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# Clinical Practice Recommendations for native Vitamin D therapy in children with CKD stages 2-5 and on dialysis

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## Abstract

Vitamin D deficiency is widely prevalent and often severe in children and adults with chronic kidney disease (CKD). Although native vitamin D (25-hydroxyvitamin D [25(OH)D]) is thought to have pleiotropic effects on many organ systems, its skeletal effects have been most widely studied. 25(OH)D deficiency is causally linked with rickets and fractures in healthy children and those with CKD, contributing to the CKD – mineral and bone disorder (MBD) complex.

There are few studies to provide evidence for vitamin D therapy or guidelines for its use in CKD. A core working group (WG) of the European Society for Paediatric Nephrology (ESPN) CKD-MBD and Dialysis WGs have developed recommendations for the evaluation, treatment, and prevention of vitamin D deficiency in children with CKD. We present clinical practice recommendations for the use of ergocalciferol [vitamin $D_2$] and cholecalciferol [vitamin $D_3$] in children with CKD stages 2 to 5 and on dialysis. A parallel document addresses treatment recommendations for active vitamin D analogue therapy.

The WG have performed an extensive literature review to include meta-analyses and randomized controlled trials in healthy children as well as children and adults with CKD, and prospective observational studies in children with CKD. The GRADE system has been 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.

## Introduction

Vitamin D deficiency is widely prevalent and often severe in children and adults with chronic kidney disease (CKD), and contributes to abnormalities in calcium (Ca), phosphate (P) and parathyroid hormone (PTH) homeostasis. The mineral dysregulation in CKD directly affects bone strength, mineralisation[1;2], and architecture[1] and is called CKD – mineral and bone disorder (CKD-MBD)[3]. CKD-MBD in childhood presents multiple obstacles to bone accrual[2;4] resulting in bone pain, deformities[5;6], growth retardation[7] and fractures[2;4].

Most tissues in the body have a vitamin D receptor and the enzymatic machinery to convert 'nutritional' 25-hydroxyvitamin D [25(OH)D] to the active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] for local use. Converging data from *in vitro*, clinical and epidemiological studies suggests that in addition to the effects of vitamin D on calcium homeostasis and PTH regulation[8], vitamin D may also play a role in the prevention of cardiovascular disease, anaemia, infectious and autoimmune conditions, renoprotection[9;10], glycaemic control and prevention of some common cancers. Both nutritional vitamin D supplements and activated vitamin D analogues are routinely used in children with CKD. However, there are few studies to provide evidence for vitamin D associated outcomes in CKD. In the absence of evidence, guidelines from international committees like Kidney Disease Outcomes Quality Initiative (KDOQI)[11;12] and

Kidney Disease Improving Global Outcomes (KDIGO)[3] tend to be deliberately vague, leaving physicians, patients and health commissioners with few definitive treatment recommendations.

We present clinical practice recommendations for the use of native vitamin D therapy (ergocalciferol [vitamin $D_2$] and cholecalciferol [vitamin $D_3$]) in children with CKD stages 2 to 5 and on dialysis (stage 5D). This document covers recommendations for the assessment of vitamin D status, optimal levels of 25(OH)D and its monitoring, and recommendations for native vitamin D supplementation. A second document in parallel with this one covers treatment recommendations for active vitamin D analogue therapy (**Ref xx**). The recent Cochrane Review on interventions for metabolic bone disease in children with CKD[13] and the evidence tables from the KDIGO CKD-MBD update document[14] were used to evaluate all available studies, and in addition, the core working group (WG) have performed an extensive literature review to include additional systematic reviews, randomized controlled trials (RCTs) and prospective observational studies. The GRADE system has been used to develop and grade the recommendations. In the absence of applicable study data, the opinion of experts from the European Society for Paediatric Nephrology (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. These clinical practice recommendations will be audited by the ESPN CKD-MBD and Dialysis WGs and revised periodically. Research recommendations to study key vitamin D outcome measures in children are suggested in the parallel document (**Ref xx**).

