
Article:
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Tables

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

	RCPCH (UK, 2013)[93]	National Osteoporosis Society (UK, 2015)[92]	The Endocrine Society (US, 2011)[42]
Deficiency defined as	< 25 nmol/L*	< 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 vs. D_3	No specific recommendation	No preference	No preference
Loading regimens			
Age under 6 months	1,000 - 3,000 IU/day orally for 4 - 8 weeks	3,000 IU/day orally for 8 - 12 weeks	2,000 IU/day orally for 6 weeks
Age 6 months - 12 years	6,000 IU/day orally for 4 - 8 weeks	6,000 IU/day orally for 8 - 12 weeks	2,000 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	2,000 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 - 1,000 IU/day orally
1 month - 18 years	400 - 1,000 IU/day orally	400 - 600 IU/day orally	600 - 1,000 IU/day orally

RCPCH: Royal College of Paediatrics and Child Health
*To convert nmol/L to ng/ml divide by 2.5

Table 2 – Physiological disturbances reported at different serum 25-hydroxyvitamin D [25(OH)D] levels

25(OH)D level (nmol/L)*	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 $1,25(OH)_2D$ 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	Hypercalcaemia and hypercalciuria

*To convert nmol/L to ng/ml divide by 2.5

PTH: Parathyroid hormone; $1,25(OH)_2D$: 1,25-dihydroxyvitamin D

Table 3A – Systematic review of the effect of native vitamin D supplementation versus placebo on bone density and bone mineral content in children without chronic kidney disease

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; 2011[53]	6 x RCTs	Healthy children Age: 8-17 y	541, 884	Bone mineral density of hip	Random	0.06 (-0.18, 0.29)	- Overall, vitamin D supplementation had no statistically significant effects on total body bone mineral content or on bone mineral density of the hip or forearm. - 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 bone mineral density and total body bone mineral content.	- Small number of studies - Small study populations - High levels of heterogeneity
				Bone mineral density of lumbar spine	Fixed	0.15 (-0.01, 0.31)		
				Total bone mineral content	Fixed	0.10 (-0.06, 0.26)		
				Bone mineral density of forearm	Random	0.04 (-0.36, 0.45)		

[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.
CI: confidence interval, RCT: randomised controlled trial

Table 3B – Randomised controlled trial of native vitamin D supplementation on bone density and bone mineral content in children without chronic kidney disease
(**Include only articles published since publication of the systematic review as listed in Table 3A)**

Author; Year	Population, Gender, Age	*n, N*[a]	City, Country	Intervention	Comparator	Duration of treatment	Results	Comments
Mølgaard; 2010[54]	Healthy children Male: 0% Age: 11-12 y	147, 221	Frederiksbergn C, Denmark	D_3 orally 200 or 400 IU /day	Placebo	1 y	- No effect on indices of bone health in the entire group. - Increased whole body bone mineral density and bone mineral content in the FF-VDR genotype subgroup.	- Limitation: sub-group analysis - The extent to which potential genetic determinants may be related to vitamin D metabolism is raised.

[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.

Table 4A - Randomised controlled trial of native vitamin D therapy versus placebo in children with chronic kidney disease

Author; Year	Population, Gender, Age	*n, N*[a]	City, Country	Intervention	Comparator	Duration of treatment	Results
Shroff; 2012[8]	CKD with eGFR: 47±8.1 ml/min/1.73 m^2 Male: 66% Age: Intervention group: 10.6±2.5 y Placebo group: 7.9 ±4.8 y	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.

