) inhibitors because of their ability to decrease proteinuria.[1] Agents that affect the RAAS include angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).[3] As the pathologic mechanism of DN is further explored, many new pathways and mechanisms for disease are beginning to be understood. This knowledge opens up new

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possibilities for drug therapy that can specifically target these areas in an effort to further preserve kidney function and delay progression to ESRD and dialysis.

DN PATHOGENESIS, PATHOPHYSIOLOGY, AND CLASSIFICATION OVERVIEW

An initial feature of DN is glomerular and tubuloepithelial hypertrophy and thickening of the glomerular and tubular basement membrane, followed by development of hyperfiltration and microalbuminuria, which progresses to proteinuria, glomerulosclerosis, and tubulointerstitial fibrosis, eventually leading to ESRD.[6] DN is classified into 4 categories based on the lesions observed under microscopy. Class I involves only glomerular basement membrane thickening without mesangial expansion or Kimmelstiel-Wilson lesions (nodules of hyaline material consistent with glomerulosclerosis). Class II is subdivided into mild (IIa) and severe (IIb) mesangial expansion. Class III includes Kimmelstiel-Wilson lesions, and class IV is defined as advanced diabetic glomerulosclerosis in which global glomerulosclerosis accounts for >50% of the specimen observed.[7]

The pathophysiology behind DN is complex and involves several mechanisms that can be targeted for drug therapy interventions. The mechanisms of disease are broad and include (1) afferent arteriole vasodilation and efferent arteriole vasoconstriction induced by hyperglycemia that can increase renal perfusion pressure, resulting in glomerular hypertension and hyperfiltration; (2) accumulation of advanced glycation end products, which can contribute to mesangial expansion; (3) inflammatory responses from increased intraglomerular pressure that can lead to the release of cytokines and renal remodeling; and (4) intracellular signaling pathways (polyol pathway, protein kinase C, hexosamine, Janus kinase, signal transducer and activator transcription, mitogen activated protein kinase, mammalian target of rapamycin, transforming growth factor β) responses to hyperglycemia and induction of extracellular matrix expansion.[8,9] In the kidney, vitamin D may be important for maintaining podocyte health, preventing epithelial-to-mesenchymal transformation, and suppressing renin gene expression and inflammation.[10] Vitamin D negatively regulates the RAAS by suppressing renin expression and plays a renoprotective role in DN.[1]

MECHANISM OF ACTION OF PARICALCITOL ON DN DISEASE PROGRESSION

Paricalcitol* is classified as a synthetic vitamin D analog of endogenous calcitriol that is used for the management of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) and ESRD. It is primarily used to activate the vitamin D–sensing receptors on the parathyroid gland and downregulate the production of parathyroid hormone (PTH) in an effort to maintain homeostasis of the vitamin D, calcium, phosphorous, and PTH system otherwise known clinically as the CKD–mineral and bone disorder syndrome.[11,12] CKD–mineral and bone disorder is the nationally recognized term used by the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative and the Kidney Disease Improving Global Outcomes organizations to define the symptoms and disease processes that occur in patients with CKD when phosphorous, calcium, and vitamin D serum concentrations are altered. These alterations affect the parathyroid gland and induce PTH secretion, thereby pulling calcium from the bone. Paricalcitol is often used to replace active vitamin D concentrations and provide a negative feedback stimulus to the parathyroid gland, turning down the secretion of PTH. The effect of paricalcitol on the development and progression of DN is thought to be anti-inflammatory and antiproteinuric in nature. In animal models, it decreases inflammatory markers, such as interleukin 6 and monocyte chemoattractant protein 1, glomerular infiltration by macrophages, and extracellular matrix deposition.[13] Paricalcitol improves endothelium-dependent vasodilatation in patients with stage 3–4 CKD, suggesting that vitamin D may exert favorable effects on the cardiovascular system.[14] The effect of paricalcitol was similar to drugs of proven efficacy in atherosclerosis prevention, such as ACEIs or ARBs, calcium antagonists,[15] and statins.[16] Paricalcitol further reduces albuminuria in patients receiving ACEI or ARB therapy.[17] The primary objective of this review is to systematically analyze the clinical trials of paricalcitol use in the treatment or prevention of DN and determine its place in therapy.

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METHODS

The Preferred Reporting Items for Systemic Reviews and Meta-analyses (PRISMA)[18] guidelines were applied throughout the literature retrieval, evaluation, inclusion, and exclusion process and served as the main protocol for this investigation (Figure). No external funding was used in this review. Data extraction was performed independently by the primary investigators. A literature search was conducted with PubMed and ClinicalTrials.gov. Limits were set to include only clinical trials in humans written in English. The search terms used were *paricalcitol* and *diabetic nephropathy*.