## Methods

### *Overview of the guideline development group composition and task distribution*

Three groups were assembled to perform different functions: a core leadership group, an external advisory panel and a voting panel. The core group comprised Paediatric Nephrologists who are board members of the ESPN CKD-MBD and Dialysis WGs, a paediatric pharmacist and a biochemist. The chair and all members of the core panel had no relevant conflicts of interest. The core leadership group was responsible for defining the scope of the project, formulating the clinical questions to be addressed by the recommendations, performing a literature review, developing evidence tables, rating the quality of evidence, conducting the voting panel, and drafting the manuscript. The external advisory group included an expert in paediatric metabolic bone disease (NB), an adult nephrologist who is the chair of the CKD-MBD WG of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA; MC), and a guideline methodologist from European Renal Best Practice, the guideline development body of the ERA-EDTA (EN). The voting group was independent of the literature review group and comprised all members of the ESPN CKD-MBD and Dialysis groups. Voting group members were sent the draft guideline document and all evidence tables and were responsible for reviewing the evidence, GRADE-ing the recommendations and suggesting re-wording of recommendations if appropriate. Comments received from all members of the voting group were collated into a single document and discussed at a meeting of the core working group with input from the external advisory group. A final document was then compiled and

circulated to the voting group for their opinion. We have not included children with CKD and their families in developing the recommendations.

***Developing the PICO questions***

Guidelines are most useful when they provide specific actionable advice on choosing between alternative approaches in particular clinical situations[15]. Therefore, as recommended by the GRADE method, we developed clinical question to be addressed by the recommendations under the following categories: the Patient (or Population) to whom the recommendation will apply; the Intervention being considered; the Comparison (which may be "no action" or an alternative intervention); and the Outcomes affected by the intervention (PICO)[15]. These PICO elements were arranged into the questions to be addressed in the literature searches. Each PICO question then formed the basis for a recommendation.

***Population covered***

We focus on children below 18 years of age with CKD stages 2-5D (estimated glomerular filtration rate below 90ml/min/1.73m$^2$, and those on dialysis) for this clinical practice recommendation. The pathophysiological processes of CKD-MBD are not seen in CKD stage 1, hence we have not addressed this cohort in these recommendations. Children with kidney transplants are not included as other confounding issues such as immunosuppressive therapy may influence vitamin D status.

***Intervention and comparators***

Recommendations have been developed on native vitamin D therapy (cholecalciferol and ergocalciferol). These have been compared with no treatment, placebo or other native vitamin D analogues.

***Outcomes addressed***

We address recommendations for serum 25(OH)D based on its skeletal effects (including biochemical effects) only. The guideline committee acknowledges that there may be potential effects of vitamin D on multiple organ systems with possible beneficial effects such as the management of anaemia of CKD[16;17], enhancing immune response[18], reduction in proteinuria and attenuating CKD progression[10;19]. However, most of these data are based on pre-clinical studies or low-grade association studies in children. The guideline committee agreed that at our current state of knowledge, vitamin D supplementation exclusively for the prevention or management of non-osseous outcomes in children with CKD cannot be recommended.

Importantly, although PTH is widely used as a surrogate end-point, it is a relatively poor marker of bone morphology in CKD[1]. There are no RCT data in CKD patients to show an effect of native vitamin D supplementation on growth or fracture risk. An association, that is likely causal, between PTH and skeletal outcomes has been shown in *in vitro* studies, animal experiments and observational studies; PTH-mediated increase in osteoclastic activity creates local foci of bone loss, and coupled with hypocalcaemia that leads to poor osteoid mineralisation, this results in a generalized decrease in bone mineral density (BMD), causing rickets and

osteopenia[20;21]. PTH is accepted as a valid surrogate through which the effects of vitamin D can be assessed. It is important that other modifiers of secondary hyperparathyroidism, including serum calcium, ionised calcium, phosphate, PTH, alkaline phosphatase, and 25(OH)D, are assessed together, with particular importance to trends in values, and appropriately managed through diet, use of calcium-based or calcium-free phosphate binder, ergo- or cholecalciferol supplementation, active vitamin D analogues and dialysis prescription.