[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.
eGFR: estimated glomerulus filtration rate, NKF-KDOQI: National Kidney Foundation–Kidney Disease Outcomes Quality Initiative, 25(OH)D: 25-hydroxyvitamin D

To convert nmol/L to ng/ml divide by 2.5

Table 4B – Prospective observational studies of native vitamin D therapy in children with chronic kidney disease

Author; Year	Population, Gender, Age	*N*	City, Country	Intervention	Duration of treatment	Results
Kari; 2013[70]	CKD stages 2-5 Male: 58% Age: 11.8 ± 4.6 y	19	Jeddah, Saudi Arabia	D_3 intramuscularly 300,000 IU stat	Single dose	- At 12 wk, 25(OH)D_3 levels were significantly higher than at baseline but lower than levels at 4 wk. - PTH levels decreased significantly at 12 wk. - No changes in calcium, phosphate, or ALP levels
Kari; 2012[69]	CKD stages 2-5 Male: 69% Age: 9.6 ± 4.6 y	45	Jeddah, Saudi Arabia	D_3 orally 2000 IU/day	26 wk	- 25(OH)D level normalized only in 11% of the patients - 25(OH)D increased from 35.5 ± 20.5 nmol/L 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, alkaline phosphatase, or creatinine.
Hari; 2010[68]	CKD stages 2-4 Male: 86% Age: 7.7±3.8 y	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) nmol/L to 115.5 (95% CI 86.3, 111.5) nmol/L at 6 wk. - Median PTH decreased significantly from 51.3 (95% CI 46.7, 71.5) to 37.1 (29.0, 54.6) pg/ml at 6 wk. - Serum calcium and phosphorus did not change significantly.
Belostotsky; 2009[67]	CKD stage not specified Age: 13.6± 3.4 y	20	Manchester, UK	D_2 orally 100,000 IU stat	Single dose	- 25(OH)D increased from 3.8 –39.5 nmol/L to 17.5 – 64 nmol/L at wk 12.

25(OH)D: 25-hydroxyvitamin D; PTH: Parathyroid hormone; ALP: Alkaline phosphatase

Table 5A - Systematic reviews of native vitamin D versus placebo in adults with chronic kidney disease 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; 2012[73]	8 x RCTs 9 x observational (5 prospective, 4 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 greater than 2,000 IU/day of vitamin D. - PTH significantly decreased in eight studies with a variety of dosing protocols including both D_2 and D_3.	- Studies were mostly of low to moderate quality.
Kandula; 2011[57]	5 x RCTs	CKD stages 2-5D + transplanted Adults	264	25(OH)D	Random	13.9 ng/ml (5.6, 22.4)	- Significant increase in 25(OH)D levels with vitamin D supplementation and an associated decline in PTH. - No significant change in serum calcium, phosphorous, levels with vitamin D supplementation. - Low incidence of hypercalcemia and hyperphosphatemia 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.
				PTH	Random	−31.5 pg/ml, (−57.0, −6.1)		
	17 x observational	CKD stages 3-5D + transplanted Adults	1329	25(OH)D	Random	24.1 ng/ml (19.6, 28.6)		
				PTH	Random	-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, RCT: randomised controlled trial; 25(OH)D: 25-hydroxyvitamin D; PTH: Parathyroid hormone

Table 5B - Randomised controlled trials of native vitamin D versus placebo or no treatment in adults with chronic kidney disease and on dialysis
(**Include only articles published since publication of the systematic reviews listed in Table 5A)**

Author; Year	Population, Gender, Age	*N*	City, Country	Intervention	Comparator	Duration of treatment	Results
Thimachai; 2015[79]	CKD stages 3-4 Male: 53% Age: Intervention group: 65.9 ± 15.5 y Comparator group: 66.7 ± 15.4 y	68	Bangkok, Thailand	D_2 orally Double the dosage of NKF-KDOQI	D_2 orally Dosing as per NKF-KDOQI	8 wk	- 25(OH)D increased significantly from 52.5 ± 16.7 nmol/L to 83.5 ± 22.3 nmol/L at wk 8 in the intervention group and increased from 52.1 ± 18 nmol/L to 58.6 ± 19.7 nmol/L in the control group. - PTH levels significantly decreased at wk 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; 2014[78]	CKD stage 5D Male: 53% Age: Intervention group: 63 (52-79) y Comparator group: 46 (29-79) y	19	Warsaw, Poland	D_3 orally 2000 IU three times a week	No treatment	52 wk	- 25(OH)D levels increased significantly from 28.3 to 112.3 nmol/L at 52 wk 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 bone mineral density remained unchanged in both groups.
Bansal; 2014[74]	CKD stages 5D Male: Not reported Age: Intervention group: 75 ± 9 y	35	Haryana, India	D_3 orally 60,000 IU/wk	No treatment	6 wk	- 25(OH)D levels increased significantly from 24 ± 19 to 48.7 ± 10.7 nmol/L at 6 wk in the D_3 group and no significant change in the control group. - No significant changes in serum calcium and PTH in both groups.

