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Clinical practice recommendations for native vitamin D therapy in children with chronic kidney disease 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. The 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 2–5 and on dialysis. A parallel document addresses treatment recommendations for active vitamin D analogue therapy. The WG has 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 Grading of Recommendation, Assessment, Development and Evaluation (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.

Keywords: children, cholecalciferol, chronic kidney disease (CKD), dialysis, vitamin D

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, phosphate and parathyroid hormone (PTH) homeostasis. The mineral dysregulation in CKD directly affects bone strength, mineralization [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 suggest 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 such as 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 2–5 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 [13]. The recent Cochrane Review on interventions for metabolic bone disease in children with CKD [14] and the evidence tables from the KDIGO CKD–MBD update document [15] were used to evaluate all available studies, and in addition, the core working group (WG) has performed an extensive literature review to include additional systematic reviews, randomized controlled trials (RCTs) and prospective observational studies. The Grading of Recommendation, Assessment, Development and Evaluation (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 [13].

MATERIALS AND 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 conflict 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 (N.B.), an adult nephrologist who is the chair of the CKD–MBD WG of the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA; M.C.) and a guideline methodologist from European Renal Best Practice, the guideline development body of the ERA-EDTA (E.V.N.). 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 WG 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 [16]. Therefore, as recommended by the GRADE method, we developed clinical questions 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 (hereafter PICO) [16]. 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 <90 mL/min/1.73 m^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 [17, 18], enhancing immune response [19], reduction in proteinuria and attenuating CKD progression [10, 20]. 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 endpoint, 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 mineralization, which results in a generalized decrease in bone mineral density (BMD), causing rickets and osteopenia [21, 22]. 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, ionized 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 Stages 2–5D. However, the core leadership group acknowledged that there are few RCTs or prospective observational studies of native vitamin D treatment in children with CKD Stages 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 Stages 2–5D; (iii) all RCTs in adults with CKD Stages 2–5D; and (iv) all RCTs in healthy children or children with nutritional rickets. Medline was searched using the PubMed interface through to 1 October 2016 using the search terms and strategy detailed in Supplementary Table S1. Limits were pre-set to manuscripts published in the English language, and study design limits were applied as detailed in Supplementary Table S1. Title and abstracts were reviewed by two independent reviewers (M.W. and R.S.). When there was disagreement regarding inclusion of

the manuscript for this systematic review, a third reviewer (C.P. S.) 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 Stages 2–5D;
– all RCTs in adults with CKD Stages 2–5D; and
– 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 [14] and the evidence tables from the KDIGO CKD–MBD update document [15] were used to evaluate all available studies.

Data were extracted by at least two members of the core group, prepared in evidence tables (see all tables and Supplementary Data) 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 vitamins 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 Supplementary Tables).

GRADE system

We have followed the GRADE method to develop the recommendations (Supplementary Tables S2A and S2B). 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 [16]. This approach assigns separate grades for the quality of the evidence and for the strength of the recommendation [23]. The quality of evidence is graded as either (A) high, (B) moderate, (C) low or (D) very low, 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 Appraisal of Guidelines for Research & Evaluation (AGREE) [24] standards, an instrument that assesses the methodological rigour and transparency in which a guideline is developed.

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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 Stages 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 [25–29]:

(i) 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.
(ii) There is no significant storage in the liver.
(iii) The half-life *in vivo* is approximately 2–3 weeks.
(iv) 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 [26, 28]:

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

Laboratory measurement of circulating 25(OH)D is challenging due to its hydrophobic nature. Also, a stereoisomer 3-epi-$25(OH)D_3$, which 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 [30].

There are three techniques for measuring 25(OH)D concentrations in serum or plasma [31–33]:

(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 [34]. Although most chromatographic methods are developed and optimized in-house, commercial kits are also available.

The 25(OH)D assays differ markedly with significant inter-assay and inter-laboratory variability [31–33, 35–39]. 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 [40]. It is encouraged that laboratories performing vitamin D analysis participate in the Vitamin D External Quality Assessment Scheme (http://www.deqas.org/) to ensure high analytical standards [37–40]. 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 with manual assays [39]. 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 [41]. 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 $1,25(OH)_2D$ 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 Stages 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 25(OH)D level and stage of CKD].
– If vitamin D supplementation required, check levels after 3 months. If:
  • normal levels, continue vitamin 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 [42].