***Literature search***

We initially set out to include all systematic reviews of RCTs and individual RCTs on native vitamin D therapy in children with CKD 2-5D. However, the core leadership group acknowledged there are few RCTs or prospective observational studies of native vitamin D treatment in children with CKD 2-5D. We have therefore elected to perform a wider review of the literature and include studies with primary skeletal endpoints (including biochemical endpoints) in the following cohorts: (i) All systematic reviews of RCTs in healthy children, children with nutritional rickets and adults; (ii) All systematic reviews of RCTs, individual RCTs and prospective observational studies in children with CKD 2-5D; (iii) All RCTs in adults with CKD 2-5D; (iv) All RCTs in healthy children or children with nutritional rickets. Medline was searched using the Pubmed interface through to 1st October 2016 using the search terms and strategy detailed in Supplemental table 1. Limits were pre-set to manuscripts published in the English language, and study design limits were applied as detailed in Supplemental table 1. Title and abstracts were reviewed by two independent reviewers (MW and RS). When there was disagreement regarding inclusion of the manuscript for this systematic review, a third reviewer (CS) determined whether the manuscript was eligible.

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- All systematic reviews of RCTs in healthy children, children with nutritional rickets and adults
- All systematic reviews of RCTs, individual RCTs and prospective observational studies in children with CKD 2-5D
- All RCTs in adults with CKD 2-5D
- All RCTs in healthy children or children with nutritional rickets

In addition, the recent Cochrane Review on interventions for metabolic bone disease in children with CKD[13] and the evidence tables from the KDIGO CKD-MBD update document[14] were used to evaluate all available studies.

Data were extracted by at least 2 members of the core group, prepared in evidence tables (see all tables and supplement section) and GRADE-ed by all members of the core group. Only studies in the English language were included. Studies where skeletal endpoints were not applicable to the paediatric population (e.g. falls or hip fracture) were excluded. Comparison

between vitamin $D_2$ and $D_3$ was performed based on their effects on serum 25(OH)D levels. Some studies that were outside the remit of the literature review but contributed important information have been included in the discussion but did not influence the GRADE-ing of recommendations. Risk of bias assessment was only performed for RCTs in children due to resource constraints (see Supplemental Tables).

***GRADE system***

We have followed the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) method to develop the recommendations (Supplemental Tables 2A and 2B). Key aspects of this method include identification of the most important clinical questions for which treatment recommendations are needed, specification of the important outcomes, and use of a tested approach for deriving recommendations from the evidence[15]. This approach assigns separate grades for the quality of the evidence and for the strength of the recommendation[22]. The quality of evidence is graded as either high (A), moderate (B), low (C), or very low (D), and the strength of a recommendation as either level 1 (strong) or level 2 (weak or discretionary).

***AGREE-2 system***

We have developed our guideline based on the ***A**ppraisal of **G**uidelines for **Re**search & **E**valuation (AGREE)*[23] standards, an instrument that assesses the methodological rigour and transparency in which a guideline is developed.

**Clinical Practice Recommendations**

1. ***Assessing vitamin D status***

**Recommendation: We recommend measuring serum 25(OH)D concentration for assessing the vitamin D status of children with CKD 2-5D.**

**GRADE:** This statement is based on *in vitro* data and therefore not graded.

**Evidence and rationale:** Serum concentrations of 25(OH)D are the best marker of the vitamin D status of an individual because[24-28]:

1. all pre-vitamin D metabolites from cutaneous synthesis or diet are rapidly converted into 25(OH)D with no negative feedback to limit this conversion
2. there is no significant storage in the liver
3. the half-life *in vivo* is approximately 2 - 3 weeks
4. in serum (and plasma) 25(OH)D is stable and resistant to repeated freeze-thaw cycles.

The serum $1,25(OH)_2D$ concentration is not a good measure of vitamin D status because[25;27]:

1. conversion to $1,25(OH)_2D$ depends on the availability of its substrate 25(OH)D
2. conversion of 25(OH)D to $1,25(OH)_2D$ is tightly regulated by circulating PTH, fibroblast growth factor 23 (FGF23), calcium, and phosphate
3. the half-life *in vivo* is approximately 4 hours

**Laboratory measurement** of circulating 25(OH)D is challenging due to its hydrophobic nature. Also, a stereoisomer 3-epi-25(OH)$D_3$, that differs from 25(OH)$D_3$ in the orientation of a hydroxyl group at C3, and is of unknown physiological function, may confound 25(OH)D measurements[29].

There are three techniques for measuring 25(OH)D concentrations in serum or plasma[30-32]:

*i)* competitive protein binding assays utilizing vitamin D binding protein (VDBP) as the primary binding agent for 25(OH)D

*ii)* competitive immunoassays utilizing 25(OH)D-specific antibodies as the primary binding agent. Techniques include radioimmunoassay, immuno-chemiluminescence and enzyme immunoassays. Irrespective of the mode used for detection, these assays differ with respect to the ability to discriminate between 25(OH)D metabolites - 25(OH)$D_2$, 25(OH)$D_3$ and 3-epi-25(OH)$D_3$.

