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4e Treatment

Do the benefits of using calcitriol and vitamin D receptor analogues in patients with chronic kidney disease outweigh the harms?

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Abstract

The primary indication for administration of calcitriol or vitamin D receptor analogues (VDRAs) in chronic kidney disease (CKD) is secondary hyperparathyroidism (SHPT). Prevention and treatment of SHPT appears important, as imbalances in mineral metabolism are associated with renal osteodystrophy and higher parathyroid hormone (PTH) levels are associated with increased rates of mortality and morbidity in CKD patients. There is however, a lack of controlled trial data that shows lowering PTH with calcitriol/VDRAs equates to improved clinical outcomes. Recent randomised controlled trials have concentrated on potential benefits of calcitriol/VDRAs on cardiovascular outcomes and reduction of proteinuria, and on possible differences between calcitriol and the various VDRAs. Several systematic reviews and meta-analyses have also been published, evaluating the benefits and harms of calcitriol/VDRAs. Concerns have been raised about the effectiveness of calcitriol/VDRAs for suppression of SHPT in the CKD stage 3-5 population, as well as potential adverse outcomes such as hypercalcaemia and elevation in FGF23 levels, suggesting their routine use to treat SHPT in the pre-dialysis CKD population may not be favourable. Conversely, concerns still exist about the wide PTH range in advanced CKD, and that high values may negatively impact bone quality, result in the progression of parathyroid hyperplasia and decrease the effectiveness of treatments to reduce PTH,. We discuss the current controversies relating to the challenges in the management of SHPT in patients with CKD stages 3-5, and the need for more evidence to determine the efficacy or harm of using calcitriol/VDRAs in this population.

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Introduction

Chronic kidney disease (CKD) results in a cascade of changes in mineral metabolism, which produce a rise in circulating parathyroid hormone (PTH) levels and the characteristic abnormalities of secondary hyperparathyroidism (SHPT). Management of elevated PTH levels in CKD has been a therapeutic focus for over 40 years. SHPT is associated with morbidity and mortality in patients with CKD stages 3-5D, and observational studies consistently report an increased relative risk of death in dialysis patients who have PTH values at the extremes for this population (less than twice, or greater than nine times, the upper normal limit of the assay)[1,2]. Once developed, severe SHPT may be resistant to medical/pharmacological therapy, and marked parathyroid hyperplasia when associated with hypercalcaemia necessitates treatment with a parathyroidectomy.

Treatment with 'active' vitamin D, either calcitriol or vitamin D receptor analogues (VDRAs), has been the cornerstone for the prevention and management of SHPT in patients with CKD. Observational data suggests a mortality benefit with the use of VDRAs in dialysis populations[3,4], although this has been contested by other studies[5]. Furthermore other studies suggest a benefit beyond the parathyroid-bone axis[6,7]. However, there are concerns raised by recent trials about the effectiveness of calcitriol/VDRAs in the CKD stage 3-4 population, with potential adverse outcomes such as hypercalcaemia and elevation in fibroblast growth factor 23 (FGF23) levels.

VDRAs, SHPT and CKD

The importance of renal 1,25-dihydroxycholecalciferol (calcitriol) synthesis is well described, and alterations in vitamin D metabolism are a key feature of Chronic Kidney Disease Mineral and Bone

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Disorder (CKD-MBD)[8]. The progressive decrease in renal calcitriol synthesis seen in CKD is predominantly an active process mediated by the counter-regulatory effects of increasing FGF23 levels[9], in addition to the passive effect of loss of renal parenchyma, and these decreased calcitriol levels and resulting hypocalcaemia are major stimuli to PTH secretion. The pathogenesis of SHPT in CKD is further complicated by disordered phosphate homeostasis and elevations in FGF23. The incidence and severity of SHPT increases with worsening renal function, resulting in parathyroid cell proliferation and hyperplasiaand leading to abnormalities in bone mineralisation and turnover.

There has been difficulty in establishing an appropriate target range for serum PTH in patients with CKD for several reasons. These include cross-sectional studies showing that median PTH values increase and the range widens with progressive CKD, methodological problems regarding the measurement of PTH, and increasing resistance of bone to the actions of PTH as kidney function deteriorates[10]. Additionally, the predictive value of PTH for underlying bone histology remains poor when intact PTH values are between approximately two and nine times the assay's normal upper range[11].