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

Table 1. Recommendations for native vitamin D treatment in healthy children

	RCPCH (UK, 2013) [ ]	National Osteoporosis Society (UK, 2015) [ ]	The Endocrine Society (USA, 2011) [ ]
Deficiency defined as	<25 nmol/L[a]	<25 nmol/L	<50 nmol/L
Insufficiency defined as	25–50 nmol/L	25–50 nmol/L	52.5–72.5 nmol/L
Vitamin D_2 versus D_3	No specific recommendation	No preference	No preference
Loading regimens			
Age <6 months	1000–3000 IU/day orally for 4–8 weeks	3000 IU/day orally for 8–12 weeks	2000 IU/day orally for 6 weeks
Age 6 months–12 years	6000 IU/day orally for 4–8 weeks	6000 IU/day orally for 8–12 weeks	2000 IU/day orally for 6 weeks
Age 12–18 years	10 000 IU/day orally for 4–8 weeks	10 000 IU/day orally for 8–12 weeks	2000 IU/day orally for 6 weeks
Maintenance regimens			
Alternative recommended dosages	Weekly or monthly doses	Weekly doses	Weekly doses
Up to 1 month	300–400 IU/day orally	400–600 IU/day orally	400–1000 IU/day orally
1 month–18 years	400–1000 IU/day orally	400–600 IU/day orally	600–1000 IU/day orally

RCPCH, Royal College of Paediatrics and Child Health.
[a]To convert nmol/L to ng/mL divide by 2.5.

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 75 nmol/L (>30 ng/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 [45] recommends maintaining 25(OH)D >75 nmol/L based on the effects on prevention of nutritional rickets, PTH suppression [25] and optimal gut calcium absorption [27, 46]. The Institute of Medicine [47] suggests that there is no improvement in outcome by increasing 25(OH)D concentration >50 nmol/L, largely based on the histological presence of bone disease in post-mortem specimens from healthy individuals [48]. 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 and 50 nmol/L [49]; however, underlying illnesses contributing to death may have affected the growth plate. Importantly, gut calcium absorption or increased PTH levels, which are known to precede the development of overt rickets (Table 2) [25], 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 <30 nmol/L [50–53], particularly

Table 2. Physiological disturbances reported at different serum 25(OH)D levels

25(OH)D level (nmol/L)[a]	Physiological disturbance
<10	Rickets or osteomalacia, severe hyperparathyroidism, calcium malabsorption
10–30	PTH stimulation, reduced calcium absorption
30–40	Sometimes raised PTH
>40	No further increase in 1,25(OH)$_2$D production or increased calcium absorption; abolition of seasonal variations in PTH
>75	No pathologic mineralization defects or growth plate abnormalities
>120	Associated with increased mortality
>250	risk of hypercalcaemia and hypercalciuria

[a]To convert nmol/L to ng/mL divide by 2.5.

if there is concomitant calcium deficiency [54]. Seasonal variations in 25(OH)D levels are reported [55], 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. In 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 BMD and total body bone mineral content were noted, but only on subgroup analysis in those with 25(OH)D levels below 35 nmol/L, and must be interpreted with caution (Table 3) [56]. Also, the vitamin D receptor genotype may influence this response as shown in an RCT of healthy girls (Table 4) [57].

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 >75 nmol/L had a significantly longer time to development of secondary hyperparathyroidism (hazard ratio = 0.30, 95% confidence interval = 0.09–0.93; Table 5) compared with 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

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Table 3. Systematic review of the effect of native vitamin D supplementation versus placebo on bone density and bone mineral content in children without CKD

Author (year)	No. of studies	Population, age	n, N^a	Outcomes	Meta-analysis model	Mean difference of meta-analysis (95% CI)	Results	Potential bias/ limitations
Winzenberg et al. (2011) [56]	6 × RCTs	Healthy children Age: 8–17 years	541, 884	BMD of hip BMD of lumbar spine Total bone mineral content	Random Fixed Fixed	0.06 (−0.18, 0.29) 0.15 (−0.01, 0.31) 0.10 (−0.06, 0.26)	– Overall, vitamin D supplementation had no statistically significant effects on total body bone mineral content or on BMD of the hip or forearm.	– Small number of studies. – Small study populations. – High levels of heterogeneity.
				BMD of forearm	Random	0.04 (−0.36, 0.45)	– Sub group analysis in those with low serum vitamin D concentrations (<35 nmol/L), vitamin D supplementation could result in clinically useful improvements, particularly in lumbar spine BMD and total body bone mineral content.	