*iii)* high performance liquid chromatography (HPLC) coupled with either ultraviolet, colourimetric electrochemical detectors or tandem mass spectrometry (MS/MS). The latter is termed LC-MS/MS and combines the resolving power of HPLC with the specificity of mass spectrometry[33]. Although most chromatographic methods are developed and optimized in-house, commercial kits are available too.

25(OH)D assays differ markedly with significant inter-assay and inter-laboratory variability[30-32;34-38]. There is little consensus on which assay method should be used, both in terms of the assay's precision (i.e. ability to measure 'true' 25(OH)D concentration) and repeatability within and between laboratories[39]. It is encouraged that laboratories performing vitamin D analysis participate in the Vitamin D External Quality Assessment Scheme (DEQAS; http://www.deqas.org/) to ensure high analytical standards[36-39]. The choice of measurement technique depends on clinical requirements, i.e. when ergocalciferol is used for supplementation, the assay selected must be able to detect 25(OH)$D_2$ and 25(OH)$D_3$. Immunoassays that run on automated platforms allow high sample throughput at moderate costs and analytical precision is usually higher compared to manual assays[38]. HPLC or LC-MS/MS assays require expensive equipment and skilled staff, but can differentiate between 25(OH)$D_2$, 25(OH)$D_3$ and 3-epi-25(OH)$D_3$. Clinicians must be aware of the limitations of current assays and refer to assay and laboratory-specific cut-off values.

'Free' or non-protein bound 25(OH)D is biologically active and may be particularly important in patients with proteinuria, and may explain genetic variations in total 25(OH)D levels. However, there are no commercially available assays that have been well validated[40]. Also, serum 25(OH)D concentrations may be affected by rare genetic defects in the enzymes that regulate the metabolism and degradation of 25(OH)D and 1,25$(OH)_2$D causing an increased risk of hypercalcaemia; these rare conditions are not discussed in this guideline document.

## 2. *Monitoring vitamin D concentration in serum*

**Recommendation: We suggest the following schedule for measuring serum 25(OH)D concentration in children with CKD stage 2-5D:**

- 6 – 12 monthly depending on CKD stage in children not on vitamin D treatment
- **if normal levels**, measure 6 -12 monthly (based on previous 25OHD level and stage of CKD)
- **if vit D supplementation required** – check levels after 3-months. If:
  - normal levels, continue vit D supplements as above and measure levels 6-monthly
  - low levels, consider one repeat course of 'intensive replacement treatment' as described below and repeat levels in 3-months

**GRADE**
**Strength of recommendation: 2**
**Level of evidence: D**

**Evidence and rationale:** There are no studies that examine the frequency of 25(OH)D monitoring and outcomes. Based on the long half-life and perceived safety of native vitamin D therapy, we make the above suggestions. Reports suggest that frequent vitamin D measurements are costly, confusing and without credibility[41].
In addition to measuring serum 25(OH)D levels, measurement of serum calcium and urinary calcium excretion can be very helpful in detecting a risk of vitamin D toxicity from hypercalcaemia, hypercalciuria and nephrocalcinosis. This is particularly important during the high-dose 'intensive replacement phase' of treatment and in patients with impaired renal function such as neonates. This is discussed further under recommendation 6.

**3.** ***Defining target levels of vitamin D***

**Recommendation: We suggest that serum 25(OH)D concentrations are maintained above 75nMol/L (>30ng/ml) in children with CKD stages 2 – 5D.**

**We classify vitamin D status as follows:**

| | |
|---|---|
| **sufficiency** | **> 75 nMol/L (>30 ng/ml)** |
| **insufficiency** | **50 – 75 nMol/L (20 – 30 ng/ml)** |
| **deficiency** | **12 – 50 nMol/L (5 - 20 ng/ml)** |
| **severe deficiency** | **<12 nMol/L (<5 ng/ml)** |

