

# 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)<sub>2</sub>D)] declines and is associated with hypocalcaemia, secondary hyperparathyroidism and the spectrum of CKD–mineral and bone disorder (MBD). In advanced CKD, active vitamin D analogues, including alfacalcidol, calcitriol and paricalcitol, are routinely administered. There are few studies on the use of vitamin D analogues in children with CKD and on dialysis. It is difficult to define bone-specific outcomes that can guide treatment with active vitamin D analogues in children with CKD-MBD. A core working group (WG) of the European Society for Paediatric Nephrology (ESPN) CKD-MBD and Dialysis WGs has developed recommendations for the use of active vitamin D therapy in children with CKD and on dialysis. A second document in parallel with this one covers treatment recommendations for native vitamin D therapy. 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)<sub>2</sub>D)] declines with kidney function loss. Low serum 1,25(OH)<sub>2</sub>D 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)<sub>2</sub>D<sub>3</sub>], alfacalcidol (1 $\alpha$  hydroxyvitamin D<sub>3</sub>, a synthetic prohormone that requires activation by 25-hydroxylase in the liver), and paricalcitol [a synthetic analogue of calcitriol (19nor,1,25(OH)<sub>2</sub>D<sub>2</sub>)] 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  $1,25(\text{OH})_2\text{D}$  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  $1,25(\text{OH})_2\text{D}$ , 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  $25(\text{OH})\text{D}$  and its monitoring and recommendations for native vitamin D supplementation [12]. The recent Cochrane Review [13] (Table 1) 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 secondary hyperparathyroidism, including serum calcium, ionized calcium, phosphate, PTH, AP and  $25(\text{OH})\text{D}$ . 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

**Table 1. Systematic review of RCTs of active vitamin D therapy in children with CKD Stages 2–5D**

Author; year	No. of studies	Population, age	n	Outcomes	Results
Hahn <i>et al.</i> , 2015 [13]	18 × RCTs	CKD Stage 2–5D, children	576	Bone disease	<ul style="list-style-type: none"> <li>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].</li> <li>Qualitative description of bone histology indicated improvement in children treated with vitamin D sterols (<math>1\alpha</math>-hydroxyvitamin D) [15, 16].</li> <li>No significant differences in bone histology were detected in studies comparing calcitriol and doxercalciferol [17].</li> </ul>
				Growth	<ul style="list-style-type: none"> <li>Growth rates and bone formation rate did not differ between intraperitoneal and oral routes [18, 14].</li> <li>No differences in SDS were found between oral daily or oral intermittent calcitriol therapy [19].</li> <li>No significant differences in growth rates [20, 21] were detected in studies comparing different vitamin D sterols (calcitriol, dihydrotachysterol, ergocalciferol).</li> </ul>
				PTH control	<ul style="list-style-type: none"> <li>Intraperitoneal calcitriol lowered PTH levels significantly more than oral calcitriol in one study [14], but no significant difference was found in another [18].</li> <li>No differences in PTH levels were found between oral daily and oral intermittent calcitriol therapy [22, 23, 19].</li> <li>Vitamin D sterols given orally or intravenously resulted in reduced PTH levels compared with placebo or no specific treatment.</li> </ul>
				Biochemical parameters	<ul style="list-style-type: none"> <li>The number of children with hypercalcaemia or the number of hypercalcaemic episodes did not differ between intraperitoneal and oral routes [18, 14].</li> <li>No differences in the number of children with hypercalcaemia or the number of hypercalcaemic episodes were found between oral daily or oral intermittent calcitriol therapy [22, 23, 19].</li> <li>Hypercalcaemic episodes were more common with intravenous calcitriol when compared with placebo [24].</li> <li>Increased risk of hypercalcaemia was not reported with <math>1\alpha</math>-hydroxyvitamin D or paricalcitol [25].</li> </ul>

In the Hahn *et al.* [13] review, additional interventions were compared as well as other non-skeletal outcomes.

