Clinical practice recommendations for treatment with active vitamin D analogues in children with chronic kidney disease stages 2–5 and on dialysis

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ABSTRACT

In patients with chronic kidney disease (CKD), renal synthesis of active vitamin D [1,25-dihydroxyvitamin D (1,25(OH)2D)] declines and is associated with hypocalcaemia, secondary hyperparathyroidism and the spectrum of CKD-mineral and bone disorder (MBD). This condition applies to children with CKD-MBD. The WGs have performed an extensive literature review to include systematic reviews and randomized controlled trials in adults and children with CKD and prospective observational studies in children with CKD. The Grading of Recommendation, Assessment, Development and Evaluation (GRADE) system was used to develop and grade the recommendations. In the absence of applicable study data, the opinion of experts from the ESPN CKD-MBD and Dialysis WGs is provided, but clearly GRADE-ed as such and must be carefully considered by the treating physician and adapted to individual patient needs as appropriate.

Keywords: chronic kidney disease (CKD), CKD-MBD, dialysis, pediatrics, vitamin D

INTRODUCTION

In patients with chronic kidney disease (CKD), renal synthesis of active vitamin D [1,25-dihydroxyvitamin D (1,25(OH)2D)] declines with kidney function loss. Low serum 1,25(OH)2D concentrations contribute to hypocalcaemia, secondary hyperparathyroidism and the spectrum of CKD–mineral and bone disorder (MBD) [1]. In more advanced stages of CKD, active vitamin D analogues, including calcitriol (the naturally occurring form of 1,25(OH)2D3), alfacalcidol (1α hydroxyvitamin D3, a synthetic prohormone that requires activation by
25-hydroxylase in the liver), and paricalcitol [a synthetic analogue of calcitriol (19nor,1,25(OH)2D)] are routinely administered.

It is difficult to define bone-specific outcomes that can guide treatment with active vitamin D analogues in children with CKD-MBD [2–4]. Bone biopsies are highly invasive and rarely performed in clinical practice. Histological features of renal osteodystrophy reflect cumulative long-term changes and may be influenced by other medications, such as calcium-based phosphate binders [5] and growth hormones [6]. Routine bone X-ray imaging has low sensitivity and specificity, and dual-energy X-ray absorptiometry scans may be confounded by the differential effects of parathyroid hormone (PTH) on trabecular and cortical bone [7]. Serum concentrations of PTH and alkaline phosphatase (AP) are poor markers of bone status, but at present are the only tools available in clinical practice to guide active vitamin D therapy. PTH increases with declining kidney function [8, 9] due to phosphate accumulation, which stimulates fibroblast growth factor 23 (FGF23) synthesis in bone, resulting in suppression of renal 1,25(OH)2D synthesis, active vitamin D deficiency, impaired intestinal calcium absorption and hypocalcaemia [1]. Bone mineralization defects develop even in CKD Stage 2, may precede increases in PTH [9] and have been associated with the increased fracture rate observed in CKD [10].

Resistance of bone to PTH, and of the parathyroid glands to calcium and 1,25(OH)2D, develops due to down-regulation of their vitamin D receptors (VDRs) [11]. Despite the steadily increasing number of publications on the pathomechanisms and consequences of CKD-MBD, there are few evidence-based studies to determine the optimal treatment strategy.

We present clinical practice recommendations for treatment with active vitamin D analogues in children with CKD Stages 2–5 and on dialysis (Stage 5D). A second document in parallel with this one covers treatment recommendations for the assessment of vitamin D status, optimal levels of 25(OH)D and its monitoring and recommendations for native vitamin D supplementation [12]. The recent Cochrane Review [13] and evidence tables from the Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD update document [26] were used to evaluate all available studies and, in addition, the core working group has performed an extensive literature review as described below. Most studies are small, include different vitamin D analogues, variable starting and maintenance doses and routes of administration and rely predominantly on surrogate endpoints, in particular PTH, with few data available on patient-centred outcomes such as fracture risk and growth. The spectrum of MBD includes several intricately linked modifiers of bone mineralization, bone turnover, phosphorus and mineral metabolism.

<table>
<thead>
<tr>
<th>Author, year</th>
<th>No. of studies</th>
<th>Population, age</th>
<th>n</th>
<th>Outcomes</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hahn et al., 2015 [13]</td>
<td>18 × RCTs</td>
<td>CKD Stage 2–5D, children</td>
<td>576</td>
<td>Bone disease</td>
<td>- Treatment with calcitriol by both intraperitoneal and oral routes was effective in improving bone histology [14]. However, both treatments used intermittently and in high dose increased the number of children with adynamic bone disease [14].</td>
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<td>- Qualitative description of bone histology indicated improvement in children treated with vitamin D sterols (1α-hydroxyvitamin D) [15, 16].</td>
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<td>- No significant differences in bone histology were detected in studies comparing calcitriol and doxercalciferol [17].</td>
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<td>- Growth rates and bone formation rate did not differ between intraperitoneal and oral routes [18, 14].</td>
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<td>- No differences in SDS were found between oral daily or oral intermittent calcitriol therapy [19].</td>
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<td>- No significant differences in growth rates [20, 21] were detected in studies comparing different vitamin D sterols (calcitriol, dihydrotachysterol, ergocalciferol).</td>
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<td>- Intrapерitoneal calcitriol lowered PTH levels significantly more than oral calcitriol in one study [14], but no significant difference was found in another [18].</td>
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<td>- No differences in PTH levels were found between oral daily and oral intermittent calcitriol therapy [22, 23, 19].</td>
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<td>- Vitamin D sterols given orally or intravenously resulted in reduced PTH levels compared with placebo or no specific treatment.</td>
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<td>- The number of children with hypercalcaemia or the number of hypercalcaemic episodes did not differ between intraperitoneal and oral routes [18, 14].</td>
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<td></td>
<td>- Hypercalcaemic episodes were more common with intravenous calcitriol when compared with placebo [24].</td>
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<td>- Increased risk of hypercalcaemia was not reported with 1α-hydroxyvitamin D or paricalcitol [25].</td>
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</table>