**GRADE**
**Strength of recommendation: 2**
**Level of evidence: C**

**Evidence and rationale:** There is no clear consensus on the definition of optimal vitamin D concentrations even in healthy children, and international guidelines differ in their recommendations of target 25(OH)D concentrations (Table 1). The Endocrine Society Clinical guideline[42] recommend maintaining 25(OH)D >75nMol/L based on the effects on prevention of nutritional rickets, PTH suppression[24] and optimal gut calcium absorption[26;43]. The Institute of Medicine (IOM)[44] suggests that there is no improvement in outcome by increasing 25(OH)D concentration >50nMol/L, largely based on the histological presence of bone disease in post-

mortem specimens from healthy individuals[45]. Similarly, in a study of 52 post-mortem examinations in children between 2 days and 10 years of age, 33% had growth plate abnormalities that were associated with 25(OH)D concentrations between 25 – 50nMol/L[46]; however, underlying illnesses contributing to death may have affected the growth plate. Importantly, gut calcium absorption or increased PTH levels, that are known to precede the development of overt rickets (Table 2)[24], have not been considered when defining normal 25(OH)D concentrations. In otherwise healthy children an increased incidence of nutritional rickets is reported with 25(OH)D levels <30nMol/L[47-50], particularly if there is concomitant calcium deficiency[51]. Seasonal variations in 25(OH)D levels are reported[52], emphasizing the importance of maintaining higher concentrations so as to prevent seasonal fluctuations or prolonged periods of low 25(OH)D that increase the risk of developing rickets**.** A systematic review of RCTs of native vitamin D supplementation versus placebo in otherwise healthy children who were vitamin D deficient, clinically useful improvements in lumbar spine bone mineral density and total body bone mineral content were noted, but only on sub-group analysis in those with 25(OH)D levels below 35 nMol/L, and must be interpreted with caution(Table 3A)[53]. Also, the vitamin D receptor genotype may influence this response as shown in an RCT of healthy girls (Table 3B)[54].

There are few studies in children or adults with CKD that examine the effects of 25(OH)D concentrations on bone, and the optimal target level of 25(OH)D is unclear and may need to be higher than that in the general population. In the only RCT of native vitamin D therapy in children with CKD it was shown that children on ergocalciferol who achieved 25(OH)D levels >75nMol/L had a significantly longer time to development of secondary hyperparathyroidism (hazard ratio=0.30, 95% confidence interval=0.09–0.93; Table 4A) compared to those on placebo[8].In a prospective longitudinal study of 170 children and adolescents with CKD stages 2-5D lower serum 25(OH)D and calcium levels were independently associated with lower tibial cortical volumetric BMD Z-scores[55], but no correlation was found between 25(OH)D levels and fracture risk[56]. A meta-analysis of nutritional vitamin D compounds in adult CKD and dialysis patients showed that PTH levels decreased significantly with cholecalciferol treatment[57]. Although no association has been found between 25(OH)D dose or level on PTH suppression, significantly higher doses of daily or weekly cholecalciferol treatment were used in all the RCTs in this meta-analysis. In a cross-sectional analysis of >14,000 adults with CKD stages 1-5, there was a significant inverse association of PTH and serum 25(OH)D, but no further decrease in PTH was seen with 25(OH)D above 105 – 120nMol/L in all CKD stages[58], implying that CKD patients may require significantly higher 25(OH)D levels to achieve target PTH values compared to the healthy population. K/DOQI recommend maintaining 25(OH)D concentrations above 75nMol/L[11;12] as concentrations below this are associated with hyperparathyroidism, lower BMD[59] and hip fractures in adults[60]. Higher 25(OH)D concentrations were not associated with increased rates of hypercalcaemia or hyperphosphataemia in either of the above studies. A safe upper limit for 25(OH)D is discussed under recommendation 7 below. A recent report of nearly 700 children with CKD across Europe has shown that disease-related factors and vitamin D supplementation are the main correlates of vitamin D status in children with CKD, whereas variations in the vitamin D binding protein showed only a weak association with the vitamin D status[61].

**4. *Which patients with CKD need vitamin D supplements?***

**Recommendation: We suggest using native vitamin D supplements for the treatment of vitamin D deficiency in children with CKD stages 2-5D who have serum 25(OH)D concentrations below 75nMol/L. In children with CKD stages 2-3 native vitamin D supplements may be used for the prevention or treatment of secondary hyperparathyroidism.**

**GRADE**
**Strength of recommendation: 2**
**Level of evidence: B**

**Evidence and rationale:** CKD patients are at greater risk of vitamin D deficiency because they are less active and have less sunlight exposure, uraemia reduces the endogenous synthesis of vitamin D in the skin[62], ingestion of foods that are natural sources of vitamin D may be diminished[63], there is reduced hepatic production of 25(OH)D from substrate and loss of vitamin D binding protein in the urine[64;65] or peritoneal dialysate[66].