Calcitriol or VDRA therapy has been the predominant treatment for SHPT in CKD, with a large body of clinical practice and experience. Administration of calcitriol or VDRAs, such as paricalcitol, doxercalciferol and alfacalcidol, results in suppression of PTH levels. However, these therapies can also increase serum calcium, phosphate and FGF23 levels. Calcitriol/VDRAs act through the vitamin D receptor (VDR) to inhibit PTH secretion., However, in addition to tissues involved in mineral homeostasis, the VDR has also been identified in many organs including vascular smooth muscle, endothelial cells and cardiac tissue[12,13]. There has been increasing interest in the potential pleiotropic

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effects of vitamin D therapy, including effects pm kidney disease *per se* (proteinuria, renal fibrosis and renal function) as well as cardiovascular morbidity and mortality.

Clinical guidelines and recent studies

The Kidney Disease Improving Global Outcomes (KDIGO) CKD-MBD Guidelines were published in 2009, and Table 1 outlines aspects relating to management of SHPT from these guidelines[14]. The low level of evidence, and therefore weak recommendations, highlight the lack of randomised controlled trials (RCTs) that define an optimal PTH level for patients with CKD stages 3-5. Data on clinical endpoints such as hospitalisation, fracture or mortality are similarly lacking. A recent review of the KDIGO guidelines suggested a revision of the previous statement relating to targeting normal PTH levels in pre-dialysis CKD patients, with appreciation that modest increases in PTH most likely represent an appropriate adaptive response to declining kidney function; further, it was suggested that in CKD stages 3-5, only PTH levels that were 'persistently elevated' or 'progressively rising' should warrant further investigation and management[15].

Treatment of SHPT with calcitriol/VDRAs has historically been supported by RCTs of patients with CKD stages 3-5D, showing that these agents lower levels of serum PTH compared with placebo[16-18]. Two well-conducted RCTs in patients with CKD stages 3-5 also evaluated bone histomorphometry reporting benefits with calcitriol/VDRAs compared to placebo.[19,20] These trials led to a recommendation in the 2009 guidelines to treat elevated PTH levels with calcitriol/VDRAs early in CKD to prevent parathyroid hyperplasia and skeletal consequences. However, the two RCTs involving bone biopsies were published over 20 years ago and may not be relevant to current practice,

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and although benefits were predominantly related to suppression of SHPT, adverse effects of hypercalcaemia were of concern.

Recent RCTs have been published since the 2009 KDIGO CKD-MBD guidelines, and two studies in particular have demonstrated increased incident hypercalcaemia when compared to earlier studies[21,22]. The current draft CKD-MBD guidelines (http://www.kdigo.org/clinical_practice_guidelines/CKD-MBD%20Update/KDIGO%20CKD-MBD%20Update_Public%20Review_Final.pdf: last accessed 22 January 2017) now comment that the benefit to risk ratio may no longer be favourable, with the routine use of calcitriol/VDRAs in CKD 3-5 no longer recommended, and instead these agents should be reserved for severe and progressive SHPT.

The two RCTs discussed were the PRIMO and OPERA studies, which failed to show a beneficial effect of paricalcitol on cardiac structure and function in CKD patients. A significant reduction in PTH was observed in both studies, but with an increased risk of hypercalcaemia.

The PRIMO trial evaluated the effect of paricalcitol on cardiac magnetic resonance imaging (MRI) measures of the left ventricular mass index (LVMI) and diastolic function over 48 weeks in 227 participants with CKD stage 3 and 4 and moderate left ventricular hypertrophy (LVH)[21]. Although treatment with paricalcitol promptly reduced PTH levels and maintained them within the normal range, neither the change in LVMI nor Doppler measures of diastolic dysfunction differed between treatment groups. However, episodes of hypercalcaemia were more frequent in the paricalcitol group (20.9%) compared with the placebo (0.9%) group.

The OPERA study was a trial of the effect of 52 weeks of paricalcitol on MRI measures of LVMI and echocardiograph measures of cardiac function in 60 participants with non-dialysis CKD stages 3–5

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and LVH[22]. Paricalcitol was again associated with prompt reductions in PTH but was not associated with changes in LVMI or cardiac function. Hypercalcaemia occurred in 43.3% and 3.3% of participants randomised to paricalcitol and placebo, respectively. The primary differences in the OPERA and PRIMO studies were the smaller sample size in OPERA, and that LVMI of the OPERA subjects was at least 70% greater compared with those in PRIMO. Thus, OPERA provided important evidence in a cohort with more severe CKD, more severe SHPT and frank LVH, that paricalcitol had no effect on reduction of LVMI over 12 months. In both studies, cardiovascular-related hospitalisations were lower in the treated groups but these were secondary or *post hoc* analyses requiring further confirmation. In addition there was no assessment of whether low dose treatments, avoidance of hypercalcaemia, or the targeting of a higher range for PTH values might have long-term non-cardiac benefits.