In the Hahn et al. [13] review, additional interventions were compared as well as other non-skeletal outcomes.
Secondary hyperparathyroidism, including serum calcium, ionized calcium, phosphate, PTH, AP and 25(OH)D. Vitamin D sterols are known to increase the intestinal absorption of calcium and phosphate, and active vitamin D sterols may also increase FGF23 levels. In clinical practice these must be assessed together, with particular attention to trends in values, and appropriately managed through diet, use of calcium-based or calcium-free phosphate binders, ergo- or cholecalciferol supplementation, active vitamin D analogues and dialysis prescription. A detailed literature review and discussion is beyond the scope of this guideline. In the absence of suitable studies, the opinion of experts from the European Society for Paediatric Nephrology (ESPN) CKD-MBD and Dialysis Working Groups (WGs) and members of the European Renal Association–European Dialysis Transplantation Association (ERA-EDTA) CKD-MBD WG is provided, but must be carefully considered by the treating physician and adapted to individual patient needs as appropriate.

MATERIALS AND METHODS

The guideline development process and formulation of Patient, Intervention, Comparator and Outcome (PICO) questions is as described in the recommendations for native vitamin D therapy [12]. We have followed the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) method to develop the recommendations [27] (Supplementary data, Tables 1A and 1B [12]). We have developed our guideline to the Appraisal of Guidelines for Research and Evaluation (AGREE) standards [28], an instrument that assesses the methodological rigour and transparency in which a guideline is developed.

Outcomes addressed

Only studies that have addressed the effect of vitamin D analogues on bone, including fracture risk, growth, bone histology and bone markers such as PTH or AP, have been included.

Literature search

The literature search included:

- All systematic reviews of randomized controlled trials (RCTs) on active vitamin D therapy in children and adults with CKD Stages 2–5D.
- All RCTs and prospective cohort studies in children with CKD Stages 2–5D. Only studies in the English language were included. Some studies that were outside the remit of the literature review but contributed important information were included but did not influence the GRADE- ing of recommendations. Studies where skeletal endpoints are not applicable to the paediatric population, such as falls or hip fractures, were excluded. Other factors that may influence bone health, such as physical activity, have been investigated but are beyond the scope of this recommendation.

CLINICAL PRACTICE RECOMMENDATIONS

Which groups of children will benefit from treatment with vitamin D analogues?

Recommendation: We suggest using vitamin D analogues in children with CKD Stages 2–5D who have persistently increased serum PTH concentrations above the CKD-specific target range.

GRADE

Strength of recommendation: 2
Level of evidence: B

Evidence and rationale: Vitamin D analogues decrease PTH secretion. The effect on bone morphology and growth is uncertain. CKD-specific serum PTH target ranges are discussed in the section 'Dose of active vitamin D analogues'.

Effect of vitamin D analogues on secondary hyperparathyroidism.

Deficiency in 1,25(OH)₂D increases PTH synthesis and secretion, both directly and due to the associated hypocalcaemia. There are no RCTs in children with CKD Stages 2–3 primarily assessing the effect of vitamin D analogues versus placebo or ergocalciferol/cholecalciferol on secondary hyperparathyroidism. However, uncontrolled prospective observational studies in children suggest a decline in serum PTH concentrations compared with baseline in children with CKD started on active vitamin D analogues due to secondary hyperparathyroidism (Tables 1 and 2 and Supplementary data, Table 2) [22, 30, 31]. A meta-analysis of 16 RCTs in adults with CKD not yet on dialysis and 62 RCTs in adult dialysis patients provide strong evidence on the PTH suppressive action of vitamin D analogues (Table 3) [36, 37]. In children on haemodialysis (HD), two RCTs showed a significant reduction in PTH with thrice-weekly intravenous calcitriol [24] and thrice-weekly intravenous paricalcitol [25] versus placebo control. A significantly increased risk of hypercalcaemia was reported with intravenous calcitriol [24], but not with paricalcitol [25].

Active vitamin D has anabolic and catabolic actions on bone [38, 39]. Patients with untreated CKD may develop severe calcium deficiency, with hypocalcaemia partially counteracted by increased PTH levels. A prospective cohort study in 171 children 5–21 years of age with CKD Stages 2–5D undergoing baseline and 1-year follow-up in 89 children with biochemical analyses and peripheral quantitative CT scan suggest that the use of vitamin D analogues in the presence of hypocalcaemia may lead to bone demineralization [40]. Vitamin D analogues may therefore be withheld for a short period of time until hypocalcaemia is corrected.