In an RCT conducted in 40 children with CKD stages 2 – 4, ergocalciferol supplementation significantly delayed the time to development of secondary hyperparathyroidism compared with placebo (Table 4A and Supplemental Table 3)[8]. Only one patient had CKD 4, making the recommendations only applicable to patients in CKD 2-3. Several uncontrolled trials of vitamin D2 or D3 using different treatment schedules have been conducted in children and show different responses to PTH suppression, but all confirm safety in terms of no risk of hypercalcaemia or hyperphosphataemia (Table 4B)[67-70]. In adults with CKD not on dialysis ergocalciferol reduced PTH levels by 20 to 25% in those with CKD 3, but it was ineffective in patients with stage 4 CKD[71;72]. In a systematic review[73] and meta-analysis[57] of observational studies and RCTs (Table 5A) ergocalciferol or cholecalciferol supplementation improved biochemical end-points including a reduction in PTH levels in adult CKD and dialysis patients[57;73]. Most reports suggest that in dialysis patients, and possibly in CKD 4-5, 25(OH)D supplementation alone may not be able to increase $1,25(OH)_2D$ levels (Table 5B)[74-79]. However, a recent RCT in adults on haemodialysis has shown that high dose weekly ergocalciferol supplementation (50,000 IU orally weekly) increased their serum 25(OH)D levels to a normal range (defined as >80nMol/L in this study) with no risk of hypercalcaemia or hyperphosphataemia, but 50% of patients still required active vitamin D supplementation for hyperparathyroidism[80].

In all children, particularly during periods of active growth, the body is in a positive calcium balance and it is important to keep serum calcium levels in the normal range. In children with CKD and on dialysis low serum calcium levels are associated with impaired bone mineralisation on histology[1;81] and reduced tibial cortical bone mineral density on peripheral quantitative CT scan[55], that in turn is associated with an increased fracture risk[56]. The guideline committee holds the opinion that native vitamin D therapy is used in children with CKD stages 2-5 and on

dialysis, and active vitamin D therapy added in patients who have hyperparathyroidism despite normal 25(OH)D levels, provided they do not have hypercalcaemia and/or hyperphosphataemia.

### 5. *Type of vitamin D supplement?*

**Recommendation: We suggest using either vitamin $D_2$ (ergocalciferol) or vitamin $D_3$ (cholecalciferol) treatment in children with CKD 2 – 5D to increase serum 25(OH)D levels to the target range.**

**GRADE**
**Strength of recommendation: 2**
**Level of evidence: D**

**Evidence and rationale:** Three randomized trials in healthy children and those with nutritional rickets have examined the effects of vitamin $D_2$ and vitamin $D_3$ supplementation (Tables 6A and Supplemental Table 4)[82-84]. The patient cohorts, dosage of vitamin D, frequency of administration and duration of treatment varied widely, and no difference in 25(OH)D levels was seen between $D_2$ and $D_3$ supplementation[82-84]. One systematic review in healthy adults has compared the effects of vitamin $D_2$ and vitamin $D_3$ supplementation (Table 6B)[85]. Although there was considerable heterogeneity in the dosage, route and frequency of administration as well as the type of vitamin D assay used, there was no meaningful difference between vitamin $D_2$ and vitamin $D_3$ supplementation with daily oral treatment[85]. There is only one RCT in adults on haemodialysis that has compared the effects of high dose monthly supplementation with vitamin $D_2$ versus $D_3$ which suggested that higher 25(OH)D levels are obtained with monthly $D_3$ compared with $D_2$ supplementation (Table 6C)[53;86]. The European Society of Paediatric Endocrinology[42], the US Endocrine Society[87] and the Scientific Advisory Committee on Nutrition[88] suggest using daily oral vitamin $D_2$ or vitamin $D_3$ for the prevention or treatment of nutritional rickets.