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 GRADING 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)<sub>2</sub>D 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 D<sub>2</sub> or vitamin D<sub>3</sub> 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. 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

Table 2. RCT of active vitamin D therapy in children with CKD

Author, Ref.	Population, gender (males), age (years)	N (I, C)	Country	Intervention (I)	Comparator (C)	Duration of treatment	Results
Greenbaum <i>et al.</i> [25]	CKD Stage 5D, 76%, I: 13.6 ± 4.76 C: 14.3 ± 4.15	29 (15, 14) 17 did not complete study	USA	Paricalcitol intravenously thrice weekly (Initial dose: 0.04 mcg/kg if PTH ≤500, and 0.08 mcg/kg if PTH ≥500) Dose altered according to PTH and calcium or calcium phosphate levels	Placebo intravenously thrice weekly	12 weeks	<ul style="list-style-type: none"><li>- 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)].</li><li>- No significant difference in changes in levels of serum calcium, calcium × phosphorous product, phosphorous between groups.</li><li>- No significant difference in the number of hypercalcaemia between groups.</li></ul>
Greenbaum <i>et al.</i> [24]	CKD Stage 5D, 66%, I: 15.3 ± 2.8 C: 14.0 ± 3.8	47 (21, 26) 19 lost to follow-up	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	<ul style="list-style-type: none"><li>- 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)].</li><li>- Changes in mean PTH levels during treatment were not significantly different between groups.</li><li>- Significantly greater risk of hypercalcaemia [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.</li><li>- No significant difference in the number with hyperphosphataemia between groups.</li><li>- Bone alkaline phosphatase was significantly reduced following intravenous calcitriol [mean difference –47.70 µg/L (95% CI –88.54 to –6.86)].</li><li>- No significant difference in changes in levels of serum calcium, calcium × phosphorous product and phosphorous between groups.</li></ul>
Salusky <i>et al.</i> [17] (Wesseling-Perry <i>et al.</i> [8])	CKD Stage 5D, 50%, 13.9 ± 0.5	60 (30, 30) 9/60 did not complete study	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	<ul style="list-style-type: none"><li>- 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.</li><li>- No significant difference in final PTH levels, but with significant decreases in PTH in both groups.</li><li>- No significant difference in final levels of calcium, phosphorus, serum alkaline phosphatase and FGF 23 between treatment groups.</li><li>- Values of alkaline phosphatase fell significantly while values of FGF 23 rose significantly with both groups.</li><li>- No differences in episodes of hypercalcaemia were seen between the two vitamin D therapies.</li></ul>
Schmitt <i>et al.</i> [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) 5/29 lost to follow-up	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	<ul style="list-style-type: none"><li>- The average weekly dose of calcitriol did not differ between groups (76 ± 34 versus 62 ± 34 ng/kg)</li><li>- No significant difference in the change in mean SDS.</li><li>- Significant decrease in PTH levels in both groups, but no significant differences in the decrease in PTH levels at any time points between groups.</li><li>- No significant difference in mean integrated PTH at 12 months.</li><li>- No significant differences were found for change in calcium, phosphate, calcium-phosphate product and alkaline phosphatase between groups.</li></ul>