An RCT indicated that ergocalciferol delays the onset of secondary hyperparathyroidism in children with CKD Stages 2 and 3 [41], and as described in the clinical practice recommendations for native vitamin D use [12], we suggest that either vitamin D₂ or vitamin D₃ supplementation be used to keep serum 25(OH)D levels >75 nmol/L in children with CKD Stages 2–3, even in the presence of normal PTH levels.
<table>
<thead>
<tr>
<th>Author, Ref.</th>
<th>Population, gender (males), age (years)</th>
<th>N (I, C)</th>
<th>Country</th>
<th>Intervention (I)</th>
<th>Comparator (C)</th>
<th>Duration of treatment</th>
<th>Results</th>
</tr>
</thead>
</table>
| Greenbaum et al. [25] | CKD Stage 5D, 76%, I: 13.6 ± 4.76 C: 14.3 ± 4.15 | 29 (15, 14) | USA | Paricalcitol intravenously thrice weekly (Initial dose: 0.04 mcg/kg if PTH ≤ 300, and 0.08 mcg/kg if PTH ≥ 300) Dose altered according to PTH and calcium or calcium phosphate levels | Placebo intravenously thrice weekly | 12 weeks | - Paricalcitol significantly increased the number of children who achieved a 30% decrease in PTH levels on at least two occasions during the study [risk ratio (RR) 2.80 (95% CI 0.95–8.28)].
- No significant difference in changes in levels of serum calcium, calcium × phosphorus product, phosphorous between groups.
- No significant difference in the number of hypercalcemic events between groups. |
| Greenbaum et al. [24] | CKD Stage 5D, 66%, I: 15.3 ± 2.8 C: 14.0 ± 3.8 | 47 (21, 26) | USA | Calcitriol intravenously thrice weekly (Initial dose: 0.5 mcg if PTH < 500 pg/mL, 1.0 mcg if PTH 500 to 1000 pg/mL, 1.5 mcg if PTH >1000 pg/mL) Dose altered according to PTH and calcium or calcium phosphate levels | Placebo intravenously thrice weekly | 12 weeks | - Calcitriol significantly increased the number of children who achieved a 30% decrease in PTH levels on at least two occasions [RR 2.72 (95% CI 1.12–6.61)].
- Changes in mean PTH levels during treatment were not significantly different between groups.
- Significantly greater risk of hypercalcemia [risk difference (RD): 0.24 (95% CI 0.05–0.43)] and elevated serum calcium × phosphorus products [RD: 0.34 (95% CI 0.12–0.56)] in children treated with calcitriol.
- No significant difference in the number with hyperphosphatemic between groups.
- Bone alkaline phosphatase was significantly reduced following intravenous calcitriol [mean difference -47.70 μg/L (95% CI −88.54 to −6.86)].
- No significant difference in changes in levels of serum calcium, calcium × phosphorus product and phosphorous between groups.
- No significant difference in bone histology parameters of bone formation rate, percentage eroded bone, percentage osteoid volume, percentage osteoid surface, osteoid maturation time and percentage bone volume between treatment groups.
- No significant difference in final PTH levels, but with significant decreases in PTH in both groups.
- No significant difference in final levels of calcium, phosphorus, serum alkaline phosphatase and FGF 23 between treatment groups.
- Values of alkaline phosphatase fell significantly while values of FGF 23 rose significantly with both groups.
- No differences in episodes of hypercalcemia were seen between the two vitamin D therapies. |
| Salusky et al. [17] (Wesseling-Perry et al. [8]) | CKD Stage 5D, 50%, I: 13.9 ± 0.5 | 60 (30, 30) | USA | Doxercalciferol orally thrice weekly Initial dose depended on PTH level, then titrated to keep PTH at 300 to 400 pg/mL and Ca 8.4 to 10.2 mg/dL. | Calcitriol orally thrice weekly | 8 months | - No significant difference in bone histology parameters of bone formation rate, percentage eroded bone, percentage osteoid volume, percentage osteoid surface, osteoid maturation time and percentage bone volume between treatment groups.
- No significant difference in final PTH levels, but with significant decreases in PTH in both groups.
- No significant difference in final levels of calcium, phosphorus, serum alkaline phosphatase and FGF 23 between treatment groups.
- Values of alkaline phosphatase fell significantly while values of FGF 23 rose significantly with both groups.
- No differences in episodes of hypercalcemia were seen between the two vitamin D therapies. |
| Schmitt et al. [19] | CKD Stages 3–5 88%, I: 5.5 (2.4–8.4) C: 5.1 (1.4–9.1) (subset of participants included in Ardissino 2000 [29]) | 29 (14, 15) | Europe | Calcitriol orally twice weekly (35 ng/kg twice weekly. After 1 month, dose adjusted for PTH level) | Calcitriol orally daily (10 ng/kg/ day. After 1 month, dose adjusted for PTH level) | 12 months | - The average weekly dose of calcitriol did not differ between groups (76 ± 34 versus 62 ± 34 ng/kg).
- No significant difference in the change in mean SDS.
- Significant decrease in PTH levels in both groups, but no significant differences in the decrease in PTH levels at any time points between groups.
- No significant difference in mean integrated PTH at 12 months.
- No significant differences were found for change in calcium, phosphate, calcium-phosphate product and alkaline phosphatase between groups.
- No significant difference in the number of episodes of hypercalcemic or hyperphosphataemic events between groups. |
<table>
<thead>
<tr>
<th>Study</th>
<th>CKD Stage</th>
<th>%</th>
<th>PTH (I: C)</th>
<th>Patients</th>
<th>Country</th>
<th>Treatment</th>
<th>Treatment</th>
<th>Weeks</th>
<th>Outcome</th>
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</table>
| Ardissino et al. [23]         | CKD Stages 3–5, 76%, 8.4 ± 4.7 | 59 (30, 29) | Europe | Calcitriol orally twice weekly (35 ng/kg twice weekly) | 8 weeks | - The dose of calcitriol did not differ between groups (70.1 ± 3.4 ng/kg versus 69.7 ± 4.3 ng/kg).  
- No significant differences in the decrease in PTH levels at 8 weeks between groups.  
- No significant differences in the number with reduction in PTH at 8 weeks between groups.  
- No significant difference in the number of hypercalcaemic or hyperphosphataemic patients between groups.  
- The dose of calcitriol for the full 12 months of study did not differ between groups.  
- Bone histology was improved in both groups, but 33% of patients developed adynamic bone lesion.  
- Bone formation rates did not differ significantly between treatment groups.  
- Mean PTH levels were significantly lower with intraperitoneal calcitriol compared with oral [mean difference —501.00 pg/mL (95% CI —721.54 to —280.46)].  
- Serum total and ionized calcium levels were higher in subjects treated with intraperitoneal calcitriol, whereas serum phosphorus and alkaline phosphatase levels were higher in those given oral calcitriol.  
- Maximum calcium levels and the number of children with hypercalcaemia or hyperphosphataemia did not differ between groups.  
- Growth rate was compared with the 12 pre-study months with daily oral calcitriol (40% lower total weekly dose).  
- Mean SDS did not differ between groups at 6 months.  
- Renal osteodystrophy scores did not differ between groups at 6 months.  
- No significant differences were found in PTH levels between groups.  
- No significant differences in serum calcium or phosphorus were found between groups.  
- No significant differences were found in the number of children with hypercalcaemia between groups.  
- The mean calcitriol dosage was 17.1 ± 5.9 ng/kg/day or a dihydrotachysterol dosage of 13.8 ± 3.3 μg/kg/day.  
- No significant changes in growth rate during treatment with either calcitriol or dihydrotachysterol.  
- No significant difference in the number of children with hypercalcaemia between groups.  