	Comparator group: 73 ±12 y						
Delanaye; 2013[75]	CKD stage 5D Male: 70% Age: Intervention group: 75 ± 9 y Comparator group: 73 ±12 y	30	Liège, Belgium	D_3 orally 25,000 IU every 2 weeks	Placebo	52 wk	- At 52 wk, 75% of patients in the D_3 group achieved 25(OH)D ≥ 75 nmol/l, compared to 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 controls). - No significant changes in serum calcium and phosphate in both groups. - No incidence of hypercalcaemia
Gravesen; 2013[76]	CKD stages 4-5 Male: Not reported Age: Not reported	43	Copenhagen, Denmark	D_2 orally 50,000 IU/wk (*N*=26)	No treatment (*N*=17)	6 wk	- 25(OH)D levels increased significantly from < 10 to 90 ± 4 nmol/L at 6 wk in the D_2 group and no change in the control group. - No significant changes in serum calcium, phosphate, PTH and fibroblast growth factor 23 in both groups.
Marckmann; 2012[77]	CKD stage 1-5D, Tx Male: 75% Age: Intervention group: 71 (62-78) y Comparator group: 68 (59-76) y	52	Odense, Denmark	D_3 orally 40,000 IU/wk	Placebo	8 wk	- 25(OH)D levels increased significantly from 23.8 (17.2-41.4) to 154.7 (81.4-240.3) nmol/L at 8 wk in the D_3 group and no change in the controls. - In non-haemodialysis patients, there was a significant decreased in PTH on the D_3 group. - PTH changes were small and insignificant in haemodialysis patients. - Serum calcium and fibroblast growth factor 23 increased significantly in the D_3 group.

Tx: transplant; 25-hydroxyvitamin D; PTH: Parathyroid hormone

To convert nmol/L to ng/ml divide by 2.5

Table 6A – Studies of vitamin D_2 versus vitamin D_3 supplementation in children without chronic kidney disease

Author; Year	Study design	Population, Age	*N*	Intervention	Comparator	Duration of treatment	Results	Potential bias/ limitations
Gallo; 2013[82]	RCT	Healthy, 1 mo	52	D_3 orally 400 IU/day	D_2 orally 400 IU/day	12 wk	- Increase in 25(OH)D levels between the D_2 and D_3 groups did not differ at wk 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 % in each group) - No safety follow up
Thacher; 2010[84]	Prospective cohort	Healthy with nutritional rickets, 15 – 120 mo	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 metabolised more rapidly than D_3. 25(OH)D levels maintained above 75nmol/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 mo	21	D_3 orally 50,000 IU stat	D_2 orally 50,000 IU stat	Single dose		
Gordon; 2008[83]	RCT	Healthy, 8 – 24 mo	40	D_3 orally 2,000 IU/day	D_2 orally 2,000 IU/day D_2 orally 50,000 IU/wk	6 wk	- Increase in 25(OH)D levels between the D_2 and D_3 groups did not differ at wk 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.