The currently available guidelines on CKD-MBD management vary in their recommendations (Table 7): KDOQI's 2005 recommendation only mentions vitamin $D_2$ [11;12], KDIGO 2009 makes no recommendations for use of cholecalciferol over ergocalciferol[3] whereas European Renal Best Practice Group 2010 recommended cholecalciferol or other 25(OH)D analogues[89]. An RCT in children with CKD 2-4 indicated that ergocalciferol supplementation effectively increases serum 25(OH)D levels to the normal range (Table 4A)[8]. Other uncontrolled trials in children have used both ergocalciferol and cholecalciferol, but in varying treatment schedules and with variable 25(OH)D concentrations achieved (Table 4B)[67-70]. A vitamin D derivative, calcifediol (25-hydroxyvitamin D3, that requires only 1$\alpha$-hydroxylation for activation), has been approved as a modified release preparation by the FDA based upon 2 RCTs in adults CKD patients, as the gradual delivery of calcifediol is thought to improve PTH control[90]. There are no published trials in children so far.

An important cautionary point needs to be kept in mind. Pharmaceutical grade products are available for Vitamin $D_3$, but the availability of vitamin $D_2$ products with pharmaceutical quality in

doses suitable for children is limited. Pharmaceutical grade products provide assurance that the dose given is the dose prescribed whereas in non-pharmaceutical over-the-counter products there can be a huge discrepancy between the indicated and actual vitamin D dose present in the supplement [91]

### 6. *Dosage and frequency of treatment with native vitamin D supplements*

**Recommendation: We suggest using a treatment regimen, guided by age and vitamin D concentration, for the prevention and treatment of vitamin D deficiency in children with CKD 2-5D. Mega-dose vitamin D therapy is not recommended.**

**GRADE**
**Strength of recommendation: 2**
**Level of evidence: C**

**Evidence and rationale:** There is no clear consensus between guideline committees on the type of native vitamin D supplement, its dosage, frequency of administration or duration of treatment[12;42;92;93] in healthy children (Table 1) or children with CKD (Table 7). All guidelines recommend a loading regimen or intensive replacement period for a variable duration of 4 – 12 weeks followed by a maintenance regimen. Unlike the dosage recommendations for vitamin D treatment in healthy children that are based on age[42;92;93], the K/DOQI recommends escalating doses for intensive replacement depending on the baseline 25(OH)D level[12].

There is only one RCT of native vitamin D treatment in children with CKD (Table 4A)[8] that has been considered a high quality RCT with appropriate double blinding, and a low risk of bias, in the Cochrane analysis on metabolic bone disease in children with CKD[13]. This RCT has used a modified version of the K/DOQI vitamin D treatment recommendation (Table 8), adjusting doses for both baseline 25(OH)D levels and also the child's age. It showed that elevated PTH levels developed significantly later in ergocalciferol treated children, though the number with elevated PTH levels did not differ between groups at final follow-up at one year[8]. The ergocalciferol-treated children had a statistically significant increase in 25(OH)D levels between baseline and 3 months of intensive replacement treatment with 80% of children achieving 25(OH)D levels in the normal range after intensive replacement treatment, whereas only 60% children continued to have normal 25(OH)D levels after maintenance treatment. However, it was more difficult to achieve and maintain normal 25(OH)D levels in CKD stages 3–4 compared with stage 2[8], suggesting that higher doses of ergocalciferol may be required in children with CKD 3, or that a repeat course of intensive replacement treatment may be required in those who have not achieved normal 25(OH)D levels. Other non-randomised prospective studies in children with CKD[67-70] (Table 4B) have used variable doses and treatment regimens, and implied the efficacy of ergocalciferol or cholecalciferol in reducing PTH levels[68;70].

None of the studies adjust vitamin D doses for body weight or body surface area, and this may account for the variations in 25(OH)D levels achieved[94]. However, the ergocalciferol RCT did not show any variation in 25(OH)D levels achieved based on the ergocalciferol dose by body

weight or body surface area, but given the small patient numbers, this cannot be excluded and warrants further study. Until further studies in children with CKD and on dialysis are available, the guideline committee suggest using a treatment schedule guided by age and vitamin D level for native vitamin D supplementation in children with CKD 2-5D (Table 8). As per the K/DOQI recommendations, we suggest different dosing schedules for children <1 year and above 1 year in age, although there are no studies to qualify this statement. Also, particularly when using higher doses during the intensive replacement phase, physicians may choose to use a smaller dose based on the child's weight.