RESULTS

The investigators independently extracted data reported from the clinical studies that related to kidney function or damage in addition to any adverse events data attributed to paricalcitol use that was reported in the studies. Risk of selection, performance, detection, attrition, and reporting bias was assessed at the study level by investigator review. All studies reviewed were double-blinded, randomized, and placebo-controlled. This search identified 6 trials through PubMed. Two of these were excluded because one was not specific to DN and the other was a description of the study design and background characteristics of another trial. No ongoing or unpublished studies were identified through ClinicalTrials.gov, leaving 4 trials for final analysis. Two trials reported a decrease in urinary albumin excretion rate (UAER), 1 trial reported an increase in the serum phosphorous, 1 trial reported an increase in the estimated glomerular filtration rate (eGFR), and 1 trial reported no effect on inflammatory markers or endothelial function. No adverse events were reported other than an increase in serum phosphorous and calcium from 1 study. The details of these trials are further discussed in the section below.

SUMMARY OF FINDINGS FROM CLINICAL TRIALS ON PARICALCITOL USE IN DN

The background information for the studies examined in this systematic review are presented in the Table. The first study published was the Effect of Paricalcitol Capsules on Reducing Albuminuria in Patients With Type 2 Diabetic Nephropathy Being Treated With Renin-Angiotensin System Inhibitors (VITAL) in 2010.[17] This was a double-blind, placebo-controlled, multinational trial of 281 patients with T2D and existing albuminuria who were also receiving ACEI or ARB therapy. The mean patient age was 64 years, with 70% male patients. Patients' mean eGFR was 40 mL/min (as measured by the Modification of Diet in Renal Disease Study equation), and the treatment intervention dose was 1−2 μg. The secondary efficacy analysis revealed a statistically significant difference between the 2-μg paricalcitol group and the placebo group in the 24-h UAER (–28%, $P = 0.009$). A post hoc analysis of the VITAL study was published in 2013.[19] This analysis aimed to study the effect of paricalcitol on calcium and phosphate metabolism and bone markers. A statistically significant increase in serum phosphorous concentrations only occurred in the higher dose of paricalcitol at 2 –g (+0.29 mg/dL; $P < 0.001$ compared with placebo). This change was transient and most evident when paricalcitol treatment was initiated. Phosphorous gradually returned to baseline after the first 12 weeks of therapy. An increase in serum calcium also occurred and was dose dependent (low 1-μg dose of paricalcitol, +0.16 mg/dL, $P = 0.039$ compared with placebo; high 2-μg dose of paricalcitol, +0.48 mg/dL, $P < 0.001$ vs placebo). Hypercalcemia in study participants only occurred 3 times in the higher-dose paricalcitol group and once in the lower-dose paricalcitol group. Serum calcium concentrations in these patients returned to baseline when active treatment was withdrawn.

An article published in *Diabetic Medicine* in 2014 reported further benefits of paricalcitol in DN.[20] This study enrolled 48 participants (mean age, 57 years; 71% male) and aimed to measure UAER with randomization into 2 groups: paricalcitol therapy and placebo. Mean eGFR for this study population was 47 mL/min, and the treatment intervention dose was again 1−2 μg. A nonsignificant UAER reduction of 18% was observed in the paricalcitol group ($P = 0.075$). A statistically significant difference was found in the UAER reduction when compared with the placebo group change ($P = 0.03$). In addition, after eGFR calculation in both groups, a significant decline was seen in the paricalcitol group (from 44 to 41 mL/min, $P = 0.012$). However, the measured GFR was not statistically significantly different