One recent study was the first to directly compare cinacalcet and VDRAs as monotherapies to lower PTH in the dialysis population[23]. This 12-month randomised, open-label study enrolled 312 participants on haemodialysis with PTH >45pmol/L to either cinacalcet or VDRA and evaluated the percentage change in PTH level. The mean percentage change from baseline in PTH was -12.1% (-20.0% to -4.1%) in the cinacalcet arm and -7.0% (-14.9% to 0.8%) in the VDRA arm, a non-significant difference of -5.0% (-15.4% to 5.4%). There was also no difference in achievement of secondary efficacy end points between arms. Hypocalcaemia was more common in the cinacalcet arm, whereas hypercalcaemia and hyperphosphataemia occurred more often in the VDRA arm.

There has not been any other recent literature to suggest a need to revise the 2009 KDIGO guidelines regarding the use of calcitriol/VDRAs to treat SHPT in dialysis patients. However, more research is necessary to determine the appropriate setting for these agents in dialysis, including studies to

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determine at what degree of SHPT they are beneficial and address concerns about hypercalcaemia, hyperphosphataemia, vascular calcification and elevations in serum FGF23.

Potential benefits of calcitriol/VDRAs in CKD

Laboratory endpoints

The effects of calcitriol/VDRA therapy on biochemical end-points in CKD are well documented, especially in regard to reduction of PTH levels. Numerous previous studies have reported significant reductions of PTH levels with calcitriol or VDRAs in CKD stages 3 and 4 when compared to placebo[16,19,24,] and recent RCTs have also demonstrated vitamin D treatment effectively lowers PTH levels in CKD stages 3-5[21,22]. Therefore there is a well-established cause and effect between calcitriol/VDRAs and suppression of SHPT, although the effect of this on bone health remains is less clear. Their prescription for PTH suppression may also increase in Australia with the withdrawal of reimbursement for cinacalcet as a readily available therapy for the treatment of SHPT. Many of the uncertainties associated with the use of calcitriol/VDRAs mirror the ambiguity regarding the optimal PTH target, and the broader issues of using PTH as a marker of CKD-MBD. Additionally, calcitriol/VDRAs may have effects beyond the bone-parathyroid axis, with increasing evidence for a benefit of these agents on reduction of proteinuria in patients with CKD stages 3-5 (and, extrapolating this, the potential to slow progression of renal disease although this has not been reported to date). Supporting evidence is nicely summarised in the systematic review by de Borst MH *et al*[6].

Cardiovascular protection

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There may also potentially be cardiovascular benefits of calcitriol/VDRAs, although not directly shown in PRIMO and OPERA, with a recent meta-analysis reporting reduction in cardiovascular events with VDRAs despite no change in cardiac structure/function[7]. This meta-analysis involving 731 patients from seven clinical trials of calcitriol/VDRAs (5 paricalcitol, 2 calcitriol) compared with placebo or no treatment; and reported a reduced incidence of cardiovascular events with calcitriol/VDRA treatment (relative risk (RR) 0.27 [95%CI 0.13-0.59]), as well as reduced proteinuria, (RR 1.9 [95%CI 1.34-2.71]). There was an increased probability of hypercalcaemia with paricalcitol therapy, however, with RR 7.85 (95%CI 2.92-21.10), but no increased hypercalcaemic risk with calcitriol was observed in this meta-analysis.

Reduction in proteinuria

Over the last 10 years there has been an increasing appreciation of potential non-mineral effects of vitamin D therapy, including effects on blood pressure and proteinuria. Studies in animal models of CKD have suggested that proteinuria, renal fibrosis and loss of renal function may be reduced by treatment with calcitriol/VDRAs, not only as monotherapy but also as adjunctive therapy to blockade of the renin-angiotensin-aldosterone system (RAAS)[25]. There have been several recent RCTs assessing the role of calcitriol or VDRAs on reduction of proteinuria in CKD patients. The largest of these, the VITAL study, demonstrated that of 2µg paricalcitol per day achieved the secondary end point with an effect of decreasing albuminuria in 281 patients with diabetic nephropathy and RAAS blockade over 24 weeks[26]. A recent meta-analysis addressed the effect of calcitriol/VDRAs and proteinuria in CKD and included six studies (four with paricalcitol, two with calcitriol) involving 688 patients, with the vast majority on RAAS blockade[27]. Reduction in proteinuria was reported with calcitriol/VDRAs with a weighted mean difference from baseline of 16% [95%CI, 13-18%]) compared to an increase with control (6% [95%CI, 0-12%]). This analysis also suggested a dose-

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dependent effect; and the findings were consistent irrespective of study size, duration of follow-up or cause of CKD.