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Table 2. Continued

<table>
<thead>
<tr>
<th>Author, Ref.</th>
<th>Population, gender (males), age (years)</th>
<th>Country</th>
<th>Intervention (I)</th>
<th>Comparator (C)</th>
<th>Duration of treatment</th>
<th>Results</th>
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</table>
| Watson et al. [16] | CKD Stage 5D, 67%, I: 11.6 ± 6.0 C: 16.4 ± 14.0 | Canada | 1α-OH vitamin D orally 10–20 ng/kg/day | Standard treatment | 6 months | – Children treated with 1α-OH vitamin D showed reduced osteoid volume.  
– The number of children with PTH levels above the normal range of 3–25 pmol/L [RR 0.23 (95% CI 0.06–0.97)] and the mean PTH levels [mean difference –55.00 pmol/L (95% CI –83.03 to –26.97)] were significantly lower in treated children compared with controls.  
– No differences were reported in mean serum calcium and phosphorus levels at the end of treatment.  

Hodson et al. [21] | CKD Stages 2–5D, 58%, not reported | Australia | Calcitriol orally 15 ng/kg/day (dose increased until calcium reached 2.6. Final dose 5–30 ng/kg/day) | Ergocalciferol orally 0.25 mg/day (dose increased until serum calcium reached 2.6. Final dose 25–100 µg/kg/day) | 12 months | – No significant differences between treatments in the number with height velocity greater than or equal to expected.  
– Significant improvement in bone histology in 12 of 18 patients with either vitamin D therapy. Six patients excluded due to non-adherence and aluminum deposition. No significant differences between treatments in the number with improved bone histology.  
– No significant differences between treatments in final PTH levels. No significant difference in changes in levels of serum calcium, phosphorus and alkaline phosphatase between groups.  
– No significant differences were found in the number of children with hypercalcaemia between groups.  

Eke and Winterborn [15] | CKD Stages 3–4, not reported, 10.4 (6.5–18) | UK | 1α-OH vitamin D (10 ng/kg/day) | Calciferol (670 ng/kg/day) | 12 months | Qualitative description of bone histology indicated improvement in children treated with 1α-hydroxvitamin D. No significant difference was found between groups.  
– No significant differences in PTH levels at 12 months between groups.  
– No significant differences in changes in serum calcium, phosphorus, and alkaline phosphatase at 12 months between groups.  
– No significant differences were found in the number of children with hypercalcemia between groups.  

All studies listed were included in the systematic review by Hahn et al. [13].
<table>
<thead>
<tr>
<th>Author, Ref.</th>
<th>Population</th>
<th>No. of studies</th>
<th>n</th>
<th>Treatment</th>
<th>Control</th>
<th>Outcomes</th>
<th>Main results</th>
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<tbody>
<tr>
<td>Cai et al. [32]</td>
<td>CKD Stages 3–5D, adults</td>
<td>10 × RCTs</td>
<td>734</td>
<td>Paricalcitol</td>
<td>Active non-selective vitamin D receptor activators</td>
<td>PTH control</td>
<td>Paricalcitol showed no significant difference in both PTH reduction [mean difference −7.78 (95% CI −28.59–13.03), P = 0.46] and the proportion of patients who achieved ≥30% reduction of PTH [OR 1.27 (95% CI 0.87–1.85), P = 0.22]. Biochemical parameters</td>
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<tr>
<td>Han et al. [33]</td>
<td>CKD Stages 2–5D, children and adults</td>
<td>9 × RCTs</td>
<td>1093</td>
<td>Paricalcitol</td>
<td>Placebo</td>
<td>PTH control</td>
<td>Paricalcitol-treated patients had a statistically significant sustained reduction in serum PTH levels [RR 6.97 (95% CI 5.27–9.23), P &lt; 0.00001]. Biochemical parameters</td>
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<tr>
<td>Cheng et al. [34]</td>
<td>CKD Stages 2–5D, adults</td>
<td>9 × RCTs</td>
<td>832</td>
<td>Paricalcitol</td>
<td>Placebo</td>
<td>PTH control</td>
<td>Compared with placebo, paricalcitol suppressed serum PTH levels [RR 6.37 (95% CI 4.64–8.74), P &lt; 0.001]. Biochemical parameters</td>
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<tr>
<td>Zhou and Xu [35]</td>
<td>CKD Stage 5D, adults</td>
<td>6 × RCTs</td>
<td>174</td>
<td>Intravenous calcitriol intermittently</td>
<td>Oral calcitriol intermittently</td>
<td>PTH control</td>
<td>Biochemical parameters</td>
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<tr>
<td>Palmer et al. [36]</td>
<td>CKD Stage 5D, adults</td>
<td>60 × RCTs</td>
<td>2773</td>
<td>Vitamin D compounds</td>
<td>Vitamin D compounds/placebo/no treatment</td>
<td>PTH control</td>
<td>Biochemical parameters</td>
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<th>Author, Ref.</th>
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<th>n</th>
<th>Treatment</th>
<th>Control</th>
<th>Outcomes</th>
<th>Main results</th>
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<tbody>
<tr>
<td>Palmer et al. [37]</td>
<td>CKD Stages 2–5, adults</td>
<td>16 × RCTs</td>
<td>894</td>
<td>Vitamin D compounds</td>
<td>PTH control</td>
<td>Vitamin D compounds reduced serum PTH concentrations more effectively than placebo and also lowered PTH by 30% below baseline more frequently than placebo. Newer vitamin D analogues cannot yet be regarded as superior to existing treatments, although they may be at least equivalent for the suppression of PTH. Vitamin D compounds were consistently associated with elevated serum phosphorus and serum calcium. Episodes of hypercalcaemia were more frequent with vitamin D therapy. Inadequate data are available on newer vitamin D compounds to determine their ‘less calcaemic’ or ‘non-calcaemic’ status when compared with established vitamin D compounds.</td>
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Comparable data from children with more advanced stages of CKD are lacking and most children with severe CKD have multiple risk factors contributing to the development of hyperparathyroidism, which may be inadequately treated by native D alone. Vitamin D analogues may therefore be started prior to repletion of 25(OH)D stores provided the child is normocalcaemic.

