Table 1A – Systematic review of RCTs of active vitamin D therapy in children with chronic kidney disease (CKD) stages 2-5D
(Note: In the Hahn 2015 review, additional interventions were compared as well as other non-skeletal outcomes.)

Author; Year	No. of studies	Population, Age	*N*	Outcomes	Results
Hahn; 2015 (13)	18 x RCTs	CKD stage 2-5D Children	576	Bone disease	- Treatment with calcitriol by both intraperitoneal and oral routes was effective in improving bone histology (Salusky 1998). However both treatments used intermittently and in high dose increased the number of children with adynamic bone disease (Salusky 1998). - Qualitative description of bone histology indicated improvement in children treated with vitamin D sterols (1α-hydroxyvitamin D) (Eke 1983; Watson 1988). - No significant differences in bone histology were detected in studies comparing calcitriol and doxercalciferol (Salusky 2005).
				Growth	- Growth rates and bone formation rate did not differ between intraperitoneal and oral routes (Jones 1994, Salusky 1998). - No differences in height standard deviation score were found between oral daily or oral intermittent calcitriol therapy (Schmitt 2003). - No significant differences in growth rates (GFRD Study 1990; Hodson 1985) were detected in studies comparing different vitamin D sterols (calcitriol, dihydrotachysterol, ergocalciferol).
				Parathyroid hormone (PTH) control	- Intraperitoneal calcitriol lowered PTH levels significantly more than oral calcitriol in one study (Salusky 1998), but no significant difference was found in another (Jones 1994). - No differences in PTH levels were found between oral daily or oral intermittent calcitriol therapy (Klaus 1995; Ardissino 2000; Schmitt 2003). - Vitamin D sterols given orally or intravenously resulted in reduced PTH levels compared with placebo or no specific treatment.
				Biochemical parameters	- The number of children with hypercalcaemia or the number of hypercalcaemic episodes did not differ between intraperitoneal and oral routes (Jones 1994, Salusky 1998). - No differences in the number of children with hypercalcaemia or the number of hypercalcaemic episodes were found between oral daily or oral intermittent calcitriol therapy (Klaus 1995; Ardissino 2000; Schmitt 2003). - Hypercalcaemic episodes were more common with intravenous calcitriol when compared to placebo (Greenbaum 2005). - Increased risk of hypercalcaemia was not reported with 1α-hydroxyvitamin D or paricalcitol (Greenbaum 2007).

Table 1B - Randomised controlled trial of active vitamin D therapy in children with chronic kidney disease (CKD) (All studies listed were included in the systematic review by Hahn *et al.* 2015)

Author; Year	Population, Gender, Age	*N* (I, C)	Country	Intervention (I)	Comparator (C)	Duration of treatment	Results
Greenbaum; 2007 (23)	CKD stage 5D Male: 76% Age: I: 13.6 ± 4.76 y C: 14.3 ± 4.15 y	29 (15,14) 17 did not complete study	USA	Paricalcitol intravenously thrice weekly (Initial dose: 0.04 mcg/kg if PTH ≤ 500, and 0.08 mcg/kg if PTH ≥ 500) Dose altered according to PTH and calcium or calcium phosphate levels	Placebo intravenously thrice weekly	12 weeks	- Paricalcitol significantly increased the number of children who achieved a 30% fall in PTH levels on at least two occasions during the study. (RR: 2.80 (95% 0.95 to 8.28) - No significant difference in changes in levels of serum calcium, calcium-phosphorous product, phosphorous between groups. - No significant difference in the number of hypercalcaemia between groups.
Greenbaum; 2005 (22)	CKD stage 5D Male: 66% Age: I: 15.3 ± 2.8 y C: 14.0 ± 3.8 y	47 (21,26) 19 lost to follow up	USA	Calcitriol intravenously thrice weekly (Initial dose: 0.5 mcg if PTH < 500 pg/ml, 1.0 mcg if PTH 500 to 1000 pg/ml, 1.5 mcg if PTH > 1000 pg/ml) Dose altered according to PTH and calcium or calcium phosphate levels	Placebo intravenously thrice weekly	12 weeks	- Calcitriol significantly increased the number of children who achieved a 30% fall in PTH levels on at least two occasions (RR: 2.72 (95% 1.12 to 6.61). - Changes in mean PTH levels during treatment were not significantly different between groups - Significant greater risk of hypercalcaemia (RD: 0.24 95% CI 0.05 to 0.43) and elevated serum calcium-phosphorus products (RD: 0.34, 95% CI 0.12 to 0.56) in children treated with calcitriol - No significant difference in number with hyperphosphataemia between groups. - Bone ALP was significantly reduced following IV calcitriol (MD: -47.70 µg/L, 95% CI -88.54 to -6.86). - No significant difference in changes in levels of serum calcium, calcium-phosphorous product, phosphorous between groups.