During the high-dose 'intensive replacement phase' of treatment and in patients with impaired renal function such as neonates or children with CKD, we suggest measuring serum and urinary calcium to assess the risk of vitamin D toxicity from hypercalcaemia, hypercalciuria and nephrocalcinosis. In addition, clinicians are advised to take into account the vitamin D intake from formula feeds and fortified foods.

Importantly, although the 'stoss regimen' (i.e. 300,000 IU and 600,000 IU as single mega-dose vitamin D therapy) appears attractive and may overcome issues of compliance, it is not shown to affect the rate of improvement of rickets, but can cause hypercalcaemia even in healthy children[95;96]. RCTs in healthy adults have shown that high dose monthly treatment with ergocalciferol or cholecalciferol[97;98], although achieving normal 25(OH)D levels, was associated with a higher risk of fractures, particularly in the first 3 months of treatment. It is speculated that high dose native vitamin D supplements may cause an acute increase in $1,25(OH)_2D$ levels, that, in the presence of hypocalcaemia, may be catabolic to bone[97;99]. In adults with osteoporosis a single dose of 300,000IU cholecalciferol caused a 50% increase in FGF23 levels from baseline[100]. Given that hypercalcaemia can cause a significant acute decline in renal function particularly in CKD patients[101], and that FGF23 is associated with adverse cardiac effects, we do not recommend mega-dose vitamin D treatment regimens, such as the stoss regimen, in children with CKD. More modest high-dose treatment with 80,000 and 100,000 IU cholecalciferol is available and used in some countries, but there is no evidence for this dosing regimen. Given the longer half-life of vitamin $D_3$ compared to vitamin $D_2$, if a weekly dosing schedule is followed, vitamin $D_3$ is recommended compared to vitamin $D_2$. Based on current knowledge, the guideline committee suggests that mega-dose monthly (or 3-monthly) treatment is avoided. There are no studies on vitamin D therapy in children with failed transplants who are in CKD or require dialysis but remain on immunosuppression, and we are not able to make a separate comment about them.

### 7. *Vitamin D toxicity*

**Recommendation: We suggest that vitamin D supplementation is stopped at serum 25(OH)D concentrations of 120nMol/L (48ng/ml). Symptomatic toxicity from Vitamin D is defined as serum 25(OH)D above 250nMol/L with hypercalcaemia, hypercalciuria and suppressed PTH.**

**GRADE**

**Strength of recommendation: 2**
**Level of evidence: D**

**Evidence and rationale:** Intoxication from vitamin D is largely reported from the use of very high doses of ergocalciferol or cholecalciferol over prolonged periods of time, or from accidental or iatrogenic overdose[102-105]. High serum 25(OH)D levels can cause hypercalcaemia and associated sequelae including pancreatitis, hypercalciuria, and if prolonged, nephrocalcinosis and renal failure. RCTs in healthy children report symptomatic toxicity only at levels >500 nMol/L[102]. Genetic variations in vitamin D metabolism may lead to elevated 25(OH)D levels at much lower doses of vitamin D treatment; these are beyond the scope of this guideline.

Patients with CKD may have reduced urinary calcium excretion and be more prone to nephrocalcinosis and renal impairment[106]. A 15-year analysis of the Third National Health and Nutrition Examination Survey (NHANES III) database of >15,000 adults in the general population has suggested a reverse J-shaped association between serum 25(OH)D and all-cause mortality, with an increased mortality at serum 25(OH)D levels above 120 nMol/L (RR = 1.5, 95% CI = 1.02–2.3)[107]. Thus, we suggest a more prudent recommendation for stopping ergocalciferol or cholecalciferol supplements at serum 25(OH)D levels of 120nMol/L, and define symptomatic toxicity at serum 25(OH)D levels >250nMol/L with hypercalcaemia, hypercalciuria and suppressed PTH.

**Summary of Recommendations**
A summary of recommendations is provided in Supplemental Table 5.

**Audit Recommendations**
The ESPN CKD-MBD and Dialysis WGs will audit the effectiveness and safety of the recommendations within its WG. Serum calcium and 25(OH)D levels and urinary calcium excretion will be measured during the intensive replacement phase of therapy as an early and sensitive measure of hypercalciuria (recommendation 6). The audit outcomes will be published and recommendations updated as necessary.

**Research Recommendations**
Research recommendations for native and active vitamin D treatment are provided in the document on 'Active Vitamin D therapy recommendations' (**Ref xx**).

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