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Interventions for metabolic bone disease in children with chronic kidney disease (Review)

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[Intervention Review]

Interventions for metabolic bone disease in children with chronic kidney disease

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ABSTRACT

Background

Bone disease is common in children with chronic kidney disease (CKD) and when untreated may result in bone deformities, bone pain, fractures and reduced growth rates. This is an update of a review first published in 2010.

Objectives

This review aimed to examine the benefits (improved growth rates, reduced risk of bone fractures and deformities, reduction in PTH levels) and harms (hypercalcaemia, blood vessel calcification, deterioration in kidney function) of interventions (including vitamin D preparations and phosphate binders) for the prevention and treatment of metabolic bone disease in children with CKD.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register to 8 September 2015 through contact with the Trial's Search Co-ordinator using search terms relevant for this review.

Selection criteria

We included randomised controlled trials (RCTs) comparing different interventions used to prevent or treat bone disease in children with CKD stages 2 to 5D.

Data collection and analysis

Data were assessed for study eligibility, risk of bias and extracted independently by two authors. Results were reported as risk ratios (RR) or risk differences (RD) with 95% confidence intervals (CI) for dichotomous outcomes. For continuous outcomes the mean difference (MD) or standardised mean difference (SMD) with 95% confidence intervals (CI) was used. Statistical analyses were performed using the random-effects model.

Main results

This review included 18 studies (576 children); three new studies were added for this update. Adequate sequence generation and allocation concealment were reported in 12 and 11 studies respectively. Only four studies reported blinding of children, investigators or outcome assessors. Nine studies were at low risk of attrition bias and 12 studies were at low risk of selective reporting bias.

Eight different interventions were compared. Two studies compared intraperitoneal (IP) with oral calcitriol. PTH levels were significantly lower with IP compared with oral calcitriol (1 study: MD -501.00 pg/mL, 95% CI -721.54 to -280.46) but the number of children with abnormal bone histology did not differ between treatments. Three studies compared intermittent with daily oral calcitriol. The change in mean height SDS (1 study: MD 0.13, 95% CI -0.22 to 0.48) and the percentage fall in parathyroid hormone (PTH) levels at eight weeks (1 study: MD -5.50%, 95% CI -32.37 to 21.37) and 12 months (1 study: MD -6.00% 95% CI -25.27 to 13.27) did not differ between treatments.

Four studies compared active vitamin D preparations (calcitriol, paricalcitol, 1α-hydroxyvitamin D) with placebo or no specific treatment. One study reported vitamin D preparations significantly reduced PTH levels (-55.00 pmol/L, 95% CI -83.03 to -26.97). There was no significant difference in hypercalcaemia risk with vitamin D preparations compared with placebo or no specific treatment (4 studies, 103 children: RD 0.08 mg/dL, 95% CI -0.08 to 0.24). However, there was heterogeneity (I^2 = 55%) with one study showing a significantly greater risk of hypercalcaemia with intravenous (IV) calcitriol administration. Two studies (97 children) compared calcitriol with other vitamin D preparations and both found no significant differences in growth between preparations.

Two studies compared ergocalciferol in patients with CKD and vitamin D deficiency. Elevated PTH levels developed significantly later in ergocalciferol treated children (1 study: hazard ratio 0.30, 95% CI 0.09 to 0.93) though the number with elevated PTH levels did not differ between groups (1 study, 40 children: RR 0.33, 95% CI 0.11 to 1.05).

Two studies compared calcium carbonate with aluminium hydroxide as phosphate binders. One study (17 children: MD -0.86 SDS, 95% CI -2.24 to 0.52) reported no significant difference in mean final height SDS between treatments. Three studies compared sevelamer with calcium-containing phosphate binders. There were no significant differences in the final calcium, phosphorus or PTH levels between binders. More episodes of hypercalcaemia occurred with calcium-containing binders. One study reported no significant differences between calcitriol and doxercalciferol in bone histology or biochemical parameters.

Authors' conclusions

Bone disease, assessed by changes in PTH levels, is improved by all vitamin D preparations. However, no consistent differences between routes of administration, frequencies of dosing or vitamin D preparations were demonstrated. Although fewer episodes of high calcium levels occurred with the non-calcium-containing phosphate binder, sevelamer, compared with calcium-containing binders, there were no differences in serum phosphorus and calcium overall and phosphorus values were reduced to similar extents. All studies were small with few data available on patient-centred outcomes (growth, bone deformities) and limited data on biochemical parameters or bone histology resulting in considerable imprecision of results thus limiting the applicability to the care of children with CKD.

PLAIN LANGUAGE SUMMARY

Interventions for metabolic bone disease in children with chronic kidney disease

Chronic kidney disease (CKD) resulting in reduced kidney function and the need for dialysis and kidney transplant is associated with abnormalities in serum calcium and phosphorus levels leading to high levels of the parathyroid hormone (PTH) and to bone disease. This may result in bone deformities, bone pain, fractures and reduced growth rates. Commonly used treatments (vitamin D compounds and phosphate binders) aim to prevent or correct these outcomes. However, these treatments may raise levels of blood calcium, allow calcium and phosphorus deposition in blood vessels and lead to early cardiovascular disease, which is known to be a problem in adults with CKD.

This review identified 18 small randomised studies involving 576 children comparing different vitamin D compounds administered via different routes and frequencies and different phosphate binders. Only five studies reported growth rates and no differences were detected between treatments. Bone disease, as assessed by changes in PTH levels, was improved by all vitamin D preparations regardless of preparation or route or frequency of administration. Fewer episodes of high blood calcium levels occurred with the non-calcium-containing binder, sevelamer, compared with calcium-containing binders. As newer treatments for renal bone disease are developed, comparisons with the current standard therapies will be required in well-designed randomised studies in children using outcome measures including those of direct clinical relevance to children and their families such as rates of growth, reduction in bone fractures and bone pain and reduction in calcification in blood vessels.

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) causes disordered regulation of mineral metabolism (Wesseling-Perry 2013). Because this disorder results in renal osteodystrophy and vascular and/or soft tissue calcification, the manifestations of the disorder are now known as chronic kidney disease mineral and bone disorder (CKD-MBD) (Moe 2006). CKD-MBD is defined as a systemic disorder of bone and mineral metabolism due to CKD and manifested by one or a combination of:

- abnormalities of calcium. phosphorus, parathyroid hormone (PTH) or vitamin D metabolism;
- abnormalities in bone turnover, mineralization, volume, linear growth or strength; and
- vascular or other soft tissue calcification.

In children CKD-MBD may be associated with increased fracture rates, reduced linear growth, bony deformities and chronic pain. In a review of 890 children on peritoneal dialysis, 5% had limb deformities, 1.4% had bone pain and 1.5% had vascular calcification (Borzych 2010). Abnormalities of bone turnover, mineralization and volume in CKD-MBD can be quantitated using bone histomorphometry. The predominant lesion noted on bone biopsy in children on dialysis is one of high bone turnover (in 57% to 100% of patients) with low turnover bone disease much less common (4% of patients) (Bakkaloglu 2010; Hodson 1982; Salusky 2005a). Abnormal skeletal mineralization is commonly associated with both high and low turnover bone disease in dialysis patients. Among children with CKD stages 2-4, high turnover bone disease was seen in 29% of children with CKD stage 4 but was not seen in children with stage 2 disease and was uncommon in children with stage 3 disease (Wesseling-Perry 2012; Hodson 1982). In contrast mineralization abnormalities occurred in 43% children with stage 2 CKD and in 86% of children with stage 4 CKD (Wesseling-Perry 2012); these findings confirm previous findings in early stages of CKD (Hodson 1982). Low turnover bone disease is rare in children not on dialysis.

Although bone disease may not be evident on bone histology in early CKD and plasma levels of calcium and phosphorus are normal, increased levels of the hormone fibroblast growth factor 23 (FGF23) (Wesseling-Perry 2013) increase renal phosphate excretion and inhibit 1α-hydroxylase activity thus suppressing circulating levels of 1, 25 $(OH)_2$D leading to increased levels of parathyroid hormone (PTH).

Bone biopsy is an invasive procedure and is now generally limited to research studies so that radiological and biochemical abnormalities are used as surrogate measures of bone disease in CKD-MBD. Radiological diagnosis is insensitive and cannot distinguish low-turnover or adynamic bone disease from the high turnover state of secondary hyperparathyroidism. Biochemical abnormalities of parathyroid hormone, serum calcium and phosphate levels are frequently used as markers of bone disease if outside of the recommended KDOQI or European guideline parameters (KDOQI 2005; Klaus 2006). Abnormalities of these values, suggestive of histological changes, have been demonstrated in 28% to 81% of children with CKD stages 2-5 (Blaszak 2005; Seikaly 2003). These biochemical abnormalities have also been used to specifically diagnose low turnover bone disease. In 41 dialysed children (31 peritoneal dialysis), low turnover bone disease was diagnosed in 48% based on the presence of elevated serum calcium with parathyroid hormone (PTH) values below recommended levels (Avila-Diaz 2006). PTH levels are most commonly used to monitor the effectiveness of therapy. However optimal target ranges are unclear in part because earlier PTH assays measured active and inactive PTH fragments and newer assays still show considerable variation between PTH assays.

In the absence of clinical symptoms and signs, it has been unclear until recently what impact CKD-MBD has on the outcome for children with CKD. Recent data have demonstrated an increased risk of coronary arterial calcification in young adults on dialysis (Goodman 2000) while elevated levels of PTH and phosphate are independent risk factors for left ventricular hypertrophy (Bakkaloglu 2011). These factors have been associated with increased mortality in children and young adults with CKD.

Description of the intervention

Treatment of CKD-MBD aims to normalise mineral metabolism and minimise progression of extraskeletal calcification by maintaining blood levels of calcium and phosphorus close to the normal range for age and maintaining PTH levels at levels considered to be appropriate for the stage of CKD. The mainstays of treatment are with phosphate binders (calcium or non-calcium containing) and vitamin D metabolites (calcitriol, 1α-hydroxyvitamin D, newer vitamin D analogues). Dietary measures are instituted to reduce phosphate intake while maintaining adequate calcium and vitamin D intake. Also calcium levels in the dialysis fluid can be manipulated to maintain normocalcaemia. New agents include calcimimetic agents (cinacalcet), which control secondary hyperparathyroidism. For medically unresponsive patients, parathyroidectomy may be required.

How the intervention might work

Early in the development of CKD, circulating levels of 1,25 $(OH)_2$ vitamin D falls following suppression of the renal enzyme 1-α-hydoxylase by FGF23, resulting in reduced calcium absorption from the gut and increased PTH levels (Wesseling-Perry 2013). Increased PTH levels initially maintain serum calcium levels by increasing bone resorption and by stimulating 1-α-hydoxylase activity. With further decline in glomerular filtration rate (GFR), phosphate levels rise. These lower calcium levels and further suppress renal enzyme 1-α-hydoxylase levels so PTH levels rise further. PTH increases bone turnover leading to renal osteodystrophy. Therefore therapies which increase gut absorption of calcium, reduce phosphate levels and increase circulating levels of 1,25 $(OH)_2$ vitamin D will reduce PTH levels. However both calcium-containing phosphate binders and vitamin D metabolites may cause hypercalcaemia and elevated calcium-phosphorus product and predispose to vascular and soft tissue calcification. Calcimimetic agents modulate the calcium sensitive receptor in parathyroid glands, increase intracellular calcium and decrease PTH release.

Why it is important to do this review

There are a large number of studies reporting the efficacy of various medications and dietary manipulations to prevent and treat CKD-MBD in children and there is extensive clinical experience confirming that current treatment of CKD-MBD has reduced the

severity of bony deformities and fractures over the past few decades. However there remains considerable uncertainty in children about the vascular outcomes related to treatment or non-treatment of CKD-MBD. In addition because of the recognised severity of potential side-effects and the uncertain efficacy of some of the therapeutic agents used to treat CKD-MBD, it is appropriate to critically review the treatment options.

OBJECTIVES

This review aimed to examine the benefits (improved growth rates, reduced risk of bone fractures and deformities, reduction in PTH levels) and harms (hypercalcaemia, blood vessel calcification, deterioration in kidney function) of interventions (including vitamin D preparations and phosphate binders) for the prevention and treatment of metabolic bone disease in children with CKD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (studies in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) examining treatments for the prevention and treatment of CKD-MBD in children and adolescents were included**.**

Types of participants

Inclusion criteria

- Studies involving children with CKD stages 2 to 5D (glomerular filtration rate < 90 mL/min/1.73 m^2)
- Childhood was defined according to the definitions applied in the included studies, but did not exceed 21 years of age.

Exclusion criteria

Studies of children with CKD secondary to primary tubulopathies, e.g. cystinosis, or with diseases known to directly affect bones e.g. primary hyperoxaluria, and studies in children following kidney transplant were excluded. However it is possible that individual children with the above disorders might be included within an eligible study but not specifically specified. Studies of recombinant human growth hormone in children with CKD were excluded as these are included in a separate Cochrane Review (Growth Hormone in children with chronic kidney disease) (Hodson 2012).

Types of interventions

Interventions considered for inclusion were as follows.

- Dietary
- Pharmacological - specifically vitamin D or metabolites, calcimimetic and phosphate binding agents
- Surgical
- Herbal or alternative treatments
- Changes in dialysis prescription.

For each of these interventions the following comparisons were considered.

- Intervention versus placebo
- Intervention A versus intervention B
- Frequency and mode of administration (e.g. oral or intravenous (IV))
- Dose and duration of treatment.

Types of outcome measures

Primary outcomes

Patient-centred outcome measures

- Growth
- Bone fractures
- Bone deformities
- Symptoms related to hypercalcaemia
- Parathyroidectomy

Secondary outcomes

Patient-centred outcome measures

- Commencing dialysis treatment
- Dialysis-related clinical events
- Parathyroidectomy.