Continued

Table 2. Continued

Author, Ref.	Population, gender (males), age (years)	N (I, C)	Country	Intervention (I)	Comparator (C)	Duration of treatment	Results
Ardissino <i>et al.</i> [23]	CKD Stages 3–5, 76%, 8.4 ± 4.7	59 (30, 29) 85 enrolled, but only 59 included in 8 week analysis	Europe	Calcitriol orally twice weekly (35 ng/kg twice weekly)	Calcitriol orally daily (10 ng/kg/day)	8 weeks	<ul style="list-style-type: none"> <li>No significant difference in the number of episodes of hypercalcaemic or hyperphosphataemic between groups.</li> <li>The dose of calcitriol did not differ between groups (70.1 ± 3.4 ng/kg versus 69.7 ± 4.3 ng/kg).</li> <li>No significant differences in the decrease in PTH levels at 8 weeks between groups.</li> <li>No significant differences in the number with reduction in PTH at 8 weeks between groups.</li> <li>No significant difference in the number of hypercalcaemic or hyperphosphataemic patients between groups.</li> <li>The dose of calcitriol for the full 12 months of study did not differ between groups.</li> <li>Bone histology was improved in both groups, but 33% of patients developed adynamic bone lesion.</li> <li>Bone formation rates did not differ significantly between treatment groups.</li> <li>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)].</li> <li>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.</li> <li>Maximum calcium levels and the number of children with hypercalcaemia or hyperphosphataemia did not differ between groups.</li> <li>Growth rate was compared with the 12 pre-study months with daily oral calcitriol (40% lower total weekly dose).</li> <li>Mean SDS did not differ between groups at 6 months.</li> <li>Renal osteodystrophy scores did not differ between groups at 6 months.</li> <li>No significant differences were found in PTH levels between groups.</li> <li>No significant differences in serum calcium or phosphate were found between groups.</li> <li>No significant differences were found in the number of children with hypercalcaemia between groups.</li> </ul>
Salusky <i>et al.</i> [14]	CKD Stage 5D, 55%, I: 12.5 ± 1.1 I: 13.2 ± 1.3	33 (16, 17) 13 lost to follow-up	USA	Calcitriol Intraperitoneal thrice weekly Initial dose of 1 µg thrice weekly	Calcitriol orally thrice weekly	12 months	<ul style="list-style-type: none"> <li>The mean calcitriol dosage was 17.1 ± 5.9 ng/kg/day or a dihydrotachysterol dosage of 13.8 ± 3.3 µg/kg/day.</li> <li>No significant changes in growth rate during treatment with either calcitriol or dihydrotachysterol.</li> <li>No significant difference in the number of children with hypercalcaemia between groups.</li> </ul>
Jones <i>et al.</i> [18]	CKD Stage 5D, 71%, 7.2 ± 5.2	7 (7, 7)	Canada	Intraperitoneal or oral calcitriol 0.01–0.02 µg/kg/day for 3 months, then crossed over for 3 months	Intraperitoneal or oral calcitriol 0.01–0.02 µg/kg/day for 3 months, then crossed over for 3 months	2 × 3 months crossover study	<ul style="list-style-type: none"> <li>No significant differences were found in the number of children with hypercalcaemia between groups.</li> </ul>
Abitbol <i>et al.</i> [20] Chan <i>et al.</i> [30]	CKD Stages 3–4, 67%, I: 6 ± 3 C: 5 ± 3	82 (40, 42) 12/94 lost to follow-up	USA	Calcitriol orally 20 ng/kg/day Adjusted for weight every 6 months and for hypercalcaemia/elevated alkaline phosphatase for 12 months	Dihydrotachysterol 15 µg/kg/day	21.0 ± 12.4 and 22.1 ± 14.8 months	<ul style="list-style-type: none"> <li>No significant differences were found in the number of children with hypercalcaemia between groups.</li> </ul>

Watson <i>et al.</i> [16]	CKD Stage 5D, 67%, I: 11.6 ± 6.0 C: 16.4 ± 14.0	12 (6, 6)	Canada	1α-OH vitamin D orally 10–20 ng/kg/ day	Standard treatment	6 months	<ul style="list-style-type: none"><li>– Children treated with 1α-OH vitamin D showed reduced osteoid volume.</li><li>– 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.</li><li>– No differences were reported in mean serum calcium and phosphorus levels at the end of treatment.</li><li>– No significant differences between treatments in the number with height velocity greater than or equal to expected.</li><li>– 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.</li><li>– No significant differences between treatments in final PTH levels. No significant difference in changes in levels of serum calcium, phosphorous and alkaline phosphatase between groups.</li><li>– No significant differences were found in the number of children with hypercalcaemia between groups.</li><li>– Qualitative description of bone histology indicated improvement in children treated with 1α-hydroxyvitamin D. No significant difference was found between groups.</li><li>– No significant difference in PTH levels at 12 months between groups.</li><li>– No significant differences in changes in serum calcium, phosphorus, and alkaline phosphatase at 12 months between groups.</li><li>– No significant differences were found in the number of children with hypercalcaemia between groups.</li></ul>
Hodson <i>et al.</i> [21]	CKD Stages 2–5D, 58%, not reported	18 (8, 7)	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	
Eke and Winterborn [15]	CKD Stages 3–4, not reported, 10.4 (6.5–18)	16 (8, 8) 1 lost to fol- low-up	UK	1α-OH vitamin D (10 ng/kg/day)	Calciferol (670 ng/kg/day)	12 months	