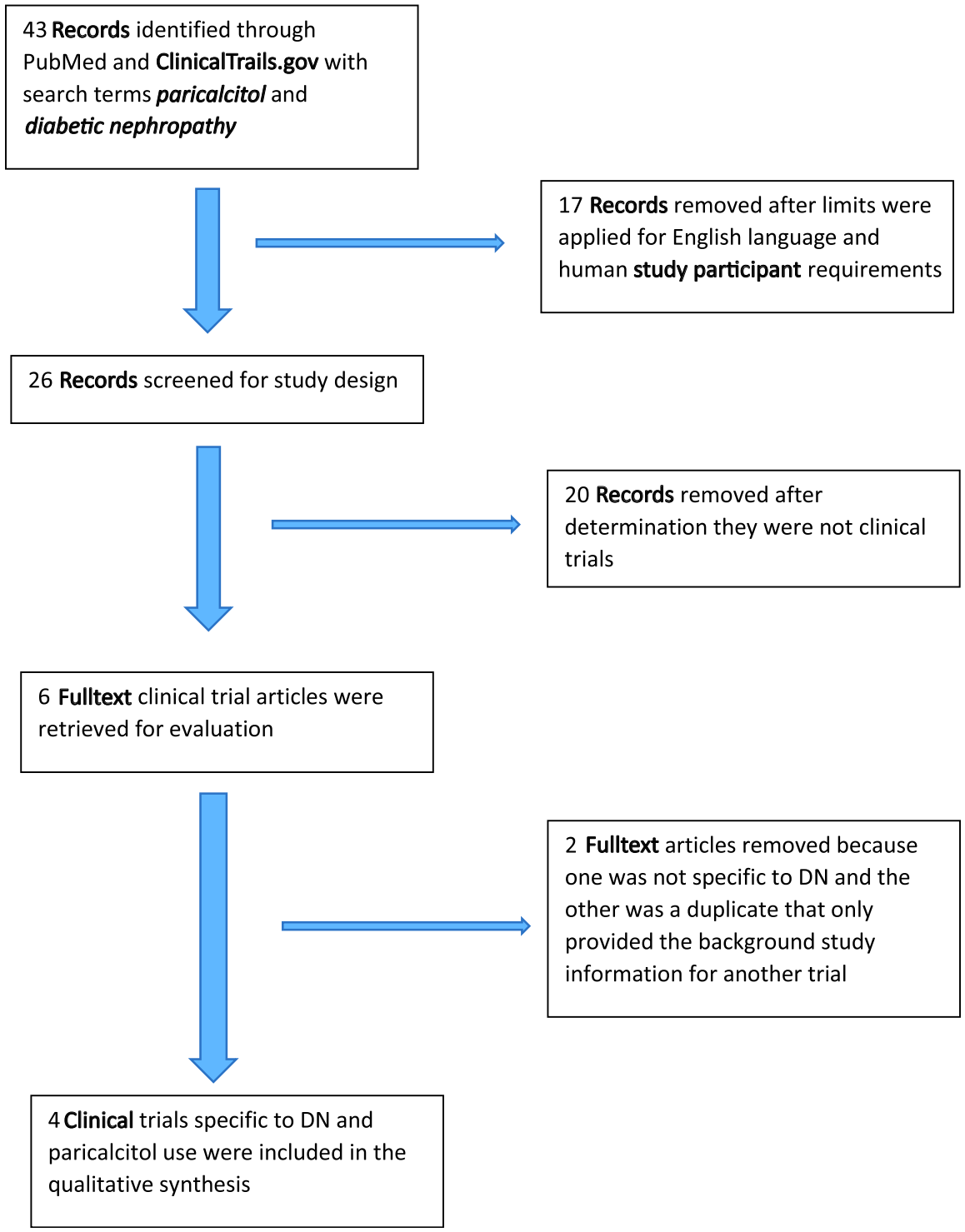

Figure. Study selection pathway. DN = diabetic nephropathy.

Table. Paricalcitol in diabetic nephropathy trials summary.

Study	Study Design	No. of Patients	Dose	End Points Measured	Results
De Zeeuw et al,[17] 2010	Multinational, placebo-controlled, double-blind trial	281	1 or 2 μg/d for 24 weeks	24-Hour urinary albumin excretion	28% Difference in the between-group comparison of 2 μg of paricalcitol vs placebo, $P = 0.009$
Coyne et al,[19] 2013	Post hoc analysis of the VITAL study	281	1 or 2 μg/d for 24 weeks	Serum phosphorous and calcium concentrations	0.29-mg/dL increase in serum phosphorous concentrations in the group receiving the higher 2 doses of paricalcitol, $P < 0.001$; dose-dependent increase in serum calcium also occurred
Joergensen et al,[20] 2014	Double-blind, randomized, placebo-controlled, crossover trial	48	1−2 μg/d for 12 weeks	UAER, eGFR, measured GFR	18% Decrease in UAER, $P = 0.075$; 3-mL/min decline in eGFR in paricalcitol group; no statistically significant change in measured GFR
Thethi et al,[21] 2015	Double-blind, randomized, placebo-controlled trial	60	1 μg/d for 3 months	ICAM-1, MCP-1, TNF-α, and IL-6	No end points had statistically significant differences between the paricalcitol and placebo groups

eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; ICAM-1 = intercellular adhesion molecule 1; IL-6 = interleukin 6; MCP-1 = monocyte chemoattractant protein 1; TNF-α = tumor necrosis factor α; UAER = urinary albumin excretion rate; VITAL = Effect of Paricalcitol Capsules on Reducing Albuminuria in Patients With Type 2 Diabetic Nephropathy Being Treated With Renin-Angiotensin System Inhibitors.

between the paricalcitol and placebo groups (44 and 46 mL/min respectively; $P = 0.20$).

Finally, an article published in the *Journal of Diabetes and Its Complications* in 2015 presented the inflammatory benefits of paricalcitol therapy in DN.[21] This trial enrolled 60 patients (mean age, 63 years; 67% male), and the inflammatory end points measured were intercellular adhesion molecule 1, monocyte chemoattractant protein 1, tumor necrosis factor α, and interleukin 6. The mean eGFR was 46 mL/min, and the intervention dose was 1 μg. After paricalcitol treatment, none of these biomarkers changed significantly compared with the placebo group ($P > 0.05$).