CI, confidence interval.

^an represents the number of participants who had received D_2 or D_3; N represents the number of participants enrolled in the full study.

Table 4. RCTs of native vitamin D supplementation on bone density and bone mineral content in children without CKD (include only articles published since publication of the systematic review as listed in Table 3)

Author (year)	Population, gender, age	n, N^a	City, country	Intervention	Comparator	Duration of treatment	Results	Comments
Mølgaard et al. (2010) [57]	Healthy children Male: 0% Age: 11–12 years	147, 221	Frederiksbergn C, Denmark	D_3 orally 200 or 400 IU/day	Placebo	1 year	– No effect on indices of bone health in the entire group. – Increased whole body BMD and bone mineral content in the FF-VDR genotype subgroup.	– Limitation: subgroup analysis. – The extent to which potential genetic determinants may be related to vitamin D metabolism is raised.

^an represents the number of participants who had received D_2 or D_3; N represents the number of participants enrolled in the full study.

Table 5. RCTs of native vitamin D therapy versus placebo in children with CKD

Author (year)	Population, gender, age	n, N[a]	City, country	Intervention	Comparator	Duration of treatment	Results
Shroff et al. (2012) [8]	CKD with eGFR: 47 ± 8.1 mL/min/1.73 m^2 Male: 66% Age: Intervention group: 10.6 ± 2.5 years Placebo group: 7.9 ± 4.8 years	24, 47	London, UK	D_2 orally Dosing as per modified NKF-KDOQI	Placebo	Median 52 weeks	– Children receiving D_2 had a significantly longer time to development of secondary hyperparathyroidism (hazard ratio = 0.30, 95% confidence interval = 0.09–0.93, P = 0.05) compared with those children on placebo. – In the intervention group, 80% children achieved 25(OH)D levels >75 nmol/L after intensive replacement treatment (month 3), whereas only 12 of 20 (60%) children continued to have 25(OH)D levels >75 nmol/L after maintenance treatment. – It was more difficult to achieve and maintain normal 25(OH)D levels in CKD Stages 3–4 compared with Stage 2. – No hypercalcaemia or other treatment-related side effects.

To convert nmol/L to ng/mL divide by 2.5.
eGFR, estimated glomerular filtration rate; NKF-KDOQI, National Kidney Foundation-Kidney Disease Outcomes Quality Initiative.
[a]n represents the number of participants who had received D_2 or D_3; N represents the number of participants enrolled in the full study.

associated with lower tibial cortical volumetric BMD Z-scores [2], but no correlation was found between 25(OH)D levels and fracture risk [58]. A meta-analysis of nutritional vitamin D compounds in adult CKD and dialysis patients showed that PTH levels decreased significantly with cholecalciferol treatment [59]. 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 105–120 nmol/L in all CKD stages [60], implying that CKD patients may require significantly higher 25(OH)D levels to achieve target PTH values compared with the healthy population. KDOQI recommends maintaining 25(OH)D concentrations above 75 nmol/L [11, 12] as concentrations below this are associated with hyperparathyroidism, lower BMD [61] and hip fractures in adults [62]. 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 VDBP showed only a weak association with the vitamin D status [63].

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 75 nmol/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 [64], ingestion of foods that are natural sources of vitamin D may be diminished [65], there is reduced hepatic production of 25(OH)D from substrate and because of loss of VDBP in the urine [66, 67] or peritoneal dialysate [68].

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 5 and Supplementary Table S3) [8]. Only one patient had CKD Stage 4, making the recommendations only applicable to patients in CKD Stages 2–3. Several uncontrolled trials of vitamin D_2 or D_3 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 6) [69–72]. In adults with CKD not on dialysis ergocalciferol reduced PTH levels by 20–25% in those with CKD Stage 3, but it was ineffective in patients with CKD Stage 4 [73, 74]. In a systematic review [75] and meta-analysis [59] of observational studies and RCTs (Table 7), ergocalciferol or cholecalciferol supplementation improved biochemical endpoints including a reduction in PTH levels in adult CKD and dialysis patients [59, 75]. Most reports suggest that in dialysis patients, and possibly in CKD Stages 4–5, 25(OH)D supplementation alone may not be able to increase 1,25(OH)$_2$D levels (Table 8) [76–81]. 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 >80 nmol/L in this study) with no risk of hypercalcaemia or hyperphosphataemia, but 50% of patients