PTH alone is a relatively poor marker of bone morphology in CKD [5]. It is important that the modifiers of secondary hyperparathyroidism serum calcium, phosphate, PTH, AP, and 25(OH)D are assessed together, with particular emphasis on trends in values, and appropriately managed through diet, use of calcium-based or calcium-free phosphate binder, ergo- or cholecalciferol supplementation and dialysis prescription. As discussed in the recommendations for native vitamin D therapy [12], serum 1,25(OH)2D levels are not a good measure of vitamin D status and should not be measured other than in specific research studies. The role of other potentially pathogenic factors such as Klotho and FGF23 in the diagnosis, prevention and treatment of MBD in children with CKD has not yet been defined.

Effect of vitamin D analogues on bone morphology. RCTs of alfacalcidol or calcitriol versus native vitamin D in children with CKD Stages 2–3 [15] and on dialysis [21] indicate a qualitative and quantitative improvement in histological indices of renal osteodystrophy with both native vitamin D and active vitamin D analogues, but all studies are small and most are of short duration (Table 2). A prospective uncontrolled trial in 14 children on peritoneal dialysis (PD) who were treated with thrice-weekly oral or intraperitoneal calcitriol and follow-up biopsies after 12 months suggested a high risk of adynamic bone disease with intermittent oral calcitriol therapy [42]. An RCT comparing oral to intraperitoneal calcitriol administration in 33 children demonstrated a reduction in bone formation rate and improvement of the lesions of secondary hyperparathyroidism, but one-third of children developed adynamic bone disease (Table 2) [14]. Two uncontrolled trials performed in the late 1970s including 17 mostly prepubertal children with CKD Stages 4–5D demonstrated an increase in serum calcium and a decrease in PTH and alkaline phosphate concentrations with calcitriol [31, 43]. Healing of rickets and subperiosteal erosions was seen on X-rays after 6 and 12 months, respectively. Importantly, most of these studies [14, 15, 21, 31, 42–44] were performed before the KDIGO turnover, mineralization and volume (TMV) classification [45] of bone histology was developed, and some before the intact PTH assay became available and before non-calcium-based phosphate binders were available [15, 21, 31, 43]. A randomized comparison of calcitriol and doxercalciferol in 60 children on PD applying the TMV classification demonstrated similar PTH suppressive action and reduced bone formation rate. Mineralization defects were highly prevalent and persisted in both groups and question a positive effect of both vitamin D analogues on bone morphology [8]. Moreover, in people with calcium deficiency, 1,25(OH)2D enhances bone resorption and simultaneously inhibits bone mineralization so as to preserve serum calcium in a normal range at the expense of bone mass [46]. Given the variable doses of different vitamin D analogues used in different studies, small patient numbers and short follow-up, it is difficult to draw conclusions on the effect of vitamin D analogues on bone morphology.

Effect of vitamin D analogues on growth. Two uncontrolled prospective observational studies in children with CKD Stages 3–5 and severe bone disease published in 1978 and 1981 suggested improved growth in 4 of 6 and 8 of 11 children treated with vitamin D analogues over a mean of 12–32 months [31, 43]. Subsequent RCTs have not examined the effect of vitamin D analogues versus placebo on growth. A 1-year RCT comparing calcitriol versus ergocalciferol in 18 children with CKD Stages 3–5D reported similar growth rates in both groups (Table 2 and Supplementary Table 2) [21]. A randomized cross-over comparison of 3 months intraperitoneal versus oral calcitriol in 7 children on PD [18] and a randomized 12-months comparison of daily versus twice-weekly calcitriol in 24 children with CKD Stages 3–5 did not reveal any difference in the change in standard deviation score (SDS) between groups [19]. Linear
growth did not differ in 94 children with pre-dialysis CKD treated by calcitriol or dihydrotachysterol over 6 months [30]. A prospective 1-year observation of high-dose thrice-weekly calcitriol in 16 prepubertal children on PD showed a decline in individual growth rate as compared with the 12 pre-study months on daily oral calcitriol at a 60% lower weekly dose relative to body weight [44]. Impaired linear growth was particularly evident in four children with adynamic bone disease. Similar results were obtained in an RCT in children with CKD Stages 3–5. Mean serum PTH and AP levels positively correlated with the change in SDS [19]. However, these findings could not be reconfirmed in a large registry data set comprising 890 children on PD who showed time-averaged PTH concentrations >500 pg/mL associated with impaired longitudinal growth [47]. Prospective observational studies have shown that PTH levels within the normal range allow for normal growth velocity in children with pre-dialysis CKD [48] without increasing the risk for vascular calcification [49]. In summary, small patient numbers, variable age, pubertal stage, CKD stage, short follow-up as well as different preparations and routes of administration of vitamin D analogues preclude drawing any conclusions on the growth-modifying effects of vitamin D analogues, either directly or indirectly via suppression of PTH.