All studies listed were included in the systematic review by Hahn *et al.* [13].

Table 3. Systematic reviews of active vitamin D therapy in adults with CKD

Author, Ref.	Population	No. of studies	n	Treatment	Control	Outcomes	Main results
Cai <i>et al.</i> [32]	CKD Stages 3–5D, adults	10 × RCTs	734	Paricalcitol	Active non-selective vitamin D receptor activators	PTH control  Biochemical parameters  Adverse events (AE)	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 $\geq 30\%$ reduction of PTH [OR 1.27 (95% CI 0.87–1.85), $P = 0.22$ ].  No statistical differences were found in terms of serum calcium, episodes of hypercalcaemia, serum phosphorus, calcium $\times$ phosphorus products and bone metabolism index.  No statistically significant differences were observed in the incidence of total AEs and serious AEs.
Han <i>et al.</i> [33]	CKD Stages 2–5D, children and adults	9 × RCTs	1093	Paricalcitol	Placebo	PTH control  Biochemical parameters	Paricalcitol-treated patients had a statistically significant sustained reduction in serum PTH levels [RR 6.97 (95% CI 5.27–9.23), $P < 0.00001$ ].  No statistically significant difference in the incidence of hypercalcaemia between the groups, although a trend towards hypercalcaemia was evident in the paricalcitol-treated groups. No statistically significant difference in the incidence of hyperphosphataemia between the groups.  There was a statistically significant increase in the incidence of an elevated calcium $\times$ phosphorus product between the paricalcitol- and placebo-treated groups [RR 1.97 (95% CI 1.06–3.67), $P = 0.03$ ].
Cheng <i>et al.</i> [34]	CKD Stages 2–5D, adults	9 × RCTs	832	Paricalcitol	Placebo	PTH control  Biochemical parameters Adverse events (AE)	Compared with placebo, paricalcitol suppressed serum PTH levels [RR 6.37 (95% CI 4.64–8.74), $P < 0.001$ ].  No statistically significant difference in the incidence of hypercalcaemia between the groups. Patients receiving paricalcitol therapy did not have an increased risk of AEs and serious AEs.
Zhou and Xu [35]	CKD Stage 5D, adults	6 × RCTs	174	Intravenous calcitriol intermittently	Oral calcitriol intermittently	PTH control  Biochemical parameters	No significant differences between the two routes in suppressing PTH levels.  No significant differences between the two routes in the incidence of hypercalcaemia and hyperphosphataemia.  No significant differences between the two routes in alkaline phosphatase levels.
Palmer <i>et al.</i> [36]	CKD Stage 5D, adults	60 × RCTs	2773	Vitamin D compounds	Vitamin D compounds/ placebo/no treatment	PTH control  Biochemical parameters	Established vitamin D compounds (calcitriol, alfacalcidol, or 24,25-dihydroxycholecalciferol) suppressed PTH compared with placebo. Newer vitamin D compounds (paricalcitol, maxacalcitol, doxercalciferol) lowered PTH compared with placebo.  No recommendation regarding the efficacy of intravenous compared with equivalent oral vitamin D compounds can be made due to limitations of available study data.  Newer vitamin D compounds cannot yet be regarded as superior to existing treatments. Vitamin D compounds compared with placebo were associated with increased risks of hypercalcaemia and hyperphosphataemia (findings did not reach statistical significance).  Inadequate data are available on newer vitamin D compounds to determine their ‘less calcaemic’ or ‘non-calcaemic’ status when compared with calcitriol or alfacalcidol.