Progression of renal impairment

Although calcitriol/VDRAs have not been shown to date to reduce the rate of deterioration of kidney function in CKD, reduction of proteinuria with calcitriol/VDRAs may potentially be beneficial to slow down progression of CKD. In the REIN study, treatment with angiotensin-converting enzyme (ACE) inhibitors reduced proteinuria by 15% which was associated with a reduced risk of reaching end-stage kidney disease (ESKD)[28]. Although the potential mechanism of action for calcitriol/VDRAs to reduce proteinuria is unclear, experimental studies suggest that renoprotection by reducing proteinuria could be caused by suppression of renin transcription, reduction in podocyte injury, anti-proliferative effects or anti-fibrotic effects, or a combination. In a recent *post hoc* propensity score-matched analysis derived from a prospective cohort study of 240 patients with CKD stage 4-5, the use of calcitriol/VDRAs was independently associated with preservation of renal function[29]. However, definitive trials demonstrating that calcitriol/VDRAs slow progression to ESKD are lacking.

Vitamin D supplementation

"Nutritional" vitamin D supplementation (vitamin D2 and D3) can also effectively suppress PTH, although this therapy appears to become less effective in advanced CKD[30,31]. Several studies have demonstrated that correction of vitamin D deficiency (as defined by low serum 25-hydroxyvitamin D levels) in CKD does not adequately manage SHPT, and most patients require treatment with calcitriol/VDRAs[31-33]. One recent study compared nutritional vitamin D, cholecalciferol 4000units/day for one month then 2000units/day, with doxercalciferol (1µg/day) over 3 months in CKD stages 3 and 4; and reported greater reduction in PTH with doxercalciferol (27 vs 10%, although not statistically

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significant)[30]. There was a mild increase in serum calcium and urinary calcium excretion with doxercalciferol in this study but within the normal ranges, and otherwise no significant differences were observed between the treatments.

More recent studies have reported the effectiveness of using extended-release calcifediol, a novel vitamin D prohormone repletion therapy, to correct low serum 25-hydroxyvitamin D and improve SHPT. One RCT of 429 patients with CKD stages 3-4 showed at least a 10% reduction of intact PTH levels in 72% of participants, with no significant impact on calcium, phosphate or FGF23 levels[34]. Calcifediol may be a safe and effective treatment for SHPT in pre-dialysis CKD patients without increased risk of hypercalcaemia or other mineral disturbances"; however, no trials assessing patient-centred clinical outcomes or comparison studies of calcifediol with calcitriol/VDRAs have been performed to date.

Potential harms of calcitriol/VDRAs in CKD

The hypercalcaemic risk with calcitriol/VDRAs is one of the predominant concerns with this therapy in CKD. and this risk was greater in the treatment arm of the recent placebo-controlled trials, the PRIMO and OPERA studies, compared to previous studies. This raises safety concerns when the clinical benefit remains ambiguous. Limitations of these systematic reviews include the small number of studies, small sample sizes, heterogeneity of populations and short term follow-up. Most studies also had inadequate power and insufficient follow up to ascertain outcomes properly. If initiated for severe and progressive SHPT, calcitriol/VDRAs should be started with low doses, independent of the initial PTH concentration, and then titrated based on the PTH response, to ensure hypercalcaemia is avoided.

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Whether VDRAs are more effective and have less risk of hypercalcaemia than calcitriol was assessed in one recent RCT which compared 24 weeks treatment with either calcitriol (0.25µg/day) or paricalcitol (1 µg/day), in 110 patients with CKD and PTH >120pg/mL[35]. Adjustments of vitamin D therapy were made to achieve 40-60% suppression of PTH, with the primary endpoint being hypercalcaemia >10.5mg/dL. PTH was suppressed similarly in both groups (52% vs 46%) and hypercalcaemia in both groups was very rare in this study (only 3 with paricalcitol and 1 with calcitriol).