**Type of vitamin D supplementation**

Recommendation: We suggest that any vitamin D analogue can be used to reduce PTH levels in children with CKD Stages 2–5D.

**GRADE**

Strength of recommendation: 2
Level of evidence: C

Evidence and rationale: Vitamin D analogues that are available for use in paediatric CKD patients include 1-alfa-calcidol, calcitriol, paricalcitol and doxercalciferol. There are no head-to-head trials of all the vitamin D analogues and only limited data from a single RCT comparing calcitriol and doxercalciferol [8] (Table 2 and Supplementary data, Table 2). Importantly, none of the studies have reported important patient-level outcomes such as fracture risk or growth.

An RCT in 60 children on PD compared the effects of two different phosphate binders, calcium carbonate and sevelamer, and two different vitamin D analogues, doxercalciferol and calcitriol, in a 2 × 2 longitudinal factorial design to examine their effects on bone histology over an 8-month study period [8]. The cumulative active vitamin D dose did not differ between groups. Comparison of thrice-weekly doxercalciferol versus thrice-weekly calcitriol demonstrated equivalent control of bone turnover, a reduction in PTH and an increase in FGF23 irrespective of the type of phosphate binder [8]. Bone formation rates decreased in all patients and were within normal range in 72% of patients, although a greater improvement in eroded surface was seen with doxercalciferol rather than calcitriol-treated patients. The small patient numbers in the 2 × 2 design preclude a full assessment of vitamin D effect independent of the effect of calcium intake from calcium-based binders [8]. An earlier study from the same group studied 29 PD patients using a similar crossover trial design, but focusing on phosphate binder effects, showed very similar results [17].

Paricalcitol is a selective vitamin D analogue that reduces PTH and is thought to cause less hypercalcaemia. In children, three RCTs have examined the effect of paricalcitol. A double-blind, placebo-controlled trial in 29 children on HD over 12 weeks demonstrated the efficacy of intravenous paricalcitol in reducing PTH by >30% without increasing serum calcium or serum phosphorus [25]. A recent double-blind placebo-controlled trial in 36 children with CKD Stages 3–4 demonstrated that oral paricalcitol is well tolerated and significantly reduced PTH without increasing serum calcium or phosphorus [50]. There are no head-to-head studies in children with CKD Stages 2–5D comparing the effects of paricalcitol and other vitamin D analogues on the development of hypercalcaemia. However, there are several studies in adults that have compared paricalcitol with calcitriol or other vitamin D analogues. A systematic review of paricalcitol use in adult CKD patients not yet on dialysis included nine RCTs and showed that paricalcitol was effective in lowering PTH; however, an elevation in serum calcium and phosphate and a trend towards the development of hypercalcaemia was noted [33]. A second systematic review on paricalcitol including adults with CKD Stages 2–5D did not identify any increased risk for hypercalcaemia [34]. A meta-analysis of two RCTs performed in adult patients with CKD with calcitriol and five RCTs with paricalcitol in adults [51] suggests an increased probability of hypercalcaemia with paricalcitol. A recent meta-analysis concludes that the quality of the evidence available is poor and there are no data to indicate any superiority of paricalcitol over other active non-selective vitamin D receptor activators in lowering PTH or reducing the burden of mineral loading [32].

Two RCTs comparing the effects of calcitriol versus dihydrotachysterol in children with CKD did not observe any significant differences between calcitriol and dihydrotachysterol with respect to linear growth and the risk of hypercalcaemia [20, 30]. Dihydrotachysterol is rarely used now, hence this study is not discussed further. Importantly, hypercalcaemia may be a dose-related effect of all vitamin D analogues, and this was not evaluated in any of the studies or systematic reviews.

**Route of vitamin D analogue administration**

Recommendation: We suggest that daily oral calcitriol is safe, effective and well tolerated in children with CKD Stages 2–5D.

**GRADE**

Strength of recommendation: 2
Level of evidence: B

Evidence and rationale: Four RCTs and some prospective trials have addressed different routes and time intervals of calcitriol administration in children with CKD Stages 2–5D (Table 2 and Supplementary data, Table 2). There are no studies examining the effects of route or timings of administration of other vitamin D analogues. Three studies have compared different routes of administration of calcitriol [14, 18, 23] while three have examined the effect of different timing of calcitriol
administration on bone-related outcomes [19, 29, 52], suggesting equal efficacy and safety of daily oral administration.

**Route of administration.** Two RCTs on intraperitoneal versus oral calcitriol administration have been performed in children with CKD (Table 2 and Supplementary data, Table 2) [14, 18]. An RCT including 33 children on PD compared equivalent doses of oral and intraperitoneal calcitriol administered thrice weekly over 1 year [14]. Bone histomorphologic changes improved in both groups, but 33% of patients developed adynamic bone disease, irrespective of the route of calcitriol administration. Serum total and ionized calcium levels were higher and PTH, AP and phosphate were lower with intraperitoneal calcitriol. The number of episodes of hypercalcaemia and hyperphosphataemia were comparable between groups. An earlier study in seven children on PD using a crossover trial design showed similar calcium, phosphate and PTH levels in both groups [18]. However, small patient numbers, short follow-up (3 months) and the crossover trial design may have biased outcome with respect to growth and bone histology. Both studies reported similar peritonitis rates with intraperitoneal versus oral calcitriol but were inadequately powered to address this important safety issue. A pharmacodynamic study examined the effect of a single oral versus intravenous dose of calcitriol on intestinal calcium absorption in 20 children with CKD Stages 3–5 in a randomized crossover study design [23]. Strontium absorption, as a surrogate marker of calcium uptake, was measured over a 72-hour period after calcitriol administration. No difference was seen in strontium absorption or in the serum calcium, phosphate, PTH or AP levels [23].