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Table 6. Prospective observational studies of native vitamin D therapy in children with CKD

Author (year)	Population, gender, age	N	City, country	Intervention	Duration of treatment	Results
Kari *et al.* (2013) [69]	CKD Stages 2–5 Male: 58% Age: 11.8 ± 4.6 years	19	Jeddah, Saudi Arabia	D_3 intramuscularly 300 000 IU stat	Single dose	– At 12 weeks, 25(OH)D_3 levels were significantly higher than at baseline but lower than levels at 4 weeks. – PTH levels decreased significantly at 12 weeks. – No changes in calcium, phosphate or ALP levels.
Kari *et al.* (2012) [70]	CKD Stages 2–5 Male: 69% Age: 9.6 ± 4.6 years	45	Jeddah, Saudi Arabia	D_3 orally 2000 IU/day	26 weeks	– 25(OH)D level normalized only in 11% of the patients. – 25(OH)D increased from 35.5 ± 20.5 to 50.4 ± 33.5 nmol/L. – No improvement in PTH levels after 3 and 6 months. – No changes were observed in the levels of calcium, phosphate, ALP or creatinine.
Hari *et al.* (2010) [71]	CKD Stages 2–4 Male: 86% Age: 7.7 ± 3.8 years	42	New Delhi, India	D_3 orally 600 000 IU over 3 consecutive days	Over 3 days	– 25(OH)D increased from 41.8 (95% CI 28.3–49.5) to 115.5 (95% CI 86.3–111.5) nmol/L at 6 weeks. – Median PTH decreased significantly from 51.3 (95% CI 46.7–71.5) to 37.1 (29.0–54.6) pg/mL at 6 weeks. – Serum calcium and phosphorus did not change significantly.
Belostotsky *et al.* (2009) [72]	CKD stage not specified Age: 13.6 ± 3.4 years	20	Manchester, UK	D_2 orally 100 000 IU stat	Single dose	– 25(OH)D increased from 3.8–39.5 to 17.5–64 nmol/L at week 12.

ALP, alkaline phosphatase; CI, confidence interval.

still required active vitamin D supplementation for hyperparathyroidism [82].

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 mineralization on histology [1, 83] and reduced tibial cortical BMD on peripheral quantitative computed tomography scan [2], that in turn is associated with an increased fracture risk [58]. 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 Stages 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 vitamins D_2 and D_3 supplementation (Table 9 and

Supplementary Table S4) [84–86]. 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 vitamins D_2 and D_3 supplementation [84–86]. One systematic review in healthy adults has compared the effects of vitamins D_2 and D_3 supplementation (Table 10) [87]. 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 vitamins D_2 and D_3 supplementation with daily oral treatment [87]. 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 11) [56, 88]. The European Society of Paediatric Endocrinology [45], the US Endocrine Society [89] and the Scientific Advisory Committee on Nutrition [90] suggest using daily oral vitamin D_2 or D_3 for the prevention or treatment of nutritional rickets.

The currently available guidelines on CKD–MBD management vary in their recommendations (Table 12): 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 [91]. An RCT in children with CKD Stages 2–4 indicated that ergocalciferol supplementation effectively increases serum 25(OH)D levels to the normal range (Table 5) [8]. Other uncontrolled trials in children have used both ergocalciferol and

Table 7. Systematic reviews of native vitamin D versus placebo in adults with CKD and on dialysis

Author (year)	No. of studies	Population	N	Outcomes	Meta-analysis model	Mean difference (or relative risk) of meta-analysis (95% CI)	Results	Potential bias/limitations
Alvarez et al. (2012) [75]	8 × RCTs 9 × observational (five prospective, four retrospective)	CKD Stages 2–5 Adults and children	1046	N/A	N/A	N/A	– Achievement of optimal vitamin D status [25(OH)D ≥75 nmol/L] in patients with early CKD may require >2000 IU/day of vitamin D. – PTH significantly decreased in eight studies with a variety of dosing protocols including both D₂ and D₃.	– Studies were mostly of low to moderate quality.
Kandula et al. (2011) [59]	5 × RCTs	CKD Stages 2–5D + transplanted Adults	264	25(OH)D PTH	Random Random	13.9 ng/mL (5.6, 22.4) −31.5 pg/mL (−57.0, −6.1)	– Significant increase in 25(OH)D levels with vitamin D supplementation and an associated decline in PTH. – No significant change in serum calcium or phosphorus levels with vitamin D supplementation. – Low incidence of hypercalcaemia and hyperphosphataemia with vitamin D supplementation.	– Studies were mostly of low to moderate quality. – Allocation concealment was unclear in the included RCTs, and participants, investigators and outcome assessors were not blinded except for one study.
	17 × observational	CKD Stages 3–5D + transplanted Adults	1329	25(OH)D PTH	Random Random	24.1 ng/mL (19.6, 28.6) −41.7 pg/mL (−55.8, −27.7)		