Salusky; 2005 (41) (Wesseling-Perry; 2011) (8)	CKD stage 5D Male: 50% Age: 13.9 ± 0.5 y	60 (30,30) 9/60 did not complete study	USA	Doxercalciferol orally thrice weekly	Calcitriol orally thrice weekly	8 months	- No significant difference in bone histology parameters of bone formation rate, percentage eroded bone, percentage osteoid volume, percentage osteoid surface, osteoid maturation time and percentage bone volume between treatment groups. - No significant difference in final PTH levels, but with significant falls in values of PTH in both groups. - No significant difference in final levels of calcium, phosphorus, serum alkaline phosphatase and fibroblast growth factor 23 between treatment groups. - Values of alkaline phosphatise fell significantly while values of fibroblast growth factor 23 rose significantly with both groups. - No differences in episodes of hypercalcaemia were seen between the two vitamin D therapies.
				Initial dose depended on PTH level, then titrated to keep PTH at 300 to 400 pg/mL and Ca 8.4 to 10.2 mg/dL.			
Schmitt; 2003 (37)	CKD stage 3-5 Male: 88% Age: I: 5.5 (2.4-8.4) y C: 5.1 (1.4-9.1) y (Subset of participants included in Ardissino 2000)	29 (14,15) 5/29 lost to follow up	Europe	Calcitriol orally twice weekly (35 ng/kg twice weekly. After 1 month dose adjusted for PTH level)	Calcitriol orally Daily (10ng/kg/day. After 1 month dose adjusted for PTH level)	12 months	- The average weekly dose of calcitriol did not differ between groups (76±34 vs. 62±34 ng/kg) - No significant difference in change in mean height standard deviation score. - Significant decrease in PTH levels in both groups, but no significant differences in the fall in PTH levels at any time points between groups. - No significant difference in mean integrated PTH at 12 months. - No significant differences were found for change in calcium, phosphate, calcium phosphate product and alkaline phosphatase between groups. - No significant difference in the number of

							episodes of hypercalcaemic or hyperphosphataemic between groups.
Ardissino; 2000 (48)	CKD stage 3 - 5 Male: 76% Age: 8.4 ± 4.7 y	59 (30,29) 85 enrolled but only 59 included in 8 week analysis	Europe	Calcitriol orally twice weekly (35 ng/kg twice weekly)	Calcitriol orally daily (10ng/kg/day)	8 weeks	- The dose of calcitriol did not differ between groups (70.1 ± 3.4 ng/kg vs. 69.7 ± 4.3 ng/kg) - No significant differences in the fall in PTH levels at 8 weeks between groups. - No significant differences in the number with reduction in PTH at 8 weeks between groups. - No significant difference in the number of hypercalcaemic or hyperphosphataemic between groups.
Salusky; 1998 (31)	CKD stage 5D Male: 55% Age: I: 12.5 ± 1.1 y I: 13.2 ± 1.3 y	33 (16,17) 13 lost to follow up	USA	Calcitriol Intraperitoneal thrice weekly	Calcitriol orally thrice weekly	12 months	- The dose of calcitriol for the full 12 months of study did not differ between groups. - Bone histology was improved in both groups, 33% of patients developed adynamic bone lesion. - Bone formation rates did not differ significantly between treatment groups. - Mean PTH levels were significantly lower with IP calcitriol compared with oral (MD -501.00 pg/mL, 95% CI -721.54 to -280.46). - Serum total and ionized calcium levels were higher in subjects treated with IP calcitriol, whereas serum phosphorus and alkaline phosphatase levels were higher in those given oral calcitriol. - Maximum calcium levels, and the number of children with hypercalcaemia or hyperphosphataemia did not different between groups. - Growth rate was compared to the 12 pre-study months with daily oral calcitriol (40% lower total weekly dose)
				Initial dose of 1 micrograms thrice weekly			