In a prospective uncontrolled trial, six children not responding to oral calcitriol treatment for >12 months were given intraperitoneal calcitriol and showed a significant decrease in PTH levels after 9 months, but also significantly more episodes of hypercalcaemia and hyperphosphataemia on intraperitoneal treatment [53]. Calcitriol is no longer licensed for intraperitoneal use.

**Time intervals of administration**

Two RCTs have compared daily versus twice- or thrice-weekly calcitriol intake in paediatric CKD patients (Table 2 and Supplementary Table 2) [19, 29]. A fixed body weight–adjusted dose of twice-weekly oral calcitriol over 8 weeks in 59 children with CKD Stages 2–5 achieved equal suppression of PTH and similar serum calcium, phosphate and AP levels as the equivalent once-daily oral dose [29]. In a 1-year extension trial in 24 prepubertal children from the above study, the calcitriol dose was titrated according to serum PTH levels to examine the effect of daily versus pulsed oral calcitriol therapy on growth and PTH control. There was no difference between groups with respect to SDS, serum PTH, AP, calcium, and phosphate levels [19].

Two prospective trials (including children on PD) examined the effect of high-dose intermittent (thrice weekly) oral or intravenous calcitriol on changes in bone histology and growth after 12 months in children with biopsy-proven bone changes of secondary hyperparathyroidism [42, 44]. In the first study, bone histology improved in 12 of 14 children, with reduced bone formation rate in all and resolution of osteitis fibrosa in 10 of 11 children, but 6 developed adynamic bone disease [42]. The second study from the same group showed that high-dose intermittent calcitriol therapy adversely affects linear growth, particularly in children who developed adynamic bone disease. Historical controls were used for this study and the growth rate was lower on high-dose intermittent calcitriol therapy as compared with the pre-study year when daily oral calcitriol at a 60% lower average daily dose was used [44]. These studies predate the TMV classification for bone disease and hence changes are more descriptive than similar reports in recent studies. A meta-analysis of six RCTs in a total of 174 adults with CKD (Table 3) suggests similar suppression of PTH and AP and a similar risk of hypercalcaemia and hyperphosphataemia with intermittent intravenous versus oral calcitriol [36]. None of these trials were double-blinded, all were potentially confounded by a selection bias and two had significant dropout rates.

In conclusion, daily oral calcitriol is safe and effective, but corresponding data for 1-alphacalcidiol and other vitamin D analogues are lacking. Current evidence in children does not support intermittent oral or intravenous calcitriol administration. Intravenous calcitriol may be considered in children on HD with poor adherence to daily oral calcitriol treatment. Overall, studies suggest that the response to calcitriol treatment in children with CKD depends more on the dose rather than the route or frequency of administration, with high-dose intermittent oral or intravenous treatment being associated with adynamic bone disease [42, 44]. The presence of pre-existing bone disease or secondary hyperparathyroidism and autonomy of the parathyroid gland cells from physiological regulators of PTH synthesis and secretion may also strongly influence the response to calcitriol therapy [2, 54].

**Dose of active vitamin D analogues: therapeutic targets and safety**

Recommendation: We suggest starting vitamin D analogues in the lowest dose to achieve target PTH concentrations and maintain normocalcaemia. Subsequent titration of vitamin D therapy may be performed based on trends in serum calcium, phosphate and PTH levels.

GRADE
Strength of recommendation: 2
Level of evidence: D

Evidence and rationale: Current treatment regimens initiate and titrate active vitamin D therapy with the aim of controlling secondary hyperparathyroidism. The predictive power of PTH is limited by high interassay variability of up to 150% and a low specificity as the N-terminal 7-84 PTH fragment, which is measured together with 1-84 PTH in most of the currently used PTH assays [55], possibly antagonizes 1-84 PTH actions [56, 48]. Despite the limitations of PTH as a biomarker of bone disease in CKD, there are some data to suggest that PTH levels predict the type of renal osteodystrophy in children on PD [57]. PTH levels >200 pg/mL and serum calcium levels <2.5 mmol/L (10 mg/dL) were reported to predict high bone turnover with a sensitivity of 85% and a specificity of 100% in children on PD. Serum PTH levels <150 pg/mL together with serum calcium concentrations...
>2.5 mmol/L predicted adynamic bone disease with a sensitivity of 100% and a specificity of 92% [57]. Subsequent studies have shown a considerable overlap of PTH levels and the type of bone disease in children on dialysis [58, 59]. Applying the TMV classification in 161 bone biopsies from children on PD, the highest prediction rate for normal bone turnover and mineralization was seen with PTH <400 pg/mL and AP <400 IU/L [5]. In 16 prepubertal children on PD and high-dose thrice-weekly calcitriol [44] and 24 prepubertal children with CKD Stages 3–5 on daily versus thrice-weekly calcitriol [19], the 1-year growth rate correlated with time-averaged serum PTH and AP levels (Table 2 and Supplementary data, Table 2).