To convert ng/mL to nmol/L multiply by 2.5; N represents the number of participants enrolled in the full study.
CI, confidence interval.

cholecalciferol, but in varying treatment schedules and with variable 25(OH)D concentrations achieved (Table 6) [69–72]. A vitamin D derivative, calcifediol (25-hydroxyvitamin D3, which requires only 1α-hydroxylation for activation), has been approved as a modified release preparation by the Food and Drug Administration based upon two RCTs in adults CKD patients, as the gradual delivery of calcifediol is thought to improve PTH control [92]. 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 D₃, but the availability of vitamin D₂ 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 [93].

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 Stages 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, 43–45] in healthy children (Table 1) or children with CKD (Table 12). 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 [43–45], the KDOQI 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 5) [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 [14]. This RCT used a modified version of the KDOQI vitamin D treatment recommendation (Table 13), 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 1 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

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Table 8. RCTs of native vitamin D versus placebo or no treatment in adults with CKD and on dialysis (include only articles published since publication of the systematic reviews listed in Table 7)

Author (year)	Population, gender, age	N	City, country	Intervention	Comparator	Duration of treatment	Results
Thimachai *et al.* (2015) [76]	CKD Stages 3–4 Male: 53% Age: Intervention group: 65.9 ± 15.5 years Comparator group: 66.7 ± 15.4 years	68	Bangkok, Thailand	D_2 orally Double the dosage of NKF-KDOQI	D_2 orally Dosing as per NKF-KDOQI	8 weeks	– 25(OH)D increased significantly from 52.5 ± 16.7 to 83.5 ± 22.3 nmol/L at week 8 in the intervention group and increased from 52.1 ± 18 to 58.6 ± 19.7 nmol/L in the control group. – PTH levels significantly decreased at week 8 (P = 0.024) in the intervention group, and there was no change in the control group. – No significant changes in serum calcium and phosphate in both groups. – No serious adverse events reported.
Mieczkowski *et al.* (2014) [77]	CKD Stage 5D Male: 53% Age: Intervention group: 63 (52-79) years Comparator group: 46 (29-79) years	19	Warsaw, Poland	D_3 orally 2000 IU three times a week	No treatment	52 weeks	– 25(OH)D levels increased significantly from 28.3 to 112.3 nmol/L at 52 weeks in the D_3 group and no change in the controls. – Treatment with D_3 was associated with a small increase in serum calcium, but serum phosphate, PTH, alkaline phosphatase and BMD remained unchanged in both groups.
Bansal *et al.* (2014) [78]	CKD Stage 5D Male: Not reported Age: Intervention group: 75 ± 9 years Comparator group: 73 ± 12 years	35	Haryana, India	D_3 orally 60 000 IU/week	No treatment	6 weeks	– 25(OH)D levels increased significantly from 24 ± 19 to 48.7 ± 10.7 nmol/L at 6 weeks in the D_3 group and no significant change in the control group. – No significant changes in serum calcium and PTH in both groups.
Delanaye *et al.* (2013) [79]	CKD Stage 5D Male: 70% Age: Intervention group: 75 ± 9 years Comparator group: 73 ± 12 years	30	Liège, Belgium	D_3 orally 25 000 IU every 2 weeks	Placebo	52 weeks	– At 52 weeks, 75% of patients in the D_3 group achieved 25(OH)D ≥75 nmol/L, compared with 0% patients in the placebo group. – Significant difference was found in changes in PTH between the two groups (ΔPTH of −115 pg/mL in the D_3 group and +80 pg/mL in the control). – No significant changes in serum calcium and phosphate in both groups. – No incidence of hypercalcaemia.
Gravesen *et al.* (2013) [80]	CKD Stages 4–5 Male: Not reported Age: Not reported	43	Copenhagen, Denmark	D_2 orally 50 000 IU/week (N = 26)	No treatment (N = 17)	6 weeks	– 25(OH)D levels increased significantly from <10 to 90 ± 4 nmol/L at 6 weeks in the D_2 group and no change in the control group. – No significant changes in serum calcium, phosphate, PTH and FGF23 in both groups.
Marckmann *et al.* (2012) [81]	CKD Stages 1–5D, Tx Male: 75% Age: Intervention group: 71 (62–78) years Comparator group: 68 (59–76) years	52	Odense, Denmark	D_3 orally 40 000 IU/week	Placebo	8 weeks	– 25(OH)D levels increased significantly from 23.8 (95% CI 17.2–41.4) to 154.7 (81.4–240.3) nmol/L at 8 weeks in the D_3 group and no change in the controls. – In non-haemodialysis patients, there was a significant decrease in PTH on the D_3 group. – PTH changes were small and insignificant in haemodialysis patients. – Serum calcium and FGF23 increased significantly in the D_3 group.