A recent meta-analysis evaluated the use of calcitriol and VDRAs in non-dialysis patients, with the aim of comparing newer versus established vitamin D compounds[36]. Eighteen studies were included, six of which looked at vitamin D and proteinuria, twelve studied effects on renal function and fifteen assessed the incidence of hypercalcaemia. There was no significant decrease in GFR (mean difference -0.10ml/min/1.73m^2, [95%CI -0.24-0.03]) but the risk of hypercalcaemia was higher in patients given calcitriol/VDRAs compared to those given placebo or no medication (RR 4.78 [95%CI 2.20-10.37]), with greater RR for the VDRAs. Of note however, most of the trials were short-term, generally lasting no more than two years.

Conclusion and suggested future research

SHPT is an inevitable consequence of advanced CKD and the suppression of PTH levels with calcitriol/VDRA therapy has been a cornerstone of nephrology practice. The effectiveness of calcitriol/VDRAs in lowering PTH has been well established in numerous studies, and a mortality benefit of lower PTH levels has been demonstrated in many (but not all) large observational studies.

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However, there is still no evidence for patient-level outcomes from RCTs with the use of calcitriol/VDRAs in CKD, the optimal level of PTH in CKD stages 3-5 is not known, and at present their routine use in stage 3-5 CKD cannot be recommended. Instead there are concerns about the effects of higher doses of calcitriol/VDRAs on mortality outcomes in certain CKD cohorts, with their potential to promote hypercalcaemia and, potentially, vascular calcification. Consequently, the current guidelines remain intentionally vague, and are difficult to implement in clinical practice.

Many aspects pertaining to the use of calcitriol/VDRAs require further evaluation in clinical trials. These include their use in CKD 3-5, appropriate timing and doses, and use of calcitriol/VDRAs in combination with other therapies such as phosphate binders and nutritional vitamin D. The effect of calcitriol/VDRAs on the progression of SHPT and on parathyroidectomy rates also needs further investigation; and their effects on bone, fracture and musculoskeletal outcomes remain unclear. Despite the negative results of recent RCTs, there is considerable interest in the use of calcitriol/VDRAs for extra-renal indications such as improving cardiac outcomes and proteinuria. Future clinical trials need to evaluate clinically significant outcomes, in particular mortality and cardiovascular morbidity, as these will in turn inform revised versions of clinical guidelines pertaining to calcitriol/VDRA use. The withdrawal of reimbursement of cinacalcet therapy in Australia will afford an opportunity to re-evaluate the future use of calcitriol/VDRAs in CKD, as well as refining the timing of therapy, their use in combination with other therapies, and their effects on biomarkers (other than PTH) in CKD-MBD.

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Tables

Table 1: Summary of the diagnosis and treatment of SHPT in the KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD), published in 2009.*

Diagnosis
1. Serum levels of calcium, phosphate, PTH and ALP activity should be measured and monitored, beginning in CKD stage 3 (1C). 2. It is reasonable to base the frequency of monitoring serum calcium, phosphate and PTH on the presence and magnitude of abnormalities, and the rate of progression of CKD (not graded). 3. In patients with CKD stages 3-5D the measurement of serum PTH or bone-specific ALP can be used to evaluate bone disease, as markedly high or low values predict bone turnover (2B).
Treatment
1. In patients with CKD stages 3-5 not on dialysis the optimal PTH level is not known a. Patients with PTH levels above the upper normal limit should be evaluated for other abnormalities of CKD-MBD (2C), and these should be corrected (not graded).# 2. In patients with CKD stage 3-5 not on dialysis, where serum PTH is rising and remains persistently elevated despite the correction of modifiable factors, treatment with calcitriol or VDRAs should be used (2C).# 3. Initial drug selection for the treatment of elevated PTH should be based on serum calcium and phosphate levels and other aspects of CKD-MBD (not graded). 4. In patients with CKD stage 5D, PTH levels should be maintained in the range of two to nine times the upper normal limit of the assay (2C). 5. Calcitriol/VDRAs (and calcimimetics) can be used to lower PTH in patients with CKD stage 5D where PTH is elevated or rising (2B). 6. Calcitriol/VDRAs should be reduced or stopped if (i) PTH levels fall below two times the upper limit of normal in CKD stage 5D (2C), and/or (ii) patients develop hypercalcaemia (2D).

*Level of evidence in parentheses

These guideline statements will likely be revised in the updated KDIGO Guidelines in 2007

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Abbreviations: ALP, alkaline phosphatase; CKD, chronic kidney disease; PTH, parathyroid hormone; VDRAs, vitamin D receptor analogues

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