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Table 3. Continued

Author, Ref.	Population	No. of studies	n	Treatment	Control	Outcomes	Main results
Palmer <i>et al.</i> [37]	CKD Stages 2–5, adults	16 × RCTs	894	Vitamin D compounds	Vitamin D compounds/ placebo/no treatment	PTH control  Biochemical parameters	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.

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)<sub>2</sub>D 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 strength [8]. Moreover, in people with calcium deficiency, 1,25(OH)<sub>2</sub>D 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-alfacalcidol, 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  $2 \times 2$  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  $2 \times 2$  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  $\geq 30\%$  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 phosphorous [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-alpha-calcidol 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 extraskelatal (vascular) calcification.
- 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.
  - 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>.

## ACKNOWLEDGEMENTS

RS holds a fellowship with the National Institute for Health Research (NIHR).

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## FUNDING

We have received €4000 from the European Society for Paediatric Nephrology CKD and Dialysis working groups to support the development of both recommendations on native and active vitamin D therapy in children with CKD.

## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES

- Shroff R, Knott C, Rees L. The virtues of vitamin D—but how much is too much? *Pediatr Nephrol* 2010; 25: 1607–1620
- Bacchetta J, Harambat J, Cochat P *et al*. The consequences of chronic kidney disease on bone metabolism and growth in children. *Nephrol Dial Transplant* 2012; 27: 3063–3071
- Denburg MR. Skeletal manifestations of renal disease in childhood. *Curr Opin Nephrol Hypertens* 2016; 25: 292–300
- Wesseling-Perry K, Salusky IB. Chronic kidney disease: mineral and bone disorder in children. *Semin Nephrol* 2013; 33: 169–179
- Bakkaloglu SA, Wesseling-Perry K, Pereira RC *et al*. Value of the new bone classification system in pediatric renal osteodystrophy. *Clin J Am Soc Nephrol* 2010; 5: 1860–1866
- Bacchetta J, Wesseling-Perry K, Kuizon B *et al*. The skeletal consequences of growth hormone therapy in dialyzed children: a randomized trial. *Clin J Am Soc Nephrol* 2013; 8: 824–832
- Tsmpalieros A, Griffin L, Terpstra AM *et al*. Changes in DXA and quantitative CT measures of musculoskeletal outcomes following pediatric renal transplantation. *Am J Transplant* 2014; 14: 124–132
- Wesseling-Perry K, Pereira RC, Sahney S *et al*. Calcitriol and doxercalciferol are equivalent in controlling bone turnover, suppressing parathyroid hormone, and increasing fibroblast growth factor-23 in secondary hyperparathyroidism. *Kidney Int* 2011; 79: 112–119
- Wesseling-Perry K, Pereira RC, Tseng CH *et al*. Early skeletal and biochemical alterations in pediatric chronic kidney disease. *Clin J Am Soc Nephrol* 2012; 7: 146–152
- Denburg MR, Kumar J, Jemilista T *et al*. Fracture burden and risk factors in childhood CKD: results from the CKiD cohort study. *J Am Soc Nephrol* 2016; 27: 543–550
- Picton ML, Moore PR, Mawer EB *et al*. Down-regulation of human osteoblast PTH/PTHrP receptor mRNA in end-stage renal failure. *Kidney Int* 2000; 58: 1440–1449
- Shroff R, Wan M, Nagler EV *et al*. Clinical practice recommendations for native vitamin D therapy in children with chronic kidney disease stages 2–5 and on dialysis. *Nephrol Dial Transplant* 2017; 32: 1098–1113