To convert nmol/L to ng/mL divide by 2.5.

Tx, transplant; CI, confidence interval.

Table 9. Studies of vitamin D_2 versus vitamin D_3 supplementation in children without CKD

Author (year)	Study design	Population, age	N	Intervention	Comparator	Duration of treatment	Results	Potential bias/limitations
Gallo *et al.* (2013) [84]	RCT	Healthy, 1 month	52	D_3 orally 400 IU/day	D_2 orally 400 IU/day	12 weeks	– Increase in 25(OH)D levels between the D_2 and D_3 groups did not differ at week 12. – No differences were noted among groups in the proportion that achieved 25(OH)D level >75nmol/L at follow up.	– 73% of infants were taking a vitamin D supplement at baseline (although similar percentage in each group). – No safety follow up.
Thacher *et al.* (2010) [85]	Prospective cohort	Healthy with nutritional rickets, 15–120 months	28	D_3 orally 50 000 IU stat	Historic control	Single dose	– Increase in 25(OH)D levels between the D_2 and D_3 groups did not differ at day 3 in both rachitic and healthy children. – D_2 may be metabolized more rapidly than D_3. 25(OH)D levels maintained above 75 nmol/L with D_3 group at day 14.	– Historic cohort of rachitic children treated with D_2 was used as comparator. – Short follow-up.
	RCT	Healthy, 19–59 months	21	D_3 orally 50 000 IU stat	D_2 orally 50 000 IU stat	Single dose		
Gordon *et al.* (2008) [86]	RCT	Healthy, 8–24 months	40	D_3 orally 2000 IU/day	D_2 orally 2000 IU/day D_2 orally 50 000 IU/week	6 weeks	– Increase in 25(OH)D levels between the D_2 and D_3 groups did not differ at week 6. – No significant change in serum calcium, PTH or ALP with any groups.	– Short follow-up. – Weekly D_2 dose is not a direct comparison on a IU per IU basis. – Each group was also prescribed calcium supplementation.

ALP, alkaline phosphatase.

Table 10. Meta-analysis of native vitamin D_2 versus vitamin D_3 supplementation in adults without CKD

Author (year)	No. of studies	Population	n, N[a]	Meta-analysis model	Mean difference of meta-analysis (95% CI)	Results	Potential bias/limitations
Tripkovic *et al.* (2012) [87]	7 × RCTs	Adults	344, 442	Random	15.23 (6.12, 24.34)	– D_3 is more efficacious at raising serum 25(OH)D concentrations than D_2 (P = 0.001). – When the frequency of dosage administration was compared, there was a significant response for D_3 when given as a bolus dose (P = 0.0002) compared with administration of D_2, but the effect was lost with daily supplementation.	– Small number of studies. – Small and underpowered study populations. – High levels of heterogeneity: dosage of vitamin D, the frequency of supplementation and the route of administration. – Lack of data in lower D_2 or D_3 doses. – Lack of consensus in the analysis of serum 25(OH)D concentrations. – An overall general lack of attention to detail in reporting.

CI, confidence interval.
[a] n represents the number of participants who had received D_2 or D_3; N represents the number of participants enrolled in the full study.