Jones; 1994 (36)	CKD stage 5D Male: 71% Age: 7.2 ± 5.2 y	7 (7,7)	Canada	Intraperitoneal or oral calcitriol 0.01-0.02 µg/kg/d for 3 months, then crossed over for 3 months	Intraperitoneal or oral calcitriol 0.01-0.02 µg/kg/d for 3 months, then crossed over for 3 months	2 x 3 months cross over study	- Mean height standard deviation score did not differ between groups at 6 mo. - Renal osteodystrophy scores did not differ between groups at 6 months. - No significant differences were found in PTH levels between groups. - No significant differences in serum calcium or phosphate were found between groups. - No significant differences were found in the number of children with hypercalcaemia between groups.
GFRD; 1990 (47) Chan; 1994 (17)	CKD stage 3-4 Male: 67% Age: I: 6 ± 3 y C: 5 ± 3 y	82 (40, 42) 12/94 lost to follow up	USA	Calcitriol orally 20 ng/kg/day	Dihydrotachysterol 15 mcg/kg/day	21.0 ± 12.4 and 22.1 ± 14.8 months	- The mean calcitriol dosage was 17.1 ± 5.9 ng/kg per day or a dihydrotachysterol dosage of 13.8 ± 3.3 micrograms/kg per day. - No significant changes in growth rate during treatment with either calcitriol or dihydrotachysterol. - No significant difference in the number of hypercalcaemia between groups.
				Adjusted for weight every 6 months and for hypercalcaemia/elevated alkaline phosphatase for 12 months			
Watson; 1988 (64)	CKD stage 5D Male: 67% Age: I: 11.6 ± 6.0 y C: 16.4 ± 14.0 y	12 (6,6)	Canada	1α-OH vitamin D orally 10-20 ng/kg/day	Standard treatment	6 months	- Children treated with 1α-OH vitamin D showed reduced osteoid volume. - The number of children with PTH levels above the normal range of 3 to 25 pmol/L (RR: 0.23, 95% CI 0.06 to 0.97) and the mean PTH levels (MD: -55.00 pmol/L, 95% CI -83.03 to -26.97) were significantly lower in treated children compared with controls. - No differences were reported in mean serum calcium and phosphorus levels at the end of treatment.
Hodson; 1985 (29)	CKD stage 2-5D Male: 58%	18 (8,7)	Australia	Calcitriol orally 15 ng/kg/day	Ergocalciferol orally 0.25mg/day	12 months	- No significant differences between treatments in the number with height velocity ≥ expected. - Significant improvement in bone histology in

	Age: not reported			(Dose increased till calcium reached 2.6. Final dose 5 to 30 ng/kg/day)	(Dose increased till serium calcium reached 2.6. Final dose 25 to 100 mch/kg/day)		12 of 18 patients with either vitamin D therapy. 6 patients excluded due to nonadherence and aluminum deposition. No significant differences between treatments in the number with improved bone histology. - No significant differences between treatments in final PTH levels. - No significant difference in changes in levels of serum calcium, phosphorous and alkaline phosphatase between groups. - No significant differences were found in the number of children with hypercalcaemia between groups.
Eke; 1983 (28)	CKD stage 3-4 Male: not reported Age: 10.4 (6.5 – 18) y	16 (8,8) 1 lost to follow up	UK	1α-OH vitamin D (10ng/kg/day)	Calciferol (670 ng/kg/day)	12 months	- Qualitative description of bone histology indicated improvement in children treated with 1α-hydroxyvitamin D. No significant difference was found between groups. - No significant difference in PTH levels at 12 months between groups. - No significant differences in changes in serum calcium, phosphorus, and alkaline phosphatase at 12 months between groups. - No significant differences were found in the number of children with hypercalcaemia between groups.