13. Hahn D, Hodson EM, Craig JC. Interventions for metabolic bone disease in children with chronic kidney disease. *Cochrane Database Syst Rev* 2015; 11: CD008327
14. Salusky IB, Kuizon BD, Belin TR *et al*. Intermittent calcitriol therapy in secondary hyperparathyroidism: a comparison between oral and intraperitoneal administration. *Kidney Int* 1998; 54: 907–914
15. Eke FU, Winterborn MH. Effect of low dose 1 alpha-hydroxycholecalciferol on glomerular filtration rate in moderate renal failure. *Arch Dis Child* 1983; 58: 810–813
16. Watson AR, Kooh SW, Tam CS *et al*. Renal osteodystrophy in children on CAPD: a prospective trial of 1-alpha-hydroxycholecalciferol therapy. *Child Nephrol Urol* 1988; 9: 220–227
17. Salusky IB, Goodman WG, Sahney S *et al*. Sevelamer controls parathyroid hormone-induced bone disease as efficiently as calcium carbonate without increasing serum calcium levels during therapy with active vitamin D sterols. *J Am Soc Nephrol* 2005; 16: 2501–2508
18. Jones CL, Vieth R, Spino M *et al*. Comparisons between oral and intraperitoneal 1,25-dihydroxyvitamin D3 therapy in children treated with peritoneal dialysis. *Clin Nephrol* 1994; 42: 44–49
19. Schmitt CP, Ardissino G, Testa S *et al*. Growth in children with chronic renal failure on intermittent versus daily calcitriol. *Pediatr Nephrol* 2003; 18: 440–444
20. Abitol CL, Warady BA, Massie MD *et al*. Linear growth and anthropometric and nutritional measurements in children with mild to moderate renal insufficiency: a report of the Growth Failure in Children with Renal Diseases Study. *J Pediatr* 1990; 116: S46–S54
21. Hodson EM, Evans RA, Dunstan CR *et al*. Treatment of childhood renal osteodystrophy with calcitriol or ergocalciferol. *Clin Nephrol* 1985; 24: 192–200
22. Klaus G, Schmidt-Gayk H, Roth HJ *et al*. Single-dose oral calcitriol and changes of plasma 1,84iPTH in uremic children. *Adv Perit Dial* 1994; 10: 261–266
23. Ardissino G, Schmitt CP, Bianchi ML *et al*. No difference in intestinal strontium absorption after oral or IV calcitriol in children with secondary hyperparathyroidism. The European Study Group on Vitamin D in Children with Renal Failure. *Kidney Int* 2000; 58: 981–988
24. Greenbaum LA, Grenda R, Qiu P *et al*. Intravenous calcitriol for treatment of hyperparathyroidism in children on hemodialysis. *Pediatr Nephrol* 2005; 20: 622–630
25. Greenbaum LA, Benador N, Goldstein SL *et al*. Intravenous paricalcitol for treatment of secondary hyperparathyroidism in children on hemodialysis. *Am J Kidney Dis* 2007; 49: 814–823
26. Ketteler M, Elder GJ, Evenepoel P *et al*. Revisiting KDIGO clinical practice guideline on chronic kidney disease-mineral and bone disorder: a commentary from a Kidney Disease: Improving Global Outcomes controversies conference. *Kidney Int* 2015; 87: 502–528
27. Guyatt GH, Oxman AD, Vist GE *et al*. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924–926
28. Brouwers MC, Kho ME, Browman GP *et al*. AGREE II: advancing guideline development, reporting, and evaluation in health care. *Prev Med* 2010; 51: 421–424
29. Ardissino G, Schmitt CP, Testa S *et al*. Calcitriol pulse therapy is not more effective than daily calcitriol therapy in controlling secondary hyperparathyroidism in children with chronic renal failure. European Study Group on Vitamin D in Children with Renal Failure. *Pediatr Nephrol* 2000; 14: 664–668
30. Chan JC, McEnery PT, Chinchilli VM *et al*. A prospective, double-blind study of growth failure in children with chronic renal insufficiency and the effectiveness of treatment with calcitriol versus dihydrotachysterol. The Growth Failure in Children with Renal Diseases Investigators. *J Pediatr* 1994; 124: 520–528
31. Chesney RW, Moorthy AV, Eisman JA *et al*. Increased growth after long-term oral 1alpha,25-vitamin D3 in childhood renal osteodystrophy. *N Engl J Med* 1978; 298: 238–242
32. Cai P, Tang X, Qin W *et al*. Comparison between paricalcitol and active non-selective vitamin D receptor activator for secondary hyperparathyroidism in chronic kidney disease: a systematic review and meta-analysis of randomized controlled trials. *Int Urol Nephrol* 2016; 48: 571–584