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 Stage 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-randomized prospective studies in children with CKD [69–72] (Table 6) have used variable doses and treatment regimens, and implied the efficacy of ergocalciferol or cholecalciferol in reducing PTH levels [69, 71].

None of the studies adjust vitamin D doses for body weight or body surface area, and this may account for the variations in

Table 11. Studies of vitamin D_2 versus vitamin D_3 supplementation in adults with CKD

Author (year)	Study design	Population, gender, age	N	Intervention	Comparator	Duration of treatment	Results
Daroux *et al.* (2013) [88]	RCT	CDK Stage 5D Male: 67% Age: Intervention group: 68.5 ± 14 years Comparator group: 65.3 ± 14.3 years 66.4 ± 18.6 years	39	D_3 orally 200 000 IU/month (single dose)	D_2 orally 200 000 IU/month (single dose) or D_2 orally 200 000 IU/month (in divided doses)	12 weeks	– Increase in 25(OH)D levels was significantly higher in the D_3 group compared with either of the D_2 groups at week 12. – 25(OH)D increased to levels >75 nmol/L in 84% of group D_3 patients, but in only 15 and 27% of group D_2 (single dose) and D_2 (divided doses) patients, respectively.

Table 12. Recommendations for native D treatment from renal guidelines on CKD metabolic bone disease

	European Renal Best Practice Group (2010) [ ]	KDIGO (2009) [ ]	NKF-KDOQI (2003) [ ]
Deficiency defined as	<30 nmol/L[a]	Not defined	<37.5 nmol/L (severe deficiency <12.5 nmol/L)
Insufficiency defined as	30–75 nmol/L	Not defined	40–75 nmol/L
Vitamin D_2 versus D_3	D_3 or other 25(OH)D analogues	No specific recommendation	Only D_2 discussed
Loading regimens			
For all ages (infants to 18 years)	As per general population	As per general population	Dosing based on level: <12.5 nmol/L: 8000 IU/day orally for 4 weeks, then 4000 IU/day orally for 8 weeks 12.5–37.5 nmol/L: 4000 IU/day orally for 12 weeks 40–75 nmol/L: 2000 IU/day orally for 12 weeks
Maintenance regimens			
Age 1 month–18 years	As per general population	As per general population	Weekly doses OR Supplement with vitamin D containing multivitamin preparation

[a]To convert nmol/L to ng/mL divide by 2.5.

Table 13. Suggested treatment for vitamin D supplementation in children with CKD and on dialysis

Age	25(OH)D serum (nmol/L)[a]	Vitamin D supplementation dose (daily)	Monitoring
Intensive replacement phase			
<1 year		600 IU/day[b]	– Serum calcium and urinary calcium levels 1–3 monthly based on CKD stage
>1 year[b]	<12	8000 IU/day	– 25(OH)D levels: after 3 months
	12–50	4000 IU/day	
	50–75	2000 IU/day	
Maintenance phase			
<1 year	>75[d]	400 IU/day	– 25(OH)D levels: 6–12 monthly
>1 year[c]		1000–2000 IU/day based on CKD stage	

[a]To convert nmol/L to ng/mL divide by 2.5.
[b]In infants <1 year, a fixed dose is recommended irrespective of the level of 25(OH)D.
[c]Consider adjusting dose by body size (weight or body surface area).
[d]If levels remain <75nmol/L, then give doses as per the 'Intensive replacement' schedule for a further course of intensive replacement and recheck levels.

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 suggests using a treatment schedule guided by age and vitamin D level for native vitamin D supplementation in children with CKD Stages 2–5D (Table 13). As per the KDOQI recommendations, we suggest different dosing schedules for children <1 year and >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 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, which, in the presence of hypocalcaemia, may be catabolic to bone [97, 99]. In adults with osteoporosis, a single dose of 300 000 IU 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 with 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 thrice-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 120 nmol/L (48 ng/mL). Symptomatic toxicity from vitamin D is defined as serum 25(OH)D above 250 nmol/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 (relative risk = 1.5, 95% confidence interval = 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 120 nmol/L, and define symptomatic toxicity at serum 25(OH)D levels >250 nmol/L with hypercalcaemia, hypercalciuria and suppressed PTH.

SUMMARY OF RECOMMENDATIONS

A summary of recommendations is provided in Supplementary Table S5.

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' [13].

SUPPLEMENTARY DATA

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

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