DISCUSSION

Efficacy outcomes measured in studies evaluating paricalcitol for DN include changes in eGFR, measured GFR, urine albumin to creatinine ratio, decreases in albuminuria, and effect on inflammatory

markers. The studies evaluated used 1–2 μg of paricalcitol because this is the standard daily dose for paricalcitol and the available capsule sizes. Two of the 4 examined studies provide evidence of the effect of paricalcitol on DN by way of reduction in urine albumin to creatinine ratio and UAER when compared with placebo. The largest study to date using paricalcitol in DN was the VITAL study, with 281 patients, which provides compelling evidence of the benefit of adding 2 μg of paricalcitol to existing RAAS therapy. The study by Joergensen et al,[20] which enrolled fewer patients (n = 48), reported a statistically significant reduction in UAER when compared with placebo. Doses used in this study fluctuated from 1 to 2 μg. Thethi et al[21] were unable to detect statistical significance for change in inflammatory mediators. The studies by Joergensen et al[20] and Thethi et al[21] were limited by fewer patients, enrolling only 48 and 60 patients, respectively.

The clinical consequences of starting treatment with paricalcitol early (ie, early stages of CKD) in patients with DN are present but minimal. As expected, PTH serum concentrations are decreased, which may be beneficial to the patient because this would decrease calcium removal from bone and reduce the risk of osteopenia. Only minimal transient effects on calcium and phosphorous serum concentrations were observed, indicating that the use of paricalcitol for DN causes minimal risk to the patient. Patients with a history of or additional risk factors for hypercalcemia might need additional consideration before starting this agent. In addition, although eGFR decreased in the study by Joergensen et al,[20] the measured GFR change was not statistically significant. This decrease in eGFR has been explained elsewhere as the possible effect of vitamin D receptor activation on creatinine metabolism and not impairment of creatinine clearance through the kidneys.[22] Another study found that this drug produces a slight, fully reversible reduction in the GFR, which was independent of blood pressure, and this functional effect may depend on an interference of paricalcitol with the regulation of glomerular microcirculation by the nitric oxide system.[14]

Currently, there is no published morbidity and mortality data on paricalcitol's use in DN. It is unclear whether these benefits of paricalcitol will prolong a patient's time to dialysis or slow the progression of CKD. In addition, the 4 studies were double-blind, randomized, placebo-controlled clinical trials that controlled for bias. The VITAL study and the study by Joergensen et al[20] were funded by AbbVie, the company that markets paricalcitol, and the authors of the studies disclosed this information.

There are 2 other agents—calcitriol and doxercalciferol—that activate the vitamin D receptor. Calcitriol has been studied in humans and reduces albuminuria in conjunction with RAAS inhibition.[23] Doxercalciferol is a similar vitamin D analog to paricalcitol; animal model data indicate a reduction in proteinuria when combined with ARB therapy,[24] but no studies have been initiated in humans.

RELEVANCE TO PATIENT CARE AND CLINICAL PRACTICE

Because RAAS blockade is limited by adverse effects, such as hyperkalemia and acute kidney injury,[25] adjunctive therapies, such as paricalcitol, that can lower residual proteinuria but without these drawbacks, may be beneficial. The studies reviewed provide evidence that paricalcitol, when added to RAAS inhibitor therapy, will reduce proteinuria in patients with DN compared with placebo. There is no compelling evidence regarding other markers of kidney function preservation, such as prolonged time to dialysis, positive changes in GFR, or decreased morbidity or mortality.

Practitioners should be aware that the eGFR reported in most laboratory analyses is not the true measure of a patient's GFR and could appear falsely decreased in patients receiving paricalcitol therapy.[22] An important point to remember is that calcium and phosphorous serum concentrations may be slightly elevated with the use of paricalcitol, as reported by the ad hoc analysis of the VITAL study. If a patient's medication profile or medical history reveals additional risk of hypercalcemia, additional consideration should be taken before starting paricalcitol treatment.

CONCLUSION

In patients with DN who are also receiving RAAS inhibitor therapy, paricalcitol may be added to further reduce albuminuria. The potential decrease in eGFR may be seen when using this agent; however, it is not indicative of true decline in

kidney function. Furthermore, considerations should be made regarding the patient's additional risk factors and history of electrolyte imbalances, particularly calcium and phosphorous. Larger, long-term, randomized and controlled human studies comparing the effect of paricalcitol and other vitamin D analogues on DN, proteinuria, renal function, progression to ESRD, and mortality are needed.

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DISCLOSURES

The authors have indicated that they have no conflicts of interest regarding the content of this article.

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