33. Han T, Rong G, Quan D *et al*. Meta-analysis: the efficacy and safety of paricalcitol for the treatment of secondary hyperparathyroidism and proteinuria in chronic kidney disease. *Biomed Res Int* 2013; 2013: 320560
34. Cheng J, Zhang W, Zhang X *et al*. Efficacy and safety of paricalcitol therapy for chronic kidney disease: a meta-analysis. *Clin J Am Soc Nephrol* 2012; 7: 391–400
35. Zhou H, Xu C. Comparison of intermittent intravenous and oral calcitriol in the treatment of secondary hyperparathyroidism in chronic hemodialysis patients: a meta-analysis of randomized controlled trials. *Clin Nephrol* 2009; 71: 276–285
36. Palmer SC, McGregor DO, Craig JC *et al*. Vitamin D compounds for people with chronic kidney disease not requiring dialysis. *Cochrane Database Syst Rev* 2009; 4: CD008175
37. Palmer SC, McGregor DO, Craig JC *et al*. Vitamin D compounds for people with chronic kidney disease requiring dialysis. *Cochrane Database Syst Rev* 2009; 4: CD005633
38. Haussler MR, Whitfield GK, Kaneko I *et al*. Molecular mechanisms of vitamin D action. *Calcif Tissue Int* 2013; 92: 77–98
39. Lieben L, Masuyama R, Torrekens S *et al*. Normocalcemia is maintained in mice under conditions of calcium malabsorption by vitamin D-induced inhibition of bone mineralization. *J Clin Invest* 2012; 122: 1803–1815
40. Denburg MR, Tsampalieros AK, de Boer IH *et al*. Mineral metabolism and cortical volumetric bone mineral density in childhood chronic kidney disease. *J Clin Endocrinol Metab* 2013; 98: 1930–1938
41. Shroff R, Wan M, Gullett A *et al*. Ergocalciferol supplementation in children with CKD delays the onset of secondary hyperparathyroidism: a randomized trial. *Clin J Am Soc Nephrol* 2012; 7: 216–223
42. Goodman WG, Ramirez JA, Belin TR *et al*. Development of adynamic bone in patients with secondary hyperparathyroidism after intermittent calcitriol therapy. *Kidney Int* 1994; 46: 1160–1166
43. Chan JC, Kodroff MB, Landwehr DM. Effects of 1,25-dihydroxyvitamin-D3 on renal function, mineral balance, and growth in children with severe chronic renal failure. *Pediatrics* 1981; 68: 559–571
44. Kuizon BD, Goodman WG, Juppner H *et al*. Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. *Kidney Int* 1998; 53: 205–211
45. Moe S, Drueke T, Cunningham J *et al*. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; 69: 1945–1953.
46. Suda T, Takahashi F, Takahashi N. Bone effects of vitamin D - discrepancies between in vivo and in vitro studies. *Arch Biochem Biophys* 2012; 523: 22–29
47. Borzych D, Rees L, Ha IS *et al*. The bone and mineral disorder of children undergoing chronic peritoneal dialysis. *Kidney Int* 2010; 78: 1295–1304
48. Waller SC, Ridout D, Cantor T, Rees L. Parathyroid hormone and growth in children with chronic renal failure. *Kidney Int* 2005; 67: 2338–2345
49. Shroff RC, Donald AE, Hiorns MP *et al*. Mineral metabolism and vascular damage in children on dialysis. *J Am Soc Nephrol* 2007; 18: 2996–3003
50. Webb N, Lerner G, Warady B *et al*. Paricalcitol is effective and well-tolerated in children with stages 3 to 5 chronic kidney disease. *Pediatr Nephrol* 2017 (in press)
51. Li XH, Feng L, Yang ZH, Liao YH. The effect of active vitamin d on cardiovascular outcomes in predialysis chronic kidney diseases: a systematic review and meta-analysis. *Nephrology (Carlton)* 2015; 20: 706–714
52. Salusky IB, Goodman WG, Kuizon BD. Implications of intermittent calcitriol therapy on growth and secondary hyperparathyroidism. *Pediatr Nephrol* 2000; 14: 641–645
53. Cano FJ, Azocar MA, Guerrero JL *et al*. Intraperitoneal calcitriol in infants on peritoneal dialysis. *Perit Dial Int* 2007; 27: 681–686
54. Wesseling-Perry K. Bone disease in pediatric chronic kidney disease. *Pediatr Nephrol* 2013; 28: 569–576
55. Rubin MR, Silverberg SJ, D'amour P *et al*. An N-terminal molecular form of parathyroid hormone (PTH) distinct from hPTH(1 84) is overproduced in parathyroid carcinoma. *Clin Chem* 2007; 53: 1470–1476
56. Slatopolsky E, Finch J, Clay P *et al*. A novel mechanism for skeletal resistance in uremia. *Kidney Int* 2000; 58: 753–761
57. Salusky IB, Ramirez JA, Oppenheim W *et al*. Biochemical markers of renal osteodystrophy in pediatric patients undergoing CAPD/CCPD. *Kidney Int* 1994; 45: 253–258