There is little evidence to define PTH target levels in children with CKD Stages 2–5D and international guideline committees have suggested different recommendations, with PTH targets ranging from normal in CKD Stages 2–4 to 2- to 9-fold above the upper limit of normal in children on dialysis [60–62]. There are no RCTs or high-quality prospective trials since the publication of these recommendations that can guide evidence-based management of secondary hyperparathyroidism. PTH levels were elevated even in early CKD: in a study of 52 children in pre-dialysis CKD, 36% of patients with Stage 2, 71% with Stage 3 and 93% with Stage 4/5 CKD had elevated PTH, and this correlated with defective skeletal mineralization [9]. However, the potential benefits of the phosphaturic action of increased serum PTH concentrations in the early stages of CKD have not been delineated. A prospective observational study in 11 children initiating renal replacement therapy showed that histological indices of bone turnover did not correlate with growth rate and high-turnover bone disease was seen at lower PTH levels than previously described [63]; the small sample size and wide age range of the population make interpretation difficult. Data from 890 children on PD prospectively collected six monthly in the International Pediatric Peritoneal Dialysis Network demonstrated an association of time-averaged PTH concentrations >500 pg/mL with impaired longitudinal growth [47]; respective receiver operating characteristics analyses defined optimal an PTH target range of 1.7–3 times the upper limit of normal in children on PD [64]. High PTH levels may adversely influence vascular calcification. In a prospective cohort study of children on dialysis, mean time-averaged PTH levels up to two times greater than normal levels were associated with normal carotid artery intima-media thickness and pulse wave velocity, whereas in children with higher PTH levels, intima-media thickness, pulse wave velocity and prevalence and severity of coronary artery calcification were increased [49]. A cross-sectional study in 52 children demonstrated defective mineralization in 29% of patients with CKD Stage 2, 42% with CKD Stage 3 and 79% with CKD Stages 4 and 5, associated with lower serum calcium and increased PTH concentrations [9]. A prospective long-term cohort study in 537 children with CKD Stages 2–3 demonstrated a 2- to 3-fold increased fracture risk associated with higher PTH concentrations [10]. The 2006 recommendations of the European Paediatric Dialysis Working Group suggest keeping PTH levels within the normal range in CKD Stages 2–5 and up to two to three times the upper limit of normal in dialyzed children [62]. Findings from the prospective observational studies performed since then are in line with these recommendations; respective RCTs have not been accomplished. We do not have any evidence to change these recommendations.

### Safety of vitamin D analogues

It is not known if different doses of vitamin D analogues adjusted for body weight are required in infants and young children compared with older children. In five paediatric RCTs, 10–17 ng/kg body weight/day of calcitriol [19, 21, 29] or alfacalcidol [15, 16] were administered to children of different ages. Preceding treatment with vitamin D analogues was not discussed. No head-to-head comparisons of different vitamin D analogues has been performed to determine comparable doses or safety issues. Cochrane analysis [13] and all the RCTs of calcitriol or alfacalcidol in children with CKD Stages 2–5D have shown an increase in serum calcium and phosphate levels, but no difference in hypercalcaemia or hyperphosphataemia risk with different vitamin D analogues or different routes of administration or intermittent versus daily treatment was identified. A 12-week study in children on HD could not find any increase in hypercalcaemia or hyperphosphataemia with paricalcitol versus placebo treatment, but small patient numbers, a high dropout rate and short study duration make it difficult to comment on safety outcomes [25].

Cochrane analyses on active vitamin D analogues in adults with CKD [36] and adults on dialysis [37] comprising a total of 16 and 60 RCTs, respectively, provide strong evidence for the PTH suppressive action of active vitamin D analogues together with a significant risk of hypercalcaemia and hyperphosphataemia. In view of the potential risk of hypercalcaemia and hyperphosphataemia associated with vitamin D analogues, and the impact of diet, medications like phosphate binders and dialysis on mineral homeostasis, the dosage of vitamin D analogues needs careful titration based on trends and concurrent changes in serum calcium, phosphate and PTH. A meta-analysis of 31 RCTs comprising 2621 adult patients with CKD Stages 2–5 showed that vitamin D analogues lead to an increase in serum creatinine, although five RCTs applying serum creatinine independent of glomerular filtration rate (GFR) determination methods did not demonstrate a significant change in GFR [65]. Episodes of hypercalcaemia were more frequent with vitamin D analogues, but there was no difference in mortality or cardiovascular outcomes [65].

### SUMMARY OF RECOMMENDATIONS

A summary of recommendations is provided in Supplementary Table 3.

### RESEARCH RECOMMENDATIONS

We recommend the following key areas of study to provide future evidence-based recommendations for native and active vitamin D therapy in children with CKD Stages 2–5D:

1. To determine the target range for serum 25(OH)D concentration, including free vitamin D concentration, that is
required for the prevention and treatment of MBD in children with CKD Stages 2–5D.

2. To define the optimal treatment schedule for native vitamin D treatment that achieves target serum 25(OH)D levels for the prevention and treatment of mineral bone disease in children with CKD Stages 2–5D. The type of native vitamin D (ergocalciferol or cholecalciferol) and regimen (dosage and frequency of administration) require further study.

3. In children with CKD Stages 2–5D, what are the adverse effects of different treatment regimens (including native and active vitamin D analogues, dosage and frequency of administration) on hypercalcaemia, hypercalciuria, nephrocalcinosis, kidney injury and extraskeletal (vascular) calcification.

4. In children with CKD Stages 2–5D, does treatment with native vitamin D or active vitamin D analogues improve patient-related outcomes? Important outcomes include increased bone mineral density, muscle strength, linear growth and a reduced risk of fractures.

5. To develop new surrogate measures of vitamin D effects on bone turnover and mineralization in children with CKD Stages 2–5D by comparing bone histology with novel biomarker profiles and novel bone imaging techniques.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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REFERENCES


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CONFLICT OF INTEREST STATEMENT

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