RCT: randomised controlled trial; 25(OH)D: 25-hydroxyvitamin D; PTH: Parathyroid hormone; ALP: Alkaline phosphatase

Table 6B – Meta-analysis of native vitamin D_2 versus vitamin D_3 supplementation in adults without chronic kidney disease

Author; Year	No. of studies	Population	*n, N*[a]	Meta-analysis model	Mean difference of meta-analysis (95% CI)	Results	Potential bias / limitations
Tripkovic; 2012[85]	7 x RCTs	Adults	344, 442	Random	15.23 (6.12, 24.34)	- D_3 is more efficacious at raising serum 25(OH)D concentrations than is 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.

[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.
CI: confidence interval, RCT: randomised controlled trial; 25(OH)D: 25-hydroxyvitamin D

Table 6C – Studies of vitamin D_2 versus vitamin D_3 supplementation in adults with chronic kidney disease (CKD)

Author; Year	Study design	Population, Gender, Age	*N*	Intervention	Comparator	Duration of treatment	Results
Daroux; 2013[86]	RCT	CDK stage 5D Male: 67% Age: Intervention group: 68.5 ± 14 y Comparator group 65.3 ± 14.3 y 66.4 ± 18.6 y	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 wk	- Increase in 25(OH)D levels was significantly higher in the D_3 group compared to either of the D_2 groups at wk 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.

RCT: randomised controlled trial; 25(OH)D: 25-hydroxyvitamin D

Table 7 – Recommendations for native D treatment from renal guidelines on chronic kidney disease metabolic bone disease

	European Renal Best Practice Group (2010)[89]	KDIGO (2009)[3]	NKF-KDOQI (2005)[12]
Deficiency defined as	< 30 nmol/L*	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 vs. 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: 8,000 IU/day orally for 4 weeks then 4,000 IU/day orally for 8 weeks 12.5 – 37.5 nmol/L: 4,000 IU/day orally for 12 weeks 40 - 75 nmol/L: 2,000 IU/day orally for 12 weeks
Maintenance regimens			
Age 1 month to 18 years	As per general population	As per general population	Weekly doses OR Supplement with vitamin D containing multivitamin preparation

KDIGO: Kidney disease improving global outcomes, NKF-KDOQI: National Kidney Foundation–Kidney Disease Outcomes Quality Initiative; 25(OH)D: 25-hydroxyvitamin D

* To convert nmol/L to ng/ml divide by 2.5

Table 8 – Suggested treatment for vitamin D supplementation in children with chronic kidney disease and on dialysis

<table>
<tr><th colspan="4">Intensive replacement phase</th></tr>
<tr><th>Age</th><th>25(OH)D serum (nMol/L)***</th><th>Vitamin D supplementation dose (daily)</th><th>Monitoring</th></tr>
<tr><td>< 1 year</td><td></td><td>600 IU / day*</td><td rowspan="4">- Serum calcium and urinary calcium levels 1-3 monthly based on CKD stage
- 25(OH)D levels: after 3 months</td></tr>
<tr><td rowspan="3">>1 year*</td><td>< 12</td><td>8000 IU / day</td></tr>
<tr><td>12 - 50</td><td>4000 IU / day</td></tr>
<tr><td>50 – 75</td><td>2000 IU / day</td></tr>
<tr><th colspan="4">Maintenance phase</th></tr>
<tr><td>< 1 year</td><td rowspan="2">>75****</td><td>400 IU / day</td><td rowspan="2">- 25(OH)D levels: 6-12 monthly</td></tr>
<tr><td>>1 year**</td><td>1000 - 2000 IU /day based on CKD stage</td></tr>
</table>

25(OH)D: 25-hydroxyvitamin D

* In infants under 1 year a fixed dose is recommended irrespective of the level of 25(OH)D

** Consider adjusting dose by body size (weight or body surface area)

*** To convert nMol/L to ng/ml divide by 2.5

**** If levels remain <75nmol/L, then give doses as per the 'Intensive replacement' schedule for a further course of intensive replacement and recheck levels