58. Mathias R, Salusky I, Harman W *et al.* Renal bone disease in pediatric and young adult patients on hemodialysis in a children's hospital. *J Am Soc Nephrol* 1993; 3: 1938–1946
59. Ziolkowska H, Paniczyk-Tomaszewska M, Debinski A *et al.* Bone biopsy results and serum bone turnover parameters in uremic children. *Acta Paediatr* 2000; 89: 666–671
60. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis* 2003; 42 (4 Suppl 3): S1–S201
61. Kidney Disease: Improving Global Outcomes CKD-MBD Work Group. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease-mineral and bone disorder (CKD-MBD). *Kidney Int Suppl* 2009; 113: S1–S130
62. Klaus G, Watson A, Edefonti A *et al.* Prevention and treatment of renal osteodystrophy in children on chronic renal failure: European guidelines. *Pediatr Nephrol* 2006; 21: 151–159
63. Waller S, Shroff R, Freemont AJ, Rees L. Bone histomorphometry in children prior to commencing renal replacement therapy. *Pediatr Nephrol* 2008; 23: 1523–1529
64. Haffner D, Schaefer F. Searching the optimal PTH target range in children undergoing peritoneal dialysis: new insights from international cohort studies. *Pediatr Nephrol* 2013; 28: 537–545
65. Zhang Q, Li M, Zhang T *et al.* Effect of vitamin D receptor activators on glomerular filtration rate: a meta-analysis and systematic review. *PLoS One* 2016; 11: e0147347

Received: 22.11.2016; Editorial decision: 1.4.2017

Nephrol Dial Transplant (2017) 32: 1127–1136

doi: 10.1093/ndt/gfw201

Advance Access publication 21 May 2016

## As we grow old: nutritional considerations for older patients on dialysis

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### ABSTRACT

The number of older people on dialysis is increasing, along with a need to develop specialized health care to manage their needs. Aging-related changes occur in physiological, psychosocial and medical aspects, all of which present nutritional risk factors ranging from a decline in metabolic rate to assistance with feeding-related activities. In dialysis, these are compounded by the metabolic derangements of chronic kidney disease (CKD) and of dialysis treatment *per se*, leading to possible aggravation

of protein–energy wasting syndrome. This review discusses the nutritional derangements of the older patient on dialysis, debates the need for specific renal nutrition guidelines and summarizes potential interventions to meet their nutritional needs. Interdisciplinary collaborations between renal and geriatric clinicians should be encouraged to ensure better quality of life and outcomes for this growing segment of the dialysis population.

**Keywords:** elderly, geriatric, malnutrition, protein–energy wasting