Table 2 – Systematic reviews of active vitamin D therapy in adults with chronic kidney disease (CKD)

Author; Year	Population	No. of studies	*N*	Treatment	Control	Outcomes	Main results
Cai; 2016 (46)	CKD stage 3-5D Adults	10 x RCTs	734	Paricalcitol	Active non-selective vitamin D receptor activators	Parathyroid hormone (PTH) control	- Paricalcitol showed no significant difference in both PTH reduction (MD -7.78, 95% CI -28.59-13.03, P = 0.46) and the proportion of patients who achieved ≥ 30% reduction of PTH (OR 1.27, 95% CI 0.87-1.85, P = 0.22).
						Biochemical parameters	- No statistical differences were found in terms of serum calcium, episodes of hypercalcemia, serum phosphorus, calcium × phosphorus products, and bone metabolism index.
						Adverse events (AE)	- No statistically significant differences were observed in the incidence of total AEs and serious AEs.
Han; 2013 (43)	CKD stage 2-5D Children and Adults	9 x RCTs	1093	Paricalcitol	Placebo	PTH control	- Paricalcitol treated patients had a statistically significant sustained reduction in serum PTH levels (RR 6.97, 95%CI 5.27-9.23, P < 0.00001)
						Biochemical parameters	- No statistically significant difference in the incidence of hypercalcemia between the groups though a trend towards hypercalcemia was evident in the paricalcitol-treated groups. - No statistically significant difference in the incidence of hyperphosphatemia between the groups. - There was a statistically significant increase in the incidence of an elevated Ca × P product between the paricalcitol- and placebo-treated groups (RR 1.97, 95%CI 1.06-3.67, P=0.03).
Cheng; 2012 (44)	CKD stage 2-5D Adults	9 x RCTs	832	Paricalcitol	Placebo	PTH control	- Compared with placebo, paricalcitol suppressed serum PTH levels (RR, 6.37; 95% CI 4.64-8.74, P<0.001).
						Biochemical parameters	- No statistically significant difference in the incidence of hypercalcaemia between the groups.
						Adverse events (AE)	- Patients receiving paricalcitol therapy did not have an increased risk of AEs and serious AEs.
Zhou; 2009	CKD stage 5D	6 x RCTs	174	Intravenous calcitriol	Oral calcitriol intermittently	PTH control	- No significant differences between the two routes in suppressing PTH levels.

(52)	Adults			intermittently		Biochemical parameters	- No significant differences between the two routes in the incidence of hypercalcemia and hyperphosphatemia. - No significant differences between the two routes in alkaline phosphatise levels.
Palmer; 2009 (20)	CKD stage 5D Adults	60 x RCTs	2773	Vitamin D compounds	Vitamin D compounds/ placebo/no treatment	PTH control	- Established vitamin D compounds (calcitriol, alfacalcidol, or 24,25 dihydroxycholecalciferol) suppressed PTH compared with placebo. - Newer vitamin D compounds (paricalcitol, maxacalcitol, doxercalciferol) lowered PTH compared with placebo. - No recommendation regarding the efficacy of intravenous compared with equivalent oral vitamin D compounds can be made due to limitations of available study data. - Newer vitamin D compounds cannot yet be regarded as superior to existing treatments.
						Biochemical parameters	- Vitamin D compounds compared with placebo were associated with increased risks of hypercalcaemia and hyperphosphataemia (note: findings did not reach statistical significance) - Inadequate data are available on newer vitamin D compounds to determine their 'less calcaemic' or 'non calcaemic' status when compared with calcitriol or alfacalcidol.
Palmer; 2009 (21)	CKD stage 2-5 Adults	16 x RCTs	894	Vitamin D compounds	Vitamin D compounds/ placebo/no treatment	PTH control	- Vitamin D compounds reduced serum PTH concentrations more effectively than placebo and also lowered PTH by 30% below baseline more frequently than placebo. - Newer vitamin D analogues cannot yet be regarded as superior to existing treatments, although they may be at least equivalent for the suppression of PTH.
						Biochemical parameters	- Vitamin D compounds were consistently associated with elevated serum phosphorus and serum calcium. Episodes of hypercalcaemia were more frequent with vitamin D therapy. - Inadequate data are available on newer vitamin D compounds to determine their 'less calcaemic' or 'non calcaemic' status when compared with established vitamin D compounds.