Surrogate outcomes

- Change in bone histology
- Changes in radiological abnormalities
- Changes in PTH levels
- Changes in alkaline phosphatase (ALP) levels
- Changes in serum calcium, phosphorus and calcium-phosphorus product
- Changes in FGF23 levels

Adverse events

- Vascular or extraosseous calcifications
- Deterioration of kidney function
- Hyperphosphataemia
- Hypercalcaemia
- Elevation of calcium-phosphorus product
- Radiological deterioration of CKD-MBD
- Development of adynamic bone disease on bone histomorphometry
- Hypertension or hypotension
- Aggravation of anaemia.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register to 8 September 2015 through contact with the Trials Search Co-ordinator using search terms relevant to this review. The Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences

4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies, as well as a list of handsearched journals, conference proceedings and current awareness alerts, are available in the Specialised Register section of information about the Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of clinical practice guidelines review articles and relevant studies.
2. Letters seeking information about unpublished or incomplete studies to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

In the previous version of this review (Geary 2009) all electronically derived abstracts and study titles were assessed for subject relevance and methodological quality. All possible RCTs or quasi-RCTs which were relevant were assigned specific topic keywords in Reference Manager and the full published paper was obtained for full assessment. The review was undertaken by four authors. The search strategy described was used to obtain titles and abstracts of studies that were relevant to the review. The titles and abstracts were screened independently by DG, EH and DH, who discarded studies that were not applicable. However studies and reviews that might include relevant data or information on studies were retained initially. Three authors independently assessed retrieved abstracts, and if necessary, the full text of these studies to determine which studies satisfied the inclusion criteria.

In this update, study titles and abstracts were reviewed by two authors. Full text articles of studies considered relevant were obtained and assessed for eligibility by the same authors.

Data extraction and management

A data abstraction form was devised to record details of data elements such as outcome measures, participants and intervention of each included study for the 2009 review. Only comparisons and outcomes which were pre-specified in the protocol were included. For this review, data were abstracted by a single assessor and a sample was double checked.

For this update, data extraction and assessment of risk of bias were performed by two authors using standardised data abstraction forms. Disagreements not resolved by discussion between authors were referred to a third author. Studies reported in languages other than English were to be translated before data extraction, but no foreign language reports were identified. Where more than one report of a study was identified, data were extracted from all reports. Where there were discrepancies between reports, data from the primary source were used. Study authors were contacted for additional information about studies.

Assessment of risk of bias in included studies

Hard copies of studies were independently assessed for the methodological quality by two assessors for the 2010 review. Quality assessments were made for allocation concealment, blinding, description of withdrawals and drop-outs, numbers lost to follow-up, and whether intention-to-treat (ITT) analysis was possible.

In the 2014 update, the following terms were assessed using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias) ?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (number of children with improved growth, radiological bone changes, improved bone histology) results were expressed as risk ratio (RR) with 95% confidence intervals (CI). For numbers of children experiencing adverse effects, risk difference (RD) with 95% CI was used. For continuous outcomes scales of measurement were used to assess the effects of treatment (levels of PTH, serum levels of calcium, phosphorus and calcium-phosphorus product, and creatinine clearance (CrCl), the mean difference (MD) with 95% CI were calculated unless the scales were different; in this instance, standard mean difference (SMD) was used.

Unit of analysis issues

Data from the first phase of cross-over RCTs could not be separated so results from cross-over studies were reported qualitatively.

Dealing with missing data

We aimed to analyse available data in meta-analyses using intention-to-treat (ITT) data. However, where ITT data were only available graphically or not provided and additional information could not be obtained from study authors, per-protocol (PP) data were used in analyses.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity respectively.

Assessment of reporting biases

Because of the few studies available for each intervention, it was not possible to use funnel plots to assess for the potential existence of small study bias (Higgins 2011).

Data synthesis

Data were pooled using a random-effects model for dichotomous and continuous data.

Subgroup analysis and investigation of heterogeneity

We had planned subgroup analyses to examine certain between-study differences in participants (age, stage of CKD, type of dialysis), interventions (agent, dose and duration of treatment) and risk of bias hypothesised to explain any observed heterogeneity of treatment effects but there were insufficient studies for these to be performed.

Sensitivity analysis

We wished to perform sensitivity analyses in order to explore the influence of the following factors on effect size.

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified
- Repeating the analysis excluding any very long or large studies to establish how much they dominate the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

However except for one analysis, the maximum number of studies included in any analysis was two so we were not able to carry out any sensitivity analyses.

RESULTS

Description of studies

Results of the search

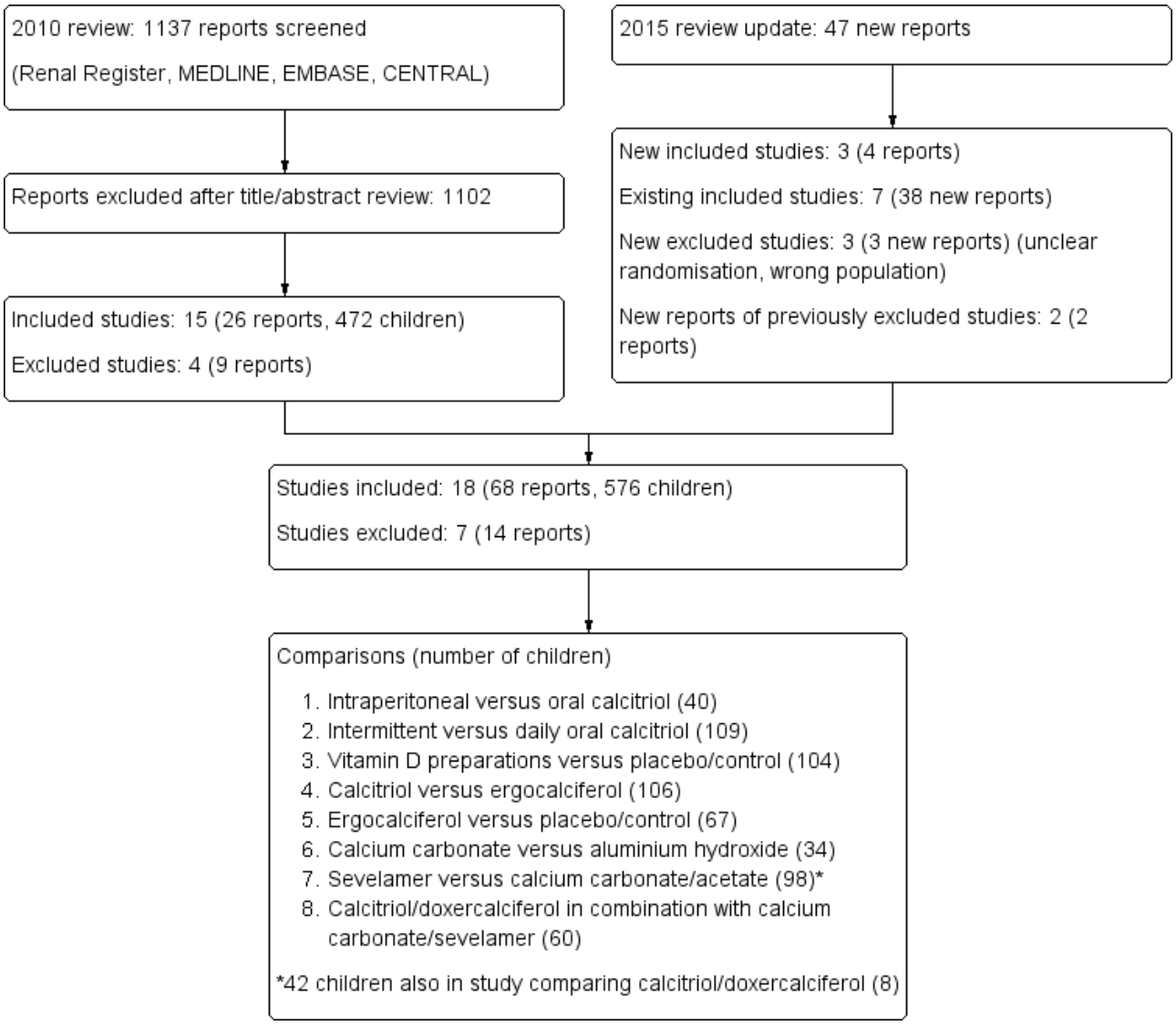
2009 review

In the 2009 review, of the 1137 titles and abstracts identified, 19 studies were identified for full text review. Of these 15 studies (26 reports) (Ardissino 2000; Eke 1983; GFRD Study 1990; Greenbaum 2005; Greenbaum 2007; Hodson 1985; Jones 1994; Klaus 1995; Mak 1985; Pieper 2006; Salusky 1991; Salusky 1998; Salusky 2005; Schmitt 2003; Watson 1988) involved the defined populations and addressed relevant interventions and were included in the review. A copy of the completed manuscript was provided before publication by Greenbaum 2007. Three studies were cross-over studies (Jones 1994; Mak 1985; Pieper 2006), and one study (Klaus 1995) was available in abstract form only. Four studies (nine reports) were excluded for ineligible intervention (Ardissino 2000a), ineligible population (El Husseini 2004; Ferraris 2000) and uncertainty as to whether the study was an RCT (Bettinelli 1986). There was no disagreement between authors regarding inclusion of studies. The 2009 review included 15 studies (26 reports) with 472 children.

2015 update

For the 2015 update 47 new reports were identified (Figure 1). Of these, four reports were of three new studies (Gulati 2010; Rianthavorn 2013; Shroff 2012) and 38 reports were of seven previously included studies (Eke 1983; GFRD Study 1990; Greenbaum 2005; Salusky 1991; Salusky 1998; Salusky 2005; Watson 1988). The remaining five new reports were excluded. Two studies were excluded as the populations were ineligible (Choudhary 2014; Kim 2006b), and in one study (Witmer 1976) randomisation was unclear. The remaining three reports were from two previously excluded studies (Ardissino 2000a; Ferraris 2000).

Figure 1. Study flow diagram



Re-evaluation of Ardissino 2000 and Schmitt 2003 indicated that the data in Schmitt 2003 represented a 12 month follow-up of 29 prepubertal children treated in Ardissino 2000. For ease of identification, we have continued to report these studies as two studies.

To allow analyses of comparisons between calcitriol and doxercalciferol and for separate reporting of the comparison between sevelamer and calcium carbonate in this 2 x 2 longitudinal factorial study, we have divided Salusky 2005 into three studies (Salusky 2005; Salusky 2005a; Salusky 2005b). Salusky 2005 includes the groups treated with sevelamer or calcium carbonate irrespective of vitamin D preparation used. Salusky 2005a includes the two groups treated with doxercalciferol while Salusky 2005b includes the two groups treated with calcitriol.

Therefore the 2015 update included 18 studies (68 reports) with 576 enrolled children.

Included studies

The 18 included studies were divided into eight treatment comparisons (Figure 1).

Intraperitoneal calcitriol versus oral calcitriol

Two studies (40 enrolled; 40 evaluated) compared intraperitoneal compared with oral calcitriol. Children receiving continuous cycling or continuous ambulatory peritoneal dialysis were treated for 12 months (Salusky 1998) or 3 months (Jones 1994). The study by Jones 1994 was a cross-over study and data could not be meta-analysed.

Intermittent oral calcitriol versus daily oral calcitriol

Three studies (109 enrolled; 104 evaluated) compared intermittent oral administration of calcitriol with daily oral administration in children with CKD stages 2 to 5 for 8 to 10 weeks (Ardissino 2000), 12 months (Schmitt 2003), or from 2 to 36 weeks (Klaus 1995).

Different vitamin D preparations versus placebo/no specific treatment

Four studies (104 enrolled; 103 evaluated) compared different vitamin D preparations administered orally or IV with placebo/no specific treatment in CKD patients stages 3 and 4 (Eke 1983) and in patients receiving peritoneal or haemodialysis (Greenbaum 2005; Greenbaum 2007; Watson 1988).

Different vitamin D preparations

Two studies (106 enrolled; 97 evaluated) compared different vitamin D preparations. GFRD Study 1990 compared oral calcitriol with oral dihydrotachysterol in children with CKD stages 3 and 4 treated for 12 months. Hodson 1985 compared oral calcitriol with oral ergocalciferol in children on dialysis or CKD stages 2 to 4.

One study (60 enrolled; 51 evaluated) compared doxercalciferol (Salusky 2005a) and calcitriol (Salusky 2005b) in combination with either sevelamer or calcium carbonate. Comparisons were reported for vitamin D preparations irrespective of the phosphate binder given.

Ergocalciferol versus placebo/control

Two studies (67 enrolled; 60 evaluated) compared ergocalciferol with placebo/no specific treatment in patients with CKD stages 2 to 5D (Rianthavorn 2013; Shroff 2012). In Rianthavorn 2013 the primary outcome was reduction in the dose of erythrocyte-stimulating agent (ESA).

Calcium carbonate versus aluminium hydroxide

Two studies (34 enrolled; 29 evaluated) compared calcium hydroxide with calcium carbonate in pre-dialysis children (Mak 1985) or those receiving peritoneal dialysis (Salusky 1991).

Sevelamer versus calcium-containing phosphate binders

Three studies (98 enrolled; 66 evaluated) compared sevelamer with calcium-containing phosphate binders in children with CKD stages 2 to 4 (Gulati 2010) or receiving dialysis (Pieper 2006; Salusky 2005) compared the non-calcium-containing sevelamer with calcium carbonate (Salusky 2005) or calcium acetate (Gulati 2010; Pieper 2006). In Salusky 2005, children were also randomised to receive doxercalciferol or calcitriol. Factorial analysis provided no evidence of treatment interaction between the two sterols so comparisons were reported for phosphate binders irrespective of vitamin D sterol given.

No RCTs examining interventions with dietary changes, surgery, alterations in dialysis prescription or calcimimetic agents were identified.

Excluded studies

Seven studies were excluded (Ardissino 2000a; Bettinelli 1986; Choudhary 2014; El Husseini 2004; Ferraris 2000; Kim 2006b; Witmer 1976). One cross-over study (Ardissino 2000a) in children with CKD examined calcium absorption only after oral or IV calcitriol. Two studies examined bone mineral density in kidney transplant patients treated with calcitonin, alendronate or 1α-hydroxyvitamin D (El Husseini 2004) or with methylprednisolone or deflazacort (Ferraris 2000). Randomisation was unclear and data was no longer available in Witmer 1976.

Risk of bias in included studies

Figure 2; Figure 3

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies

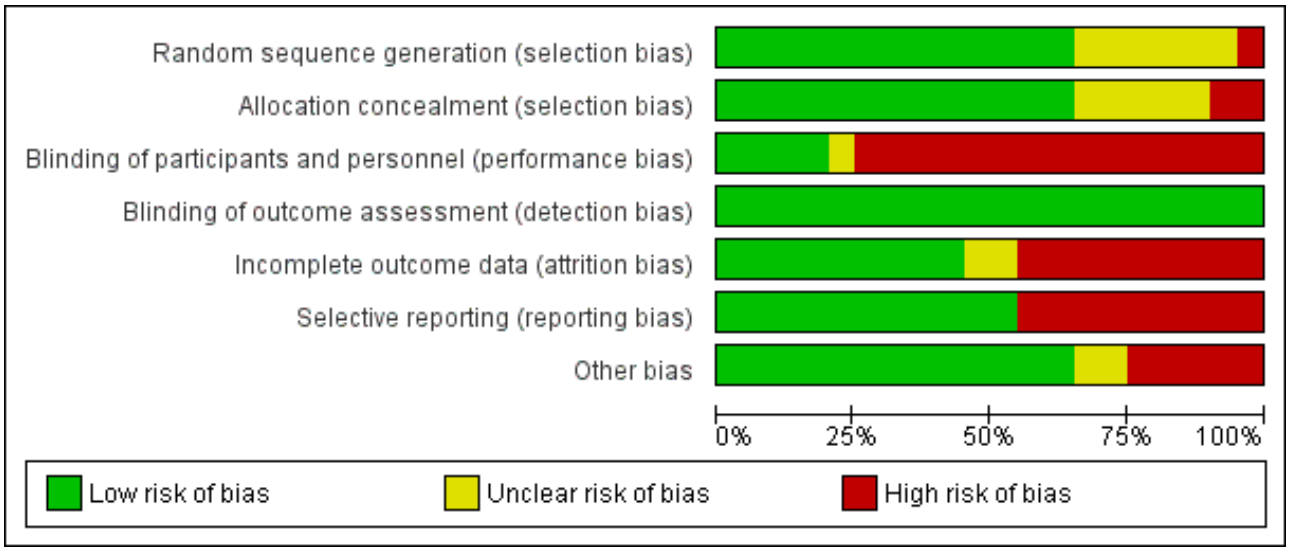


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study

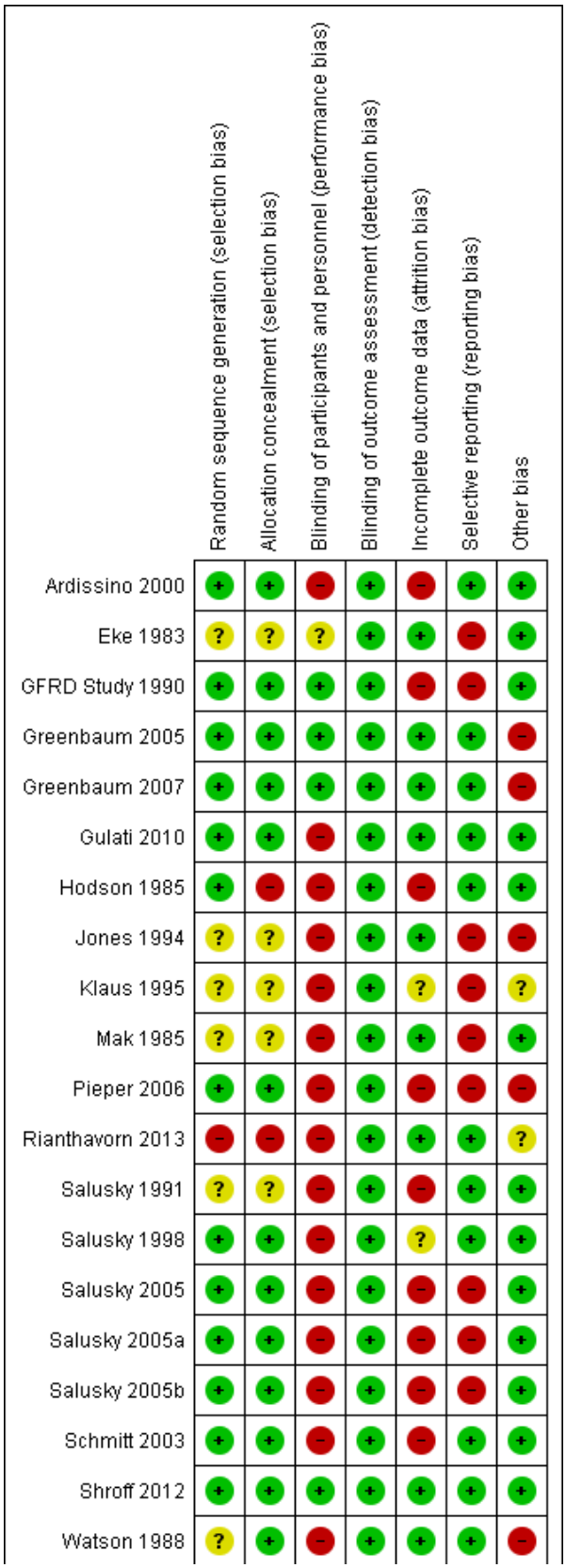
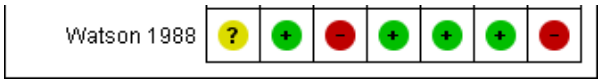


Figure 3. (Continued)



Allocation

Sequence generation was deemed to be at low risk of bias in 12 studies (Ardissino 2000; GFRD Study 1990; Greenbaum 2005; Greenbaum 2007; Gulati 2010; Hodson 1985; Pieper 2006; Salusky 1998; Salusky 2005; Schmitt 2003; Shroff 2012; Watson 1988). One study was at high risk of bias as patients were randomised sequentially (Rianthavorn 2013). In the remaining five studies, the sequence generation methodology was unclear.

Allocation concealment was at low risk of bias in 11 studies (Ardissino 2000; GFRD Study 1990; Greenbaum 2005; Greenbaum 2007; Gulati 2010; Pieper 2006; Salusky 1998; Salusky 2005; Schmitt 2003; Shroff 2012; Watson 1988). Two studies (Hodson 1985; Rianthavorn 2013) were considered at high risk of bias. Allocation concealment methodology was unclear in the remaining five studies (Eke 1983; Jones 1994; Klaus 1995; Mak 1985; Salusky 1991).

Blinding

Four studies were blinded and considered to be at low risk of bias for performance bias (GFRD Study 1990; Greenbaum 2005; Greenbaum 2007; Shroff 2012). Blinding was unclear in one study, which was reported to be double-blinded but did not clarify how this was achieved (Eke 1983). The remaining thirteen studies were not blinded and were considered at high risk of performance bias.

Since the primary outcomes (PTH level, bone mineralization) in all studies were based on laboratory assessment, and unlikely to be influenced by blinding, all included studies were considered to be at low risk of detection bias.

Incomplete outcome data

Nine studies were considered at low risk of attrition bias (Eke 1983; Greenbaum 2005; Greenbaum 2007; Gulati 2010; Jones 1994; Mak 1985; Rianthavorn 2013; Shroff 2012; Watson 1988). Seven studies were considered at high risk of attrition bias with more than 15% loss to follow-up or exclusion from analysis (Ardissino 2000; GFRD Study 1990; Hodson 1985; Pieper 2006; Salusky 1991; Salusky 2005; Schmitt 2003). In the remaining two studies attrition bias was considered unclear (Klaus 1995; Salusky 1998). Loss to follow-up or exclusion resulted commonly when children on dialysis underwent kidney transplant. Other reasons for exclusion were non-adherence to treatment, protocol violation or withdrawal by families or physicians.

Selective reporting

Studies were considered to be at high risk of reporting bias if they did not provide data on final or change in PTH, calcium, phosphorus, calcium-phosphorus product or ALP levels, bone histology, patient centred outcomes such as fractures or growth, adverse events such as hypercalcaemia or all-cause mortality. Seven studies were considered at high risk of reporting bias (Eke 1983; GFRD Study 1990; Jones 1994; Klaus 1995; Mak 1985; Pieper 2006; Salusky 2005). The remaining 11 studies were considered to be at low risk of reporting bias.

Other potential sources of bias

Eleven studies appeared to be free of other potential sources of bias (Ardissino 2000; Eke 1983; GFRD Study 1990; Gulati 2010; Hodson 1985; Mak 1985; Salusky 1991; Salusky 1998; Salusky 2005; Schmitt 2003; Shroff 2012). Five studies were funded by industry and considered at high risk of bias (Greenbaum 2005; Greenbaum 2007; Jones 1994; Pieper 2006; Watson 1988). In the remaining two studies, it was unclear whether the study was free of other potential sources of bias (Klaus 1995; Rianthavorn 2013).

Effects of interventions

Intraperitoneal versus oral calcitriol

Two studies investigated this comparison (Salusky 1998; Jones 1994) (Table 1). The first study (Jones 1994) compared IP with oral calcitriol in a cross-over study including seven children and reported that mean height standard deviation score (SDS) did not differ between groups at the end of the study. The data for each part of the cross-over could not be separated.

Salusky 1998 reported no significant differences in the number of children overall with abnormal bone histology (Analysis 1.1.1 (1 study, 33 children): RR 1.06, 95% CI 0.70 to 1.61), the number with adynamic bone disease (Analysis 1.1.2 (1 study, 33 children): RR 1.49, 95% CI 0.59 to 3.74), osteitis fibrosa (Analysis 1.1.3 (1 study, 33 children): RR 0.35, 95% CI 0.08 to 1.51), mixed or mild disease (Analysis 1.1.4 (1 study, 33 children): RR 0.46, 95% CI 0.14 to 1.46) or normal/reduced bone formation rates (Analysis 1.1.5 (1 study, 33 children): RR 1.06, 95% CI 0.66 to 1.72).

Salusky 1998 reported bone formation rates did not differ significantly between treatment groups (Analysis 1.2 (1 study, 33 children): MD -289.00 $\mu m^2/mm^2/d$, 95% CI -806.13 to 228.13).

Jones 1994 (cross-over RCT) reported that no significant differences were found in PTH levels, the number of children with hypercalcaemia and the number of peritonitis episodes between groups (Table 1). Salusky 1998. reported mean PTH levels were significantly lower with IP calcitriol compared with oral (Analysis 1.3 (1 study, 33 children): MD -501.00 pg/mL, 95% CI -721.54 to -280.46).

Salusky 1998 reported maximum serum calcium levels (Analysis 1.4 (1 study, 33 children): MD 0.70 mg/dL, 95% CI -0.55 to 1.95) and the number of children with hypercalcaemia (Analysis 1.5.1 (1 study, 33 children): RD 0.21, 95% CI -0.12 to 0.53) or hyperphosphataemia (Analysis 1.5.2 (1 study, 33 children): RD -0.05, 95% CI -0.29 to 0.19) did not differ between treatment groups. The number of peritonitis episodes/patient-month did not differ between treatment groups (Analysis 1.6 (1 study, 33 children): RD 0.01, 95% CI -0.24 to 0.26).

Intermittent oral versus daily oral calcitriol

Three parallel studies (104 evaluated children) compared intermittent oral with daily oral calcitriol (Ardissino 2000; Klaus 1995; Schmitt 2003) (Table 2).

Schmitt 2003 reported no significant difference in change in mean height SDS (Analysis 2.1 (1 study, 24 children): MD 0.13, 95% CI -0.22 to 0.48). No significant differences between treatment routes were found for any surrogate biochemical outcome.

Ardissino 2000 and Schmitt 2003 reported no significant differences in the fall in PTH levels at 8 weeks (Analysis 2.2.1 (Ardissino 2000, 59 children): MD -5.50%, 95% CI -32.37 to 21.37) and 12 months (Analysis 2.2,2 (Schmitt 2003, 48 children): MD -6.00%, 95% CI -25.27 to 13.27), the number with reduction in PTH (Analysis 2.3 (Ardissino 2000, 59 children): RR 0.88, 95% CI 0.65 to 1.19) and the mean integrated PTH levels (Analysis 2.4 (Schmitt 2003, 24 children): MD -58.00 pg/mL, 95% CI -212.55 to 96.55). In Klaus 1995, median (range) PTH levels fell significantly in both treatment groups with no differences between treatment groups (Table 2).

There were no significant differences in CrCl at eight weeks (Analysis 2.5.1 (Ardissino 2000, 59 children): MD 0.50 mL/min/1.73 m^2, 95% CI -5.72 to 6.72) or 12 months (Analysis 2.5.2 (Schmitt 2003, 24 children): MD 1.50 mL/min/1.73 m^2, 95% CI -2.04 to 5.04,), or in numbers with hypercalcaemia (Analysis 2.6.1 (2 studies, 80 children): RD -0.02, 95% CI -0.17 to 0.13; I^2 = 19%) or hyperphosphataemia (Analysis 2.6.2 (Ardissino 2000, 59 children): RD 0.03, 95% CI -0.06 to 0.12). Schmitt 2003 reported no difference in the number of episodes of hypercalcaemia or hyperphosphataemia between the treatment groups.

Active vitamin D preparations versus placebo or no specific treatment

Four parallel studies compared active vitamin D preparations (calcitriol, paricalcitol, 1α-hydroxyvitamin D) with placebo or no specific treatment (Table 3) (Eke 1983; Greenbaum 2005; Greenbaum 2007; Watson 1988). None of the studies reported any data for patient-centred outcomes.

Two parallel studies (28 children) compared 1α-hydroxyvitamin D with no specific treatment (Eke 1983; Watson 1988). Though only 1/8 children treated with 1α-hydroxyvitamin D versus 5/7 not treated had abnormal bone histology at the end of treatment, the difference was not significant due to small numbers (Analysis 3.1 (Eke 1983, 15 patients): RR 0.17, 95% CI 0.03 to 1.16). This study reported no significant difference in PTH levels at the end of the study (Table 3). Watson 1988 reported children treated with 1α-hydroxyvitamin D showed reduced osteoid volume and both the number of children with PTH levels above the normal range of 3 to 25 pmol/L (Analysis 3.2 (12 children): RR 0.23, 95% CI 0.06 to 0.97) and the mean PTH levels (Analysis 3.3 (12 children): MD -55.00 pmol/L, 95% CI -83.03 to -26.97) were significantly lower in treated children compared with controls.

Two parallel studies (57 children) compared IV calcitriol (Greenbaum 2005) or IV paricalcitol (Greenbaum 2007) given three times/week with placebo. IV vitamin D preparations (calcitriol or paricalcitol) significantly increased the number of children who achieved a 30% fall in PTH levels on at least two occasions during the study (Analysis 3.4 (2 studies, 76 children): RR 2.75, 95% CI 1.39 to 5.47; I^2 = 0%). However changes in mean PTH levels during treatment were not significantly different in children treated with IV calcitriol compared with placebo (Analysis 3.5 (1 study, 47 children): MD -203.00 pg/mL, 95% CI -506.34 to 100.34). An analysis of mean PTH levels following paricalcitol therapy was not possible as standard deviations were not provided.

Overall there was no significant difference in the risk of hypercalcaemia with vitamin D preparations compared with placebo/no specific treatment (Analysis 3.6 (4 studies, 103 children): RD 0.08, 95% CI -0.08 to 0.24; I^2 = 55%). However there was heterogeneity with one study showing a significantly greater risk of hypercalcaemia in children treated with IV calcitriol. Following IV calcitriol, the number of children with elevated serum calcium-phosphorus products (Analysis 3.7 (Greenbaum 2005, 47 children): RD 0.34, 95% CI 0.12 to 0.56) was increased compared with placebo while there was no significant difference in number with hyperphosphataemia (Analysis 3.8 (Greenbaum 2005, 47 children): RD 0.25, 95% CI -0.02 to 0.52). Mean changes in levels of serum calcium (Analysis 3.9.1 (2 studies, 76 children): MD 0.10 mg/dL, 95% CI -0.45 to 0.65; I^2 = 50%), serum calcium-phosphorus product (Analysis 3.9.2 (2 studies. 76 children): MD 0.45 mg^2/dL^2, 95% CI -7.94 to 8.83; I^2 = 42%) and serum phosphorus (Analysis 3.9.3 (2 studies, 76 children): MD -0.01 mg/dL, 95% CI -0.66 to 0.63; I^2 = 0%) did not differ between children treated with IV calcitriol or paricalcitol and placebo. Bone ALP was significantly reduced following IV calcitriol (Analysis 3.9.4 (Greenbaum 2005, 41 children): MD -47.70 µg/L, 95% CI -88.54 to -6.86). In the studies of 1α-hydroxyvitamin D no differences were reported in mean serum calcium or phosphorus levels at the end of treatment but only graphical data or data without standard deviations were provided (Table 3).

Calcitriol versus dihydrotachysterol or ergocalciferol

One study (82 children) compared the effect of calcitriol and dihydrotachysterol on growth, GFR and the number of episodes of hypercalcaemia (GFRD Study 1990). Data on growth and GFR were reported as changes in slopes of growth rates so were not amenable to meta-analysis. Growth rates did not differ between treatment groups. GFR fell during treatment in both groups but there was no difference between groups. There was no significant difference in the number of episodes of hypercalcaemia between groups (Table 4).

Hodson 1985 compared calcitriol with ergocalciferol and found no significant differences between treatments in the number with height velocity ≥ expected (Analysis 4.1 (15 children): RR 0.22, 95% CI 0.03 to 1.53), in the number with improved bone histology (Analysis 4.2 (15 children): RR 1.53, 95% CI 0.77 to 3.06) and in final PTH levels (Analysis 4.3 (15 children): MD -0.48 ng/mL, 95% CI -1.23 to 0.27). The number of children with hypercalcaemia did not differ between groups (Analysis 4.4 (15 children): RR 1.75, 95% CI 0.68 to 4.50). The mean levels of serum calcium (Analysis 4.5.1 (15 children): MD 0.18 mmol/L, 95% CI 0.01 to 0.35), serum phosphorus (Analysis 4.5.2 (15 children): MD -0.34 mmol/L, 95% CI -0.76 to 0.08) and serum ALP (Analysis 4.5.3 (15 children): MD -39.00 U/L, 95% CI -116.63 to 38.63) at the end of the study did not differ between groups.

Ergocalciferol (replacement doses) versus placebo or no treatment

Two studies (Rianthavorn 2013; Shroff 2012) compared ergocalciferol in patients with CKD and vitamin D deficiency. Fewer children treated with ergocalciferol developed secondary hyperparathyroidism but the difference was not significant due to small patient numbers (Analysis 5.1 (Shroff 2012, 40 children): RR 0.33, 95% CI 0.11 to 1.05). However the time to development of hyperparathyroidism was significantly longer in children treated

with ergocalciferol compared with placebo (hazard ratio 0.30, 95% CI 0.09-0.93) (Shroff 2012). There were no significant differences between treatment groups in final PTH (Analysis 5.2 (Rianthavorn 2013, 20 children): MD -1.16 pg/mL, 95% CI -1.04 to 0.71), phosphorus levels (Analysis 5.4 (2 studies, 60 children): MD -0.29 mg/dL, 95% CI -0.96 to 0.39; I^2 = 0%) and final calcium (Analysis 5.3 (2 studies, 60 children): MD 0.26 mg/dL, 95% CI -0.28 to 0.81; I^2 = 42%). Vitamin D (1,25 (OH)) levels (Analysis 5.5 (Shroff 2012, 40 children): MD 27.00 pmol/L, 95%CI 17.35 to 36.65) were significantly higher in the treatment group compared to control group though the differences were not clinically important. Both studies reported no adverse effects related to ergocalciferol and no child developed hypercalcaemia.

Phosphate binders: calcium carbonate versus aluminium hydroxide

Two studies (Salusky 1991 (parallel study); Mak 1985 (cross-over study) compared calcium carbonate with aluminium hydroxide as phosphate binders (Table 5). Salusky 1991 reported no significant difference in mean final height SDS between treatments (Analysis 6.1 (17 children): MD -0.86 SDS, 95% CI -2.24 to 0.52). The number with abnormal bone biopsies at the end of treatment was significantly lower in children treated with calcium carbonate compared with aluminium hydroxide (Analysis 6.2 (17 children): RR 0.35, 95% CI 0.13 to 0.95). Bone aluminium levels (Analysis 6.3 (17 children): MD -1.00 mg/kg dry weight, 95% CI -12.29 to 10.29), final PTH levels (Analysis 6.4 (17 children): MD -187.00 mL-eq/L, 95% CI -1089.25 to 715.25) and final ALP (Analysis 6.5 (17 children): MD 21.00 U/L, 95% CI -216.62 to 258.62) did not differ significantly between groups. The number with hypercalcaemia did not differ between groups (Analysis 6.6 (17 children): RD 0.31, 95% CI -0.14 to 0.77). In the cross-over study by Mak 1985 (12 children), results were not reported separately for each group. PTH levels normalised in both treatment groups. Serum calcium and phosphorus levels did not differ between groups. Plasma aluminium levels were significantly higher at the end of aluminium treatment compared with calcium carbonate treatment. Results of bone histology (overall no change), GFR (improved) and growth velocity SDS (improved) were not reported separately for treatment groups.

Phosphate binders: sevelamer compared with calcium carbonate or calcium acetate

Two parallel group (Gulati 2010; Salusky 2005) and one cross-over study (Pieper 2006) compared sevelamer with calcium carbonate or calcium acetate (Table 6). No study reported any patient-centred outcomes. There were no significant differences in the final PTH levels (Analysis 7.1 (2 studies, 48 children): MD 51.92 pg/mL, 95% CI -77.53 to 181.36; I^2 = 34%), final ALP levels (Analysis 7.2 (2 studies, 48 children): MD 90.48 IU/L, 95% CI -139.38 to 320.35; I^2 = 30%), mean serum calcium-phosphorus product (Analysis 7.3 (2 studies, 48 children): MD -1.12 mg^2/dL^2, 95% CI, -5.88 to 3.64; I^2 = 0%), mean serum calcium levels (Analysis 7.4 (2 studies, 48 children): MD -0.40 mg/dL, 95% CI -1.16 to 0.36; I^2 = 59%) or mean serum phosphorus levels (Analysis 7.5 (2 studies, 48 children): MD 0.17 mg/dL, 95% CI 0.37 to 0.71; I^2 = 0%) between groups.

Salusky 2005 reported bone histology parameters of bone formation rates, % fall in bone formation rates, eroded perimeter, osteoid seam width, and bone area did not differ between treatments (Analysis 7.6). Osteoid area (Analysis 7.6.4 (1 study, 29 children); MD 4.20%, 95% CI 0.99 to 7.41) and osteoid perimeter (Analysis 7.6.5 (1 study, 29 children): MD 13.00%, 95% CI 3.81 to 22.19) were significantly higher in sevelamer treated children but the differences were of no clinical significance. In the cross-over study by Pieper 2006 the change in PTH levels and serum ALP did not differ between groups. Similarly the change in mean serum calcium-phosphorus product, serum calcium and serum phosphorus levels did not differ between therapy groups. Salusky 2005 reported 22 episodes of hypercalcaemia with calcium carbonate compared with five in children receiving sevelamer while Pieper 2006 reported six episodes of hypercalcaemia with calcium carbonate compared with one in children receiving sevelamer. No hypercalcaemic episodes were reported by Gulati 2010.

Calcitriol versus doxercalciferol

Salusky 2005a and Salusky 2005b compared doxercalciferol plus calcium carbonate or sevelamer to calcitriol plus calcium carbonate or sevelamer (Table 4). Bone histology parameters of bone formation rate (Analysis 8.1.1 (51 children): MD 10.29 $\mu m^3/\mu m^2/d$, 95% CI -53.07 to 73.65), percentage eroded bone (Analysis 8.1.2 (51 children): MD 0.76%, 95% CI -6.19 to 7.71), percentage osteoid volume (Analysis 8.1.3 (51 children): MD -0.16%, 95% CI -9.16 to 8.83), percentage osteoid surface (Analysis 8.1.4 (51 children): MD 1.04%, 95% CI -29.63 to 31.71), osteoid maturation time (Analysis 8.1.5 (51 children): MD 0.82 days, 95% CI -14.41 to 16.05) and percentage bone volume (Analysis 8.1.6 (51 children): MD 2.19%, 95% CI -9.82 to 13.91) did not differ significantly between treatment groups. Final levels of PTH, calcium, phosphorus, serum alkaline phosphatase (ALP) and FGF23 did not differ between groups (data only shown graphically in study reports). Values of PTH and ALP fell significantly while values of FGF23 rose significantly with either vitamin D preparation. No differences in episodes of hypercalcaemia were seen between the two vitamin D therapies.

Outcomes not reported

No studies reported fractures, bone deformities, need for parathyroidectomy, dialysis-related events, symptoms related to hypercalcaemia or vascular/extra osseous calcification.

DISCUSSION

Summary of main results

We were only able to identify 18 RCTs of all interventions used for CKD-MBD in children over a period of 30 years. All identified studies examined phosphate binders or vitamin D sterols. No studies specifically examining dietary or surgical interventions, changes in dialysis prescription or calcimimetics were identified. Six studies of treatment of CKD-MBD involved phosphate binders (aluminium hydroxide) or vitamin D sterols (ergocalciferol, dihydrotachysterol) or routes of administration (intraperitoneal) which are no longer used or are uncommonly used in current clinical practice except for the small doses of ergocalciferol recommended for children with CKD and low 25 hydroxyvitamin D levels (KDOQI 2009). There were few data to assist clinicians with the prevention of complications of renal bone disease since the only patient-centred-outcome reported was growth. This was reported in five studies (GFRD Study 1990; Hodson 1985; Jones 1994; Salusky 1991; Schmitt 2003) with no significant differences identified between treatments.

Treatment with calcitriol by both intraperitoneal and oral routes was effective in improving bone histology (Salusky 1998) but

growth rates did not differ between routes (Jones 1994). The number of hypercalcaemic episodes did not differ between treatment routes although intraperitoneal calcitriol lowered PTH levels significantly more than oral calcitriol (Salusky 1998). However both treatments used intermittently and in high dose increased the number of children with adynamic bone disease (Salusky 1998). Intraperitoneal calcitriol is no longer recommended.

No differences in height SDS, PTH levels and frequency of hypercalcaemia were found between oral daily or oral intermittent calcitriol therapy (Ardissino 2000; Klaus 1995; Schmitt 2003). Oral intermittent therapy is no longer recommended.

Vitamin D sterols given orally or IV resulted in reduced PTH levels compared with placebo or no specific treatment. Hypercalcaemic episodes were more common with IV calcitriol in one study (Greenbaum 2005). Increased risk of hypercalcaemia was not reported with 1α-hydroxyvitamin D or paricalcitol. Qualitative description of bone histology indicated improvement in children treated with vitamin D sterols (Eke 1983; Watson 1988).

No significant differences in growth rates (GFRD Study 1990; Hodson 1985) or bone histology (Salusky 2005a; Salusky 2005b) were detected in studies comparing different vitamin D sterols.

Two studies (Rianthavorn 2013; Shroff 2012) compared ergocalciferol in patients with CKD and vitamin D deficiency. Although there was no significant difference in the number of children, who developed secondary hyperparathyroidism, the development of secondary hyperparathyroidism was significantly delayed while calcium levels were significantly increased with ergocalciferol compared with placebo.

Overall we found that phosphate binders (aluminium hydroxide, calcium carbonate or acetate and sevelamer) had indistinguishable effects in lowering serum phosphorus, reducing PTH and on mean height SDS but that hypercalcaemia was more common with calcium-containing binders (Gulati 2010; Mak 1985; Pieper 2006; Salusky 1991; Salusky 2005). One study suggested that bone histology remained abnormal less commonly in calcium carbonate treated children compared with those treated with aluminium hydroxide (Salusky 1991).

Overall completeness and applicability of evidence

There were significant gaps between the interventions and outcomes that we had planned to study in this systematic review and the available data. In particular, no study provided data on patient-centred outcomes such as fractures, deformities and bone pain with only three studies providing numerical data on changes in height. The majority of studies only provided surrogate biochemical outcomes of PTH, serum ALP, calcium and phosphorus levels with a few early studies also reporting on radiological changes. We did not identify any studies, which considered non-pharmacological or surgical interventions or any studies, which evaluated calcimimetic agents in children.

There were many limitations in the available data which precluded combining results across studies in meta-analyses in many cases. Criteria for diagnosis of CKD-MBD varied between studies. As well as variation in the interventions examined, there was variation on outcomes reported and in how the outcomes were measured. Many studies reported the point estimate of the results but not the SD or 95% CI. The cross-over studies only presented the combined data for both arms, rather than each arm separately, and so could not be included in the meta-analyses. Some inconsistencies in outcome reporting are inevitable when comparing studies published in different eras. Early studies tended to focus only on the incidence of hypercalcaemia as an adverse consequence of both vitamin D and phosphate binders whereas more recent studies included hyperphosphataemia and elevated serum calcium-phosphorus product, since recognition of the adverse consequences of these parameters. Similarly, reporting of radiological abnormalities was a common outcome measure historically which has now largely been discarded. The relevance of certain outcome measures has changed over time. For example, measurements of plasma or bone aluminium levels, which were of relevance when aluminium hydroxide was used as a phosphate binder is no longer relevant.

Bone histomorphometry has been considered the reference standard to assess treatment efficacy in this setting, but only two of 18 included studies (Salusky 1998; Salusky 2005; Salusky 2005a; Salusky 2005b) provided adequate and comparable bone biopsy data making the value of bone histomorphometry in assessing treatment response difficult to assess in this systematic review. In addition, bone histomorphometry of trabecular bone does not reflect the effects of CKD on cortical bone. CKD reduces cortical bone volume and alters its architecture increasing the risk of fractures in long bones.

Though a surrogate measure, reduction in PTH levels is the most commonly used measure of efficacy of therapies in CKD-MBD. However in the reported studies there was considerable variation in the way in which PTH levels were measured. PTH values were variably reported as end of study mean or median values, percentage fall in PTH, the number of children with a fall in PTH levels, the mean integrated PTH value, the mean change in PTH levels during the study and the number of children with two consecutive falls of ≥ 30% in PTH values. The potential for outcomes reporting bias is high when children are reported as having a successful outcome if their PTH value has fallen by an apparently arbitrary proportion at any time during the study period, rather than reporting whether the benefit was transient, or sustained, or what the primary outcome measure was. Also, the comparison of PTH values between studies is limited because different PTH assays have been used in different studies reflecting the variations in PTH assays over the past 30 years (Wesseling-Perry 2013).

Comparisons of new therapeutic agents or a new method for their administration against placebo are of little clinical relevance if alternative agents are already recognised as successfully treating the disorder. Such a comparison was described in four studies. Two of these studies (Eke 1983; Watson 1988) were published in the 1980s when alternative successful treatments for renal bone disease were not confirmed. However two recently published studies reported that IV calcitriol (Greenbaum 2005) or IV paricalcitol (Greenbaum 2007) reduce PTH values more effectively than placebo. These results are not remarkable because it is generally agreed that vitamin D analogues are beneficial for biochemical abnormalities associated with CKD-MBD. Of more relevance to the clinician would be knowing whether IV calcitriol or IV paricalcitol are associated with improvements in patient-centred outcomes such as improved growth rates as well as fewer episodes of hypercalcaemia and reduction in PTH levels compared with oral calcitriol. In studies evaluating newer agents, or alternative modes

of administration, it is important to compare a new agent, or its mode of administration with agents considered to represent the current standard of care using patient-centred outcomes as the primary outcomes.

Quality of the evidence

Included studies were commonly reported incompletely and were of poor methodological quality, although this may reflect pre-2001 CONSORT (Consolidated Standards of Reporting Trials) practices (www.consort-statement.org). Sequence generation and allocation concealment was adequate in 12 and 11 of 18 studies respectively. Four studies reported blinding of participants, investigators or outcome assessors. All studies were considered at low risk of detection bias because they measured laboratory-based outcomes unlikely to be influenced by lack of blinding. Seven studies reported loss of follow-up or exclusion from data analysis (attrition bias) exceeding 10% and six studies were at high risk of selective reporting bias. Absence of allocation concealment, blinding and intention-to-treat analysis tends to lead to an over-estimate of the observed treatment effects (Schulz 1995; Wood 2008). Many studies were too small to detect any differences between treatments even if differences did exist. Several studies provided outcome data qualitatively as normal or not statistically different without providing the numeric results. Although this under-reporting of data was more common in the earlier studies, it was still evident in the most recent studies (Figure 3).

Studies included small numbers of patients. Few studies used the same interventions and/or reported outcomes in the same way so therefore they could not be combined in the meta-analyses. Therefore there were insufficient data to create summary of findings tables.

Potential biases in the review process

Since the study was commenced, the literature search has been run several times up to September 2015 making it unlikely that any studies have been missed. However 40% of study reports in the Cochrane Kidney and Transplant Specialised Register have been identified by handsearching of conference proceedings so it remains possible that further studies of therapies for CKD-MBD in children will be identified as conference proceedings from different congresses are searched.

The inability to include any data from cross-over studies in meta-analyses may have resulted in bias towards the results from parallel studies. However results from cross-over studies have been included in the additional tables as well as being referred to in the text (Table 1; Table 2; Table 3; Table 4; Table 5; Table 6).

Agreements and disagreements with other studies or reviews

Systematic reviews evaluating the use of vitamin D compounds in adults identified similar limitations to their review as we did (Palmer 2009a; Palmer 2009b). In particular few studies reported patient-centred outcomes, few studies compared the newer vitamin D preparations with established ones and for each comparison there were limited numbers of studies and patients limiting the conclusions that could be drawn. While established vitamin D preparations (calcitriol,1α-hydroxyvitamin D) were not demonstrated to reduce PTH levels significantly, there was considerable heterogeneity in the analyses. Newer vitamin D preparations including paricalcitol significantly reduced mean PTH levels. All vitamin D preparations increased the risk of hypercalcaemia compared with placebo. The authors concluded that the value of vitamin D therapy on important clinical outcomes in patients with CKD remains uncertain.

In a systematic review of nutritional vitamin D compounds of four RCTs (90 participants), which included both dialysis and non-dialysis CKD patients, the PTH levels decreased significantly with vitamin D therapy (Kandula 2011).

Two systematic reviews (Navaneethan 2011; Tonelli 2007), comparing sevelamer with calcium-containing phosphate binders, identified no differences between binders for all-cause mortality or cardiovascular mortality. Following sevelamer treatment the risk of hypercalcaemia was reduced and serum calcium levels were lower. However serum phosphate levels were higher and levels of serum calcium-phosphorus product did not differ. End of treatment PTH levels were significantly higher with sevelamer compared with calcium salts (Navaneethan 2011).

As in our review, the primary outcomes reported in these systematic reviews were surrogate biochemical markers rather than patient-centred outcomes so that the clinical value of vitamin D compounds or non-calcium-containing phosphate binders in patients with CKD remains uncertain.

AUTHORS' CONCLUSIONS

Implications for practice

In conclusion, this review confirms that renal bone disease, assessed by changes in PTH levels, is improved by all vitamin D preparations. However we do not know whether a reduction in PTH levels translates to a an improvement in clinical outcomes such as improved growth rate, reduction in fracture rates or reduced risk of cardiovascular calcification. No consistent differences between different routes of administration, different frequencies of dosing or different vitamin D preparations have been demonstrated in existing RCTs. Though fewer episodes of high serum calcium levels occurred with the non-calcium-containing binder, sevelamer, compared with calcium-containing binders, both were effective in lowering serum phosphorus levels and there were no differences in serum phosphorus though calcium levels were lower in sevelamer treated children. Six existing studies evaluated agents that are no longer in general clinical use. Studies evaluating new agents, such as the phosphate binder lanthanum carbonate, new vitamin D preparations or calcimimetic agents, are required in children. However recently a sponsored study assessing efficacy and safety of cinacalcet in children with CKD and secondary hyperparathyroidism receiving dialysis was terminated by the US Food and Drug Administration because of adverse effects (NCT01277510).

Implications for research

Existing RCTs provide limited data on the efficacy of interventions for the prevention and treatment of CKD-MBD in children other than for surrogate biochemical outcomes so there remains considerable uncertainty about the benefits and harms of interventions. As newer vitamin D sterols, calcimimetic agents and phosphate binders are developed, head-to-head comparisons with the current standard therapies will be required in well-designed adequately powered paediatric RCTs using standardised outcome measures

including those of direct clinical relevance to children and their families such as growth, fractures, bone deformities and measures of bone health as well as surrogate biochemical markers.

Ideally efficacy studies should utilise an accurate non-invasive quantitative assessment of bone health that includes assessment of both cortical and trabecular bone and correlates with patient-centred outcomes such as fractures. Peripheral quantitative computed tomography may be more beneficial in determining fracture risk in kidney failure as it provides a more accurate estimate of volumetric bone mineral density (g/cm^3) with improved differentiation between cortical and trabecular bone (Sanchez 2008). It is known kidney failure affects cortical bone more significantly than trabecular bone. Paediatric data is however limited and therefore these investigations are not established in the paediatric setting (Bacchetta 2011). MicroMRI could also be investigated as a marker of bone health.

The value of new surrogate markers such as serum FGF23 should also be evaluated (Wesseling-Perry 2013).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ardissino 2000

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 8 weeks • Loss to follow-up/excluded: unclear; possibly 31%. 85 enrolled (ASN 1998 abstract) but only 59 included in 8 week analysis
Participants	• Country: Europe • Setting: international • eGFR < 75 mL/min/1.73 m^2; PTH > 70 ng/mL • Number (treatment/control): 30/29 • Mean age ± SD (years): treatment group (8.3 ± 4.8); control group (8.6 ± 4.7) • Sex (M/F): treatment group (21/9); control group (24/5) • Exclusion criteria: dialysis patients; patients on steroids; rhGH or with other disease; Ca < 8.5 mg/dL or > 11.5 mg/dL or K < 3.5 mg/dL or > 7.5 mg/dL
Interventions	Treatment group • Oral calcitriol: 35 ng/kg twice a week (70 ng/kg/wk) for 8 weeks Control group • Daily oral calcitriol: 10 ng/kg/d (70 ng/kg/wk) for 8 weeks Co-interventions • Phosphate binders
Outcomes	• Median (range) in PTH values at end of treatment • % change from baseline in PTH levels • Number with fall in PTH levels • Mean CrCl at end of treatment • Number with hypercalcaemia, hyperphosphataemia • Serum Ca x P
Notes	• Diagnosis of renal bone disease: secondary hyperparathyroidism with PTH level > 70 pg/mL

Ardissino 2000 *(Continued)*

- ALP and PTH levels presented as median and range
- Data on serum Ca x P graphical only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation stratified for PTH levels 70 to 399 ng/mL and > 399 ng/mL
Allocation concealment (selection bias)	Low risk	Central randomisation stratified for PTH levels 70 to 399 ng/mL and > 399 ng/mL
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Lack of blinding could influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Primary outcome was laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	In the full publication, all 59 reported patients completed study in full publication. However as abstract reports that 85 patients were enrolled in the study.
Selective reporting (reporting bias)	Low risk	Data available on PTH, GFR & hypercalcaemia for meta-analysis
Other bias	Low risk	No evidence of other bias

Eke 1983

Methods	• Study design: parallel RCT • Time frame: 1981 to 1983 • Follow-up period: 12 months • Loss to follow-up/excluded: 6% (1/16)
Participants	• Country: UK • Setting: single centre • GFR 20 to 50 mL/min/1.73 m^2 • Number: treatment group (8); control group (8) • Mean age: 10.4 years • Sex (M/F): not reported • Exclusion criteria: previously treated with vitamin D or its analogues
Interventions	Treatment group • Oral 1α-hydroxyvitamin D: 10 ng/kg/d for 1 year Control group • Oral calciferol: 670 ng/kg/d for 1 year Co-interventions

Eke 1983 *(Continued)*

	• Aluminium hydroxide as phosphate binder
Outcomes	• Change in GFR measured by ^{51}Cr EDTA • Bone histology, BMD • X-ray changes • Ca, phosphorus, ALP • Number with hypercalcaemia
Notes	• Graphical data only for changes in GFR, Ca, phosphorus and PTH • No clear numerical data for BMD, X-rays, ALP

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be "double-blind" study but no other information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Said to be double-blind but no other information provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are laboratory based and unlikely to be influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	One patient excluded when commenced RRT but this unlikely to influence results
Selective reporting (reporting bias)	High risk	No reporting of actual numbers for outcomes of GFR, PTH and other biochemistry
Other bias	Low risk	Leo Laboratories provided medications

GFRD Study 1990

Methods	• Study design: parallel RCT • Time frame: 1983 to 1990 • Follow-up period: minimum 6 months on treatment; 82/94 enrolled were treated for 1 year • Loss to follow-up or excluded after randomisation: 15% (12/82)
Participants	• Country: USA • Setting: national multi-centre study • Chronological age 2 to 10 years; bone age < 10 years; GFR 20 to 60; PTH > 1 SD above normal; completed 6 month run-in period • Number (treatment/control): treatment group (40); control group (42) • Mean age ± SD (years): treatment group (6 ± 3); control group (5 ± 3) • Sex (M/F): treatment group (29/11); control group (26/16)

GFRD Study 1990 *(Continued)*

	• Exclusion criteria: nephrotic syndrome; SLE; treatment with steroids; diseases requiring vitamin D therapy and/or affecting growth; previous treatment with vitamin D preparations
Interventions	Treatment group • Oral calcitriol: 20 ng/kg/d • Adjusted for weight every 6 months and for hypercalcaemia/elevated ALP for 12 months Control group • Oral DHT: 15 µg/kg/d • Adjusted for weight every 6 months and for hypercalcaemia/elevated ALP for 12 months Co-interventions • Phosphate binders, sodium bicarbonate
Outcomes	• Changes in height, weight SDS • Rate of decline in eGFR • Number with hypercalcaemia > 2.7 mmol/L (11 mg/dL)
Notes	• Changes in height SDS, weight SDS and GFR analysed with a longitudinal data analysis using repeated measurements analysis of variance • Number with hypercalcaemia reported as episodes rather than for patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central sequence of random treatment assignments
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants received identical regimens by appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants received identical regimens by appearance. Primary outcome was growth. All investigators trained to do measurements. Laboratory results measured in central laboratory
Incomplete outcome data (attrition bias) All outcomes	High risk	12 (13%) patients excluded after randomisation and unclear from which group
Selective reporting (reporting bias)	High risk	No outcomes reported in format that can be entered in meta-analyses. No results of PTH levels provided
Other bias	Low risk	NIH and other grants. Medications provided by Hoffmann-La Roche

Greenbaum 2005

Methods	• Study design: parallel RCT • Time frame: 1999

Greenbaum 2005 *(Continued)*

- Follow-up period: 12 weeks
- Loss to follow-up/left study: 40% (19/47 randomised patients)

Participants	• Country: USA, Poland • Setting: international multicentre (23 sites) • HD 3 times/week, PTH ≥ 400 pg/mL, Ca ≤ 10.5 mg/dL, Ca x P ≤ 70 mg^2/dL^2 • Number (enrolled/completed): treatment group (21/13); control group (26/15) • Mean age ± SD (years): treatment group (15.3 ± 2.8); control group (14.0 ± 3.8) • Sex (M/F): treatment group (14/7); control group (17/9) • Exclusion criteria: post-puberty; pregnancy; nursing; allergy to vitamin D; aluminium containing phosphate binders; steroids/immunosuppression; history of non-compliance; liver disease; malignancy; AKI < 3 months, planned living-related donor transplant
Interventions	Treatment group • IV calcitriol: 3 times/week (dose 0.5 µg if PTH < 500, 1.0 µg if PTH 500 to 1000, 1.5 µg if PTH > 1000) for 12 weeks Control group • IV placebo: IV 3 times/week for 12 weeks Co-interventions • Not reported
Outcomes	• Proportion with 2 consecutive ≥ 30% fall in PTH; mean change in PTH levels • Change in ALP • Number with hypercalcaemia, hyperphosphataemia, increased Ca x P
Notes	• 72 enrolled, 47 randomised and analysed, 28 completed study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation stratified by age. Information obtained from authors
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo-controlled study using IV medications
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo-controlled study using IV medications
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 (38%) did not complete study but data from these patients included in results. Data on primary outcome available in all patients
Selective reporting (reporting bias)	Low risk	All relevant outcomes are included

Greenbaum 2005 *(Continued)*

Other bias	High risk	Supported by Abbott Laboratories

Greenbaum 2007

Methods	• Study design: parallel RCT • Time frame: 2001 to 2003 • Follow-up period: 12 weeks after 2 to 6 weeks washout • Loss to follow-up: 17 did not complete study but included in analysis 0% (0/29)
Participants	• Country: USA • Setting: national, multicentre • HD for at least 1 month; PTH ≥ 300 pg/mL; Ca ≤ 10.5 mg/L, Ca x P ≤ 70 after 2 to 6 weeks run-in • Number (randomised/completed): treatment group (15/10); control group (14/2) • Mean age ± SD (years): treatment group (13.6 ± 4.76); control group (14.3 ± 4.15) • Sex (M/F): treatment group (13/2); control group (5/9) • Exclusion criteria: allergy to paricalcitol or other vitamin D; pregnant; nursing; other major illness; AKI in previous 3 months; partial parathyroidectomy in previous 12 months; aluminium binders in past 3 months or likely to need binders; poor compliance; drugs likely to affect bone metabolism
Interventions	Treatment group • IV paricalcitol: (0.04 µg/kg if PTH ≤ 500, and 0.08 µg/kg if PTH ≥ 500) 3 times/week for 12 weeks • Dose altered according to Ca and P levels Control group • IV placebo: 3 times/week for 12 weeks • Dose altered according to Ca and P levels Co-interventions • Phosphate binders through study; dialysate Ca maintained at 2.5 mmol/L or 3 mmol/L through study
Outcomes	• Proportion with > 30% fall in PTH on 2 consecutive occasions • Mean change in PTH levels • Mean changes in serum Ca, phosphorus, Ca x P levels
Notes	• Patients discontinued after 4 weeks if had 2 PTH levels > 700 pg/mL • 10 withdrawn from placebo and 4 from paricalcitol groups for increased PTH

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo and active medication given IV after dialysis

Greenbaum 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo and active medication given IV after dialysis; Primary outcome was laboratory based
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 (41%) prematurely withdrawn (5 treatment; 10 placebo) but these patients included in evaluation of primary outcome
Selective reporting (reporting bias)	Low risk	All relevant laboratory outcomes are included
Other bias	High risk	Supported by Abbott Laboratories

Gulati 2010

Methods	• Study design: open-label RCT • Time frame: April 2006 to July 2007 • Follow-up period: 12 weeks after 2 to 6 weeks washout • Loss to follow-up: Three (14%) of 22 lost to follow-up
Participants	• Country: India • Setting: Single centre • Ages 2 to 18 years, with CKD stages 3 and 4 (eGFR between 30 to 59 and 15 to 29 mL/min/1.73 m^2); Serum phosphate > 5.5 mg/dL • Number (randomised/analysed): treatment group (11/10); control group (11/9) • Mean age ± SD (years): treatment group (9.6 ± 4.8); control group (10.6 ± 4.5) • Sex (M/F): treatment group (6/5); control group (5/6) • Exclusion criteria: corrected Ca < 7 mg/dL or > 11 mg/dL; haemoglobin < 6 g/dL; prolonged prothrombin time (INR > 1.5); residing > 100 km from hospital and patients not willing to come for monthly follow-up visits
Interventions	Treatment group • Sevelamer: 400 mg 3 times/d ◦ Dose titrated at 4th and 8th week according to serum phosphate levels Control group • ◦ Calcium acetate: 667 mg 3 times/d • Dose titrated at 4th and 8th week according to serum phosphate levels Co-interventions • Patients with hypocalcaemia ≤ 7 mg/dL were treated with oral calcium carbonate
Outcomes	• Decrease in blood phosphate level • Changes in Ca, Ca x P, ALP and PTH
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Gulati 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	Low risk	Computer generated randomisation and opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding may influence management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Open label but primary outcome was laboratory based
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 (14%) of 22 lost to follow-up after randomisation
Selective reporting (reporting bias)	Low risk	All relevant laboratory outcomes and adverse events included
Other bias	Low risk	Emcure Pharmaceuticals Limited provided medication

Hodson 1985

Methods	• Study design: parallel RCT • Time frame: not reported • Follow-up period: 12 months (0.6 to 1.2 years) • Loss to follow-up/excluded: probably 37% (9/24); unclear but only 15 included in analysis
Participants	• Country: Australia • Setting: Single centre • CKD including dialysis; documented bone disease on histology • Number (randomised/analysed): treatment group (13/8); control group (11/7) • Age: not reported • Sex (M/F): 14/10 • Exclusion criteria: not reported
Interventions	Treatment group • Calcitriol: 15 ng/kg/d for 12 months, increased till Ca reached 2.6. Final dose 5 to 30 ng/kg/d Control group • Ergocalciferol: 0.25 mg/d for 12 months, increased till serum Ca reached 2.6 Final dose 25 to 100 µg/kg/d Co-interventions • Dialysis (9); bicarbonate supplements; aluminium-containing phosphate binders
Outcomes	• Bone histology • Bone radiology, bone age • Growth cm/y: % expected for bone age

Hodson 1985 *(Continued)*

	• Biochemistry: PTH, ALP, Ca, P
Notes	• Number of exclusions unclear. Reported that 6/24 excluded (4 calcitriol, 2 ergocalciferol) but only 15/24 analysed so 9/24 excluded • Only patients undergoing pre and post biopsies were included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Systematic ranking design in blocks of 4 based on severity of bone histology changes
Allocation concealment (selection bias)	High risk	Investigators aware of blocks so could influence next entry
Blinding of participants and personnel (performance bias) All outcomes	High risk	No Blinding. Lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory based outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	9/24 (38%) excluded from final analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	No evidence of other bias

Jones 1994

Methods	• Study design: cross-over RCT • Time frame: 1993 to 1994 • Follow-up period: 7 months including 1 month run-in • Loss to follow-up/exclusions: 0% (0/7)
Participants	• Country: Canada • Setting: Single centre • CCPD or CAPD • Number: 7 • Mean age ± SD: 7.2 ± 5.2 years • Sex (M/F): 5/2 • Exclusion criteria: not reported
Interventions	Treatment/control group • IP or oral calcitriol 0.01-0.02 µg/kg/d for 3 months, then crossed over for 3 months Co-interventions

Jones 1994 *(Continued)*

	• $CaCO_3$ as phosphate binder, Dietary phosphorus restriction
Outcomes	• Height SDS (mean and range) • Bone X-rays • PTH levels • Number with hypercalcaemia • Number with peritonitis
Notes	• Two phases of cross-over combined in results • Most data graphical only for individual patients

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Said to be random assignment
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes laboratory based
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed study
Selective reporting (reporting bias)	High risk	No data available in form that can be included in meta-analyses as cross over study
Other bias	High risk	Supported by Abbott Laboratories

Klaus 1995

Methods	• Study design: parallel RCT • Time frame: approximately 1993 to 1995 • Follow-up period: 10 (2 to 24 weeks) and 8 (2 to 36 weeks) for 2 groups • Loss to follow-up/excluded: 0% (0/21) • Follow-up appeared complete
Participants	• Country: Germany • Setting: National multicentre study • Children on dialysis; PTH increased > 15 pmol/L after 4 weeks or > 75 pmol/L • Number: treatment group (12); control group (9) • Mean age: not reported • Sex (M/F): not reported

Klaus 1995 *(Continued)*

	• Exclusion criteria: not reported

Interventions	Treatment group
	• Intermittent oral calcitriol: 1.0 µg 3 times/week
	  ○ Planned duration unclear
	Control group
	• Daily oral calcitriol: 0.5 µg/d
	  ○ Planned duration unclear
	Co-interventions
	• Not reported

Outcomes	• Fall in PTH values (median and range) • Number of patients with hypercalcaemia (not defined)
Notes	• Abstract only • Duration of treatment variable - therefore number of patients with hypercalcaemia may not be valid comparison • PTH values only available as medians

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Abstract only. "Patients were randomised to..." No other information provided
Allocation concealment (selection bias)	Unclear risk	Abstract only. "Patients were randomised to..." No other information provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Duration of treatment unclear so unclear whether any children left the study
Selective reporting (reporting bias)	High risk	No report on adverse effects. Biochemical data could not be included in meta-analyses
Other bias	Unclear risk	No information provided

Mak 1985

Methods	• Study design: cross-over study • Time frame: 1983 to 1984 • Follow-up period: 15 months including 3 months run-in

Mak 1985 *(Continued)*

	• Loss to follow-up/excluded: 0% (0/12)
Participants	• Country: UK • Setting: Single centre • Moderate-severe CKD (GFR 8 to 45 mL/min/1.73 m^2) • Number: 12 • Mean age ± SD: 10.4 ± 3.1 years • Sex (M/F): 7/5 • Exclusion criteria: not reported
Interventions	Treatment/control group • $CaCO_3$ or $AlOH_3$ for 6 months as sole phosphate binder. Crossed over after 6 months • Dihydrotachysterol continued at same dose throughout Co-interventions • Dietary restriction of phosphorus
Outcomes	• Bone biopsy pre-study and 12 months • Change GFR over 12 months • PTH values • Ca, P, % theoretical reabsorption of phosphate values • Growth (HVSDS) pre-study and 12 months
Notes	• Little comparative data available • Most data graphical only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	Patients said to be randomised
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients appear to be included
Selective reporting (reporting bias)	High risk	Only combined data provided for both treatment groups so no data available for meta-analyses
Other bias	Low risk	National Medical Research Fund

Pieper 2006

Methods	• Study design: cross-over study • Time frame: 2002 to 2006 • Follow-up period: 20 weeks (2 weeks washout; 8 weeks treatment in each arm) • Loss to follow-up/excluded: efficacy 55%; 22/40. 40 randomised; 34 treated (safety analysis); 30 completed first part; 23 entered cross-over; 18 completed cross-over so 22 excluded from efficacy analysis

Participants	• Country: Germany
	• Setting: national, multicentre; university teaching hospitals
	• Maintenance PD or HD; eGFR 20 to 60 mL/min/1.7 m^2; Ca < 2.75 mmol/L; PTH ≤ 500 pg/mL
	• Number
	  ○ Treatment group: sevelamer first (17); sevelamer second (13), analysed (9)
	  ○ Control group: calcium acetate first (17), calcium acetate second (10), analysed (9)
	• Mean age ± SD: 12.4 ± 4.1 years (efficacy group completing study)
	• Sex (M/F): 13/5 (efficacy group completing study)
	• Exclusion criteria: PTH > 500, Ca > 2.75; cyclosporin use; antiarrhythmic agents; anticonvulsants; pregnant; lactating; difficulty swallowing; intestinal motility disorder or substantial surgery

Interventions	Treatment group
	• Sevelamer to keep P < 2mmol/L (≥ 2 years) or < 2.25 (> 2 years)
	  ○ Starting dose equal to dose administered before study. 8 weeks
	Control group
	• Calcium acetate to keep phosphate < 2 mmol/L (≥ 2 years) or < 2.25 mmol/L (< 2 years)
	  ○ Starting dose equal to dose administered before study. 8 weeks
	Co-interventions
	• Dialysis; vitamin D

Outcomes	• Efficacy (18 patients): change in P, Ca, Ca x P, PTH • Safety (34 patients): Ca > 2.75
Notes	• Data combined for 2 arms of cross-over for efficacy and safety

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers with prior allocation to each centre
Allocation concealment (selection bias)	Low risk	Computer generated random numbers with prior allocation to each centre
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open label study. Lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are laboratory based and unlikely to be influenced by lack of blinding

Pieper 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Only 18/40 (45%) completed both parts of the cross-over study. 30 completed first part. Exclusions could have influenced overall result
Selective reporting (reporting bias)	High risk	Outcomes reported incompletely and cannot be included in meta-analyses
Other bias	High risk	Chief investigator and study supported by Genzyme Europe

Rianthavorn 2013

Methods	• Study design: RCT • Time frame: not reported • Follow-up period: not reported • Loss to follow-up/excluded: none reported
Participants	• Country: Thailand • Setting: university teaching hospital • Aged < 18 years. CKD stage 5/5D, vitamin D deficiency with levels < 30 ng/mL, Hb level 10.0 to 12.5 g/dL, serum phosphorus, 6.5 mg/dL, corrected Ca < 10.5 mg/dL, Ca x P, 65mg^2/dL^2 one month prior to recruitment • Number: treatment group (10); control group (10) • Mean age ± SD (years): treatment group (7.1 ± 5.4); control group (9.3 ± 5.3) • Sex (M/F): treatment group (7/3); control group (6/4) • Exclusion criteria: thalassaemia; chronic liver disease; gastrointestinal malabsorption; significant blood loss; PTH > 800 pg/mL; proteinuria > 2 mg/mg of urine creatinine; blood transfusion; chronic anticonvulsant therapy; prior ergocalciferol supplementation and kidney transplantation
Interventions	Treatment group • Severe vitamin D deficiency (serum 25D level < 5 ng/mL) 40,000 IU ergocalciferol weekly for 4 weeks, then 40,000 IU every second week for 8 weeks (total 320,000 IU ergocalciferol) • Mild deficiency (serum 25D level 5 to 15 ng/mL) 40,000 IU ergocalciferol every second week for 12 weeks (total 240,000 IU ergocalciferol) • For 25D insufficiency (serum 25D levels 16 to 30 ng/mL) 40,000 IU ergocalciferol every 4 weeks for 12 weeks (total 120,000 IU ergocalciferol) Control group • No specific therapy Co-interventions • Calcium carbonate for phosphate binding with phosphorus level > 5.5 mg/dL • Alfacalcidol for secondary hyperparathyroidism • Anaemia management: epoetin alfa administered subcutaneously
Outcomes	• Ca levels • PTH levels • Phosphorous levels
Notes	• Primary outcome was the effect of ergocalciferol on ESA dose
Risk of bias	

Rianthavorn 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Simple randomisation, randomisation was sequentially done (information from authors)
Allocation concealment (selection bias)	High risk	Simple randomisation, randomisation was sequentially done (information from authors)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding could affect patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory outcome and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed 12 week therapy
Selective reporting (reporting bias)	Low risk	All prespecified outcomes mentioned
Other bias	Unclear risk	Insufficient information to permit judgement

Salusky 1991

Methods	• Study design: RCT • Time frame: 1988 to 1991 • Follow-up period: 13 ± 2 months • Loss to follow-up/exclusions: 23% (5/22)
Participants	• Country: USA • Setting: university teaching hospital • Maintenance PD • Number (randomised/analysed): treatment group (12/10); control group (10/7) • Mean age ± SD (years): treatment group (15.5 ± 3.7); control group (14.1 ± 3.7) • Sex (M/F): treatment group (2/8); control group (3/4) • Exclusion criteria: aluminium-related bone disease
Interventions	Treatment group • $CaCO_3$ to maintain phosphate < 2.0 mmol/L (2.5 to 12 g/d) for 1 year Control group • $AlOH_3$ to maintain phosphate < 2.0 mmol/L (maximum dose 30 mg/kg) for 1 year Co-interventions • Calcitriol to maintain Ca 2.6 to 2.8 mmol/L
Outcomes	• Bone histology • PTH, ALP, Ca, P levels

Salusky 1991 *(Continued)*

	• Plasma aluminium levels • Number of patients with Ca > 2.8mmol/L
Notes	• Graphical data only for Ca and P levels

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Said to be randomly assigned
Allocation concealment (selection bias)	Unclear risk	Said to be randomly assigned
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding could affect patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	5 withdrawn for transplant, i.e. 23% did not complete study
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	Grants from US Public Health Service and Department of Veterans Affairs

Salusky 1998

Methods	• Study design: RCT • Time frame: 1996 to 1998 • Follow-up period: 12 months • Loss to follow-up/excluded: 28%, 13/46 did not complete study. Unclear whether exclusions pre- or post-randomisation
Participants	• Country: USA • Setting: University teaching hospital • CCPD for > 2 months; bone biopsy normal or hyperparathyroidism • Number: treatment group (16); control group (17) • Mean age ± SD (years): treatment group (12.5 ± 1.1); control group (13.2 ± 1.3) • Sex (M/F): not reported • Exclusion criteria: low turnover bone disease; parathyroidectomy in prior 12 months; immunosuppression; documented non-compliance
Interventions	Treatment group • Intraperitoneal calcitriol 1.0 µg 3 times/week for 12 months Control group

Salusky 1998 *(Continued)*

	• Oral calcitriol 1.0 µg 3 times/week for 12 months Co-interventions • $CaCO_3$ for phosphate binder
Outcomes	• Bone histology • Lowest PTH levels, maximum Ca levels, P and ALP levels • Number with Ca >11 mg/dL, P > 7.0 mg/dL • Peritonitis
Notes	• P and ALP data only available graphically

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	3 randomisation schedules according to bone histology. Blocks of 4, 6, 8 with block size determined at random
Allocation concealment (selection bias)	Low risk	Independent biostatistician
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13 (28%) of 46 did not complete study and unclear whether these excluded pre- or post-randomisation
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	Supported by grants from USPHS & Casey Lee Ball Foundation

Salusky 2005

Methods	• Study titles Salusky 2005, Salusky 2005a and Salusky 2005b represent the same RCT. The study (Salusky 2005) presents the data comparing sevelamer with calcium carbonate (Comparison 7) irrespective of vitamin D preparation. Data reported on 29 patients of 42 allocated to study • Study design: parallel RCT, 2 x 2 longitudinal factorial study design • Time frame: 2003 to 2005 • Follow-up period: 8 months • Loss to follow-up/excluded: 13/42 did not complete the study
Participants	• Country: USA • Setting: University teaching hospital • CCPD, PTH > 400 pg/mL; bone histomorphometry of secondary hyperparathyroidism • Number (randomised/analysed): treatment group 1 (21/14); treatment group 2 (21/15)

Salusky 2005 *(Continued)*

- Mean age ± SD (years): treatment group 1 (11 ± 5); treatment group 2 (15 ± 3)
- Sex (M/F): treatment group 1 (10/4); treatment group 2 (8/7)
- Exclusion criteria: previous history of poor compliance; parathyroidectomy in last 12 months; immunosuppressive agents; rhGH

Interventions	Treatment group 1 • $CaCO_3$: titrated to keep P at 4 to 6 mg/dL for 8 months • Doxercalciferol or calcitriol given 3 times/wk. 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 Treatment group 2 • Sevelamer: initial dose extrapolated from previous calcium carbonate doses; then titrated to keep P at 4 to 6 mg/dL. Continued for 8 months • Doxercalciferol or calcitriol given 3 times/week. 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 Co-interventions • 1000 mg oral calcium in sevelamer group if Ca < 8.2 mg/dL
Outcomes	Outcomes for comparison between phosphate binders • Primary outcome: Bone formation rate • Other bone histomorphometric parameters • Final levels of ALP, PTH • Average P, Ca x P, Ca
Notes	• Factorial analysis provided no evidence of treatment interaction between two sterols so comparisons reported for phosphate binders irrespective of D sterol given • 2005 report included 42 allocated patients with data on 29 (14 receiving $CaCO_3$ and 15 receiving sevelamer)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised longitudinal factorial study. Computer generated randomisation
Allocation concealment (selection bias)	Low risk	Computer generated, allocated by statistician
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants, care givers, investigators not blinded to interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes laboratory based and unlikely to be influenced by lack of blinding. Bone histology performed by scientist, who was blinded to treatment group
Incomplete outcome data (attrition bias) All outcomes	High risk	13/42 (31%) did not complete study. Lack of data on these patients could have influenced results

Salusky 2005 *(Continued)*

Selective reporting (reporting bias)	High risk	Primary outcome was bone histology; ; secondary outcomes only reported graphically
Other bias	Low risk	USPH grants and Casey Lee Ball Foundation but Bone Care International provided medications and other unrestricted support for the study

Salusky 2005a

Methods	• Study titles Salusky 2005, Salusky 2005a and Salusky 2005b represent the same RCT. The study title (Salusky 2005a) has been used to allow the presentation of data for vitamin D groups + sevelamer (treatment groups 2 and 4) • Study design: parallel RCT, 2 x 2 longitudinal factorial study design. • Time frame: 2003 to 2005 • Follow-up period: 8 months • Loss to follow-up/excluded: 15%; 9/60 did not complete study; transplant (5), non-compliance (4)
Participants	• Country: USA • Setting: University teaching hospital • CCPD, PTH > 400 pg/mL; bone histomorphometry of secondary hyperparathyroidism • Number (randomised/analysed): treatment group 2 (14/12); treatment group 4 (14/13) • Mean age ± SD (years): treatment group 2 (14.5 ± 3.7); treatment group 4 (15.0 ± 2.2) • Sex (M/F): treatment group 2 (7/7); treatment group 4 (4/10) • Exclusion criteria: previous history of poor compliance; parathyroidectomy in last 12 months; immunosuppressive agents; rhGH
Interventions	Treatment group 2 • Sevelamer: initial dose extrapolated from previous calcium carbonate doses; then titrated to keep P at 4 for 6 mg/dL • Doxercalciferol: 3 times/week. 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 • Treatment duration: 8 months Treatment group 4 • Sevelamer: initial dose extrapolated from previous calcium carbonate doses; then titrated to keep P at 4 to 6 mg/dL • Calcitriol: 3 times/week. 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 • Treatment duration: 8 months Co-interventions • 1000 mg oral calcium in sevelamer group if Ca < 8.2 mg/dL
Outcomes	Outcomes for comparison between vitamin D preparations • Bone formation rate • Other bone histomorphometric parameters • Final levels of PTH, Ca, P, FGF 23
Notes	• Factorial analysis provided no evidence of treatment interaction between two sterols so comparisons reported for phosphate binders irrespective of D sterol given • 2011 report included 60 allocated patients with data on 51 provided for 4 groups

Salusky 2005a *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised longitudinal factorial study. Computer generated randomisation
Allocation concealment (selection bias)	Low risk	Computer generated, allocated by statistician
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants, care givers, investigators not blinded to interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	9/60 (15%) did not complete study. Lack of data on these patients could have influenced results
Selective reporting (reporting bias)	High risk	Primary outcome was bone histology; secondary outcomes only reported graphically
Other bias	Low risk	USPH grants and Casey Lee Ball Foundation but Bone Care International provided medications and other unrestricted support for the study

Salusky 2005b

Methods	• Study titles Salusky 2005, Salusky 2005a and Salusky 2005b represent the same RCT. The study title (Salusky 2005b) has been used to allow the presentation of data for vitamin D groups + calcium carbonate (treatment groups 1 and 3) • Study design: parallel RCT: 2 x 2 longitudinal factorial study design • Time frame: 2003 to 2005 • Follow-up period: 8 months • Loss to follow-up/excluded: 15%; 9/60 did not complete study; transplant (5), non-compliance (4)
Participants	• Country: USA • Setting: University teaching hospital • CCPD, PTH > 400 pg/mL; bone histomorphometry of secondary hyperparathyroidism • Number (randomised/analysed): treatment group 1 (16/11); treatment group 3 (16/15) • Mean age ± SD (years): treatment group 1 (14.2 ± 3.6); treatment group 3 (12.0 ± 12) • Sex (M/F): treatment group 1 (10/6); treatment group 3 (9/7) • Exclusion criteria: previous history of poor compliance; parathyroidectomy in last 12 months; immunosuppressive agents; rhGH
Interventions	Treatment group 1 • $CaCO_3$ titrated to keep P at 4 to 6 mg/dL • Doxercalciferol: 3 times/week. 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 • Treatment duration: 8 months

Salusky 2005b *(Continued)*

	Treatment group 3 • $CaCO_3$: titrated to keep P at 4 to 6 mg/d: • Calcitriol: 3 times/week. 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 • Treatment duration: 8 months Co-interventions • 1000 mg oral Ca in sevelamer group if Ca < 8.2 mg/dL
Outcomes	Outcomes for comparison between vitamin D preparations • Bone formation rate • Other bone histomorphometric parameters • Final levels of PTH, Ca, P, FGF 23
Notes	• Factorial analysis provided no evidence of treatment interaction between two sterols so comparisons reported for phosphate binders irrespective of D sterol given • 2011 report included 60 allocated patients with data on 51 provided for 4 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised longitudinal factorial study. Computer generated randomisation
Allocation concealment (selection bias)	Low risk	Computer generated, allocated by statistician
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants, care givers, investigators not blinded to interventions
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes laboratory based and unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	9/60 (15%) did not complete study. Lack of data on these patients could have influenced results
Selective reporting (reporting bias)	High risk	Primary outcome was bone histology; secondary outcomes only reported graphically
Other bias	Low risk	USPH grants and Casey Lee Ball Foundation but Bone Care International provided medications and other unrestricted support for the study

Schmitt 2003

Methods	• Study design: RCT; data from a subset of prepubertal participants with GFR < 40 mL/min/1.73 m^2 included in Ardissino 2000 • Time frame: 1998 to 2003 • Follow-up period: 12 months

Schmitt 2003 *(Continued)*

	• Loss to follow-up/excluded post randomisation: 17% (5/29)
Participants	• Country: Europe • Setting: International, multicentre study • eGFR < 40 mL/min/1.73 m^2; PTH > 70 pg/mL • Number (randomised/analysed): treatment group (14/12); control group (15/12) • Mean age, range (years): treatment group (5.5, 2.4 to 8.4); control group (5.1, 1.4 to 9.1) • Sex (M/F): treatment group (11/1); control group (10/2) • Exclusion criteria: Ca < 8.5 mg/dL or > 11.5 mg/dL; P < 3.8 mg/dL or > 7.5 mg/dL; underlying serious disease; rhGH or corticosteroids treatment; dialysis
Interventions	Treatment group • Intermittent oral calcitriol 35 ng/kg twice weekly for 12 month. After 1 month dose adjusted for PTH level Control group • Daily oral calcitriol 10 ng/kg for 12 months. After 1 month dose adjusted for PTH levels Co-interventions • Phosphate binders and other medications according to clinical requirements
Outcomes	• Change in height SDS • Average time integrated mean plasma PTH; % maximal fall in mean PTH levels; number with reduced PTH levels • Change in estimated CrCl • Change in median ALP levels • Serum Ca x P; number with hypercalcaemia or hyperphosphataemia
Notes	• Serum Ca x P shown graphically only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally randomised according to PTH levels
Allocation concealment (selection bias)	Low risk	Centrally randomised according to PTH levels
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	not blinded but lack of blinding unlikely to influence patient management
Incomplete outcome data (attrition bias) All outcomes	High risk	5/29 (17%) left study (RRT 4, rhGH 1). Could have influenced results
Selective reporting (reporting bias)	Low risk	Data reported on all expected outcomes

Schmitt 2003 *(Continued)*

Other bias	Low risk	No evidence of other bias

Shroff 2012

Methods	• Study design: parallel RCT • Time frame: February 2009 to March 2010 • Follow-up: 6 months • Lost to follow-up: 7
Participants	• Country: UK • Setting: single centre • Aged < 18 years; eGFR 15 to 70 mL/min/m^2 calculated by Schwartz formula; normal iPTH level; low 25(OH) vitamin D levels • Number: treatment group (24); control group (23) • Mean age ± SD (years): treatment group (10.6 ± 2.5); control group (7.9 ± 4.8) • Sex (M/F): treatment group (15/9); control group (16/7) • Exclusion criteria: pre-existing hyperparathyroidism; comorbid conditions interfering with absorption of ergocalciferol, use of steroids or anticonvulsants

Interventions	Treatment group
	• Ergocalciferol replacement for 3 months
	  ○ Age < 1 year: 600 IU daily
	  ○ Age ≥ 1 year
	  ■ Vitamin D level 40 to 75 nmol/L: 2000 IU daily
	  ■ Vitamin D level 12.5 to 40 nmol/L: 4000 IU daily
	  ■ Vitamin D level < 12.5 nmol/L: 8000 IU daily
	• Ergocalciferol maintenance for 3 months
	  ○ Age < 1 year: 400 IU daily
	  ○ Age > 1 year: 2000 IU daily
	Control group
	• Sunflower oil in same volumes as D
	Co-interventions
	• Phosphate binders in some patients in both groups

Outcomes	• Time to development of hyperparathyroidism • Number with elevated PTH level • PTH, Ca, phosphorus level
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised 1:1 using blocks of 10. Random number generator
Allocation concealment (selection bias)	Low risk	Random number generator. Randomisation by trial pharmacist

Shroff 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinician and participants blinded. Identical bottles and contents matched for colour, odour and taste
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinicians/participants blinded until all data collected and evaluated. Outcomes were laboratory based
Incomplete outcome data (attrition bias) All outcomes	Low risk	All given medication completed the study
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Medications supplied by Specials Laboratory

Watson 1988

Methods	• Study design: parallel RCT • Time frame: 1985 to 1988 • Follow-up period: 6 months • Lost to follow-up: All completed study
Participants	• Country: Canada • Setting: Single centre • Starting CAPD; minimal or no renal bone disease on X-ray • Number: treatment group (6); control group (6) • Mean age ± SD (years): treatment (11.6 ± 6.0); control group (16.4 ± 14.0) • Sex (M/F): treatment group (4/2); control group (4/2) • Exclusion criteria: severe radiological or evidence of clinical bone disease
Interventions	Treatment group • 1α-hydroxyvitamin D 10-20 ng/kg/d for 6 months Control group • Standard CAPD treatment only Co-interventions • Phosphate binders; vitamins B and C supplements
Outcomes	• Bone histology • Serum Ca, phosphorus, ALP, PTH and aluminium levels • Bone X-rays • Number with hypercalcaemia
Notes	• Median derived radiological scores provided in graphical form only

Risk of bias

Bias	Authors' judgement	Support for judgement

Watson 1988 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Randomly allocated by sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding could influence patient management
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Laboratory results and bone histology assessed by investigator unaware of treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed study
Selective reporting (reporting bias)	Low risk	All relevant outcomes reported
Other bias	High risk	Supported by Leo laboratories

AKI - acute kidney injury; ALP - alkaline phosphatase; AKI - acute kidney injury; BMD - bone mineral density; Ca - serum calcium; Ca x P - calcium-phosphorus product; CAPD - continuous ambulatory peritoneal dialysis; CCPD - continuous cycling peritoneal dialysis; CKD - chronic kidney disease; CrCl - creatinine clearance; DHT - dihydrotachysterol; eGFR - estimated glomerular filtration rate; HD - haemodialysis; HVSDS - height velocity standard deviation score; IP - intraperitoneal; IV - intravenous; K - serum potassium; M/F - male/female; PD - peritoneal dialysis; PTH - parathyroid hormone; SLE - systemic lupus erythrocytosis; RCT - randomised controlled trial; rhGH - growth hormone; RRT - renal replacement therapy; SDS - standard deviation score

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ardissino 2000a	Examining calcium absorption only
Bettinelli 1986	Ten children included and 5 ceased calcitriol for second 6 months of study. Unclear as to how patients were chosen for cessation of calcitriol
Choudhary 2014	Ineligible population; children with nephrotic syndrome and normal kidney function
El Husseini 2004	Examining osteopenia in transplant patients
Ferraris 2000	Examining corticosteroids in kidney transplant patients
Kim 2006b	Wrong population
Witmer 1976	Randomisation unclear

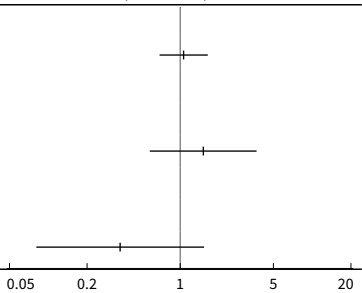
DATA AND ANALYSES

Comparison 1. Intraperitoneal versus oral calcitriol

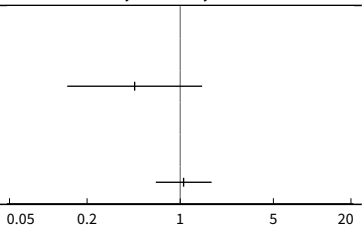
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone disease on bone histology	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Abnormal bone histology	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Adynamic bone disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Osteitis fibrosa	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Mixed or mild bone disease	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Normal or reduced bone formation	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Bone formation rate	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 PTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Maximum calcium level	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Adverse events	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected
5.1 Calcium > 11 mg/dL	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Phosphate > 7.0 mg/dL	1		Risk Difference (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Peritonitis episodes/patient-months	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Intraperitoneal versus oral calcitriol, Outcome 1 Bone disease on bone histology.

Study or subgroup	Intraperitoneal n/N	Oral n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.1 Abnormal bone histology				
Salusky 1998	12/16	12/17		1.06[0.7,1.61]
1.1.2 Adynamic bone disease				
Salusky 1998	7/16	5/17		1.49[0.59,3.74]
1.1.3 Osteitis fibrosa				
Salusky 1998	2/16	6/17		0.35[0.08,1.51]

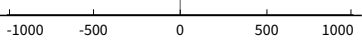


Study or subgroup	Intraperitoneal n/N	Oral n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.4 Mixed or mild bone disease				
Salusky 1998	3/16	7/17		0.46[0.14,1.46]
1.1.5 Normal or reduced bone formation				
Salusky 1998	11/16	11/17		1.06[0.66,1.72]



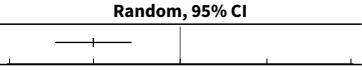
Analysis 1.2. Comparison 1 Intraperitoneal versus oral calcitriol, Outcome 2 Bone formation rate.

Study or subgroup	Intraperitoneal N	Intraperitoneal Mean(SD)	Oral N	Oral Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Salusky 1998	16	297 (472)	17	586 (973)		-289[-806.13,228.13]



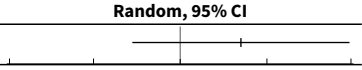
Analysis 1.3. Comparison 1 Intraperitoneal versus oral calcitriol, Outcome 3 PTH.

Study or subgroup	Intraperitoneal N	Intraperitoneal Mean(SD)	Oral N	Oral Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Salusky 1998	16	169 (228)	17	670 (400)		-501[-721.54,-280.46]



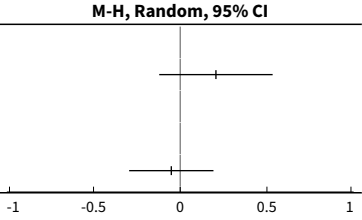
Analysis 1.4. Comparison 1 Intraperitoneal versus oral calcitriol, Outcome 4 Maximum calcium level.

Study or subgroup	Intraperitoneal N	Intraperitoneal Mean(SD)	Oral N	Oral Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Salusky 1998	16	10.4 (2)	17	9.7 (1.6)		0.7[-0.55,1.95]



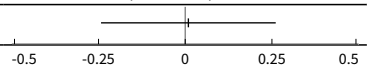
Analysis 1.5. Comparison 1 Intraperitoneal versus oral calcitriol, Outcome 5 Adverse events.

Study or subgroup	Intraperitoneal n/N	Oral n/N	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
1.5.1 Calcium > 11 mg/dL				
Salusky 1998	8/16	5/17		0.21[-0.12,0.53]
1.5.2 Phosphate > 7.0 mg/dL				
Salusky 1998	2/16	3/17		-0.05[-0.29,0.19]



Analysis 1.6. Comparison 1 Intraperitoneal versus oral calcitriol, Outcome 6 Peritonitis episodes/patient-months.

Study or subgroup	Intraperitoneal n/N	Oral n/N	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
Salusky 1998	1/10	1/11		0.01[-0.24,0.26]

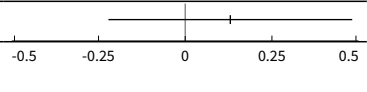


Comparison 2. Intermittent versus daily oral calcitriol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in height SDS at 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Fall in PTH	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 8 weeks	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 12 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Number with fall in PTH at 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Mean integrated PTH at 12 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Kidney function	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Final CrCl at 8 weeks [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Change in CrCl at 12 months [mL/min/1.73 m^2]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Adverse events	2		Risk Difference (M-H, Random, 95% CI)	Subtotals only
6.1 Calcium > 11.5 mg/dL	2	80	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.17, 0.13]
6.2 Phosphorus > 7.5 mg/dL	1	59	Risk Difference (M-H, Random, 95% CI)	0.03 [-0.06, 0.12]

Analysis 2.1. Comparison 2 Intermittent versus daily oral calcitriol, Outcome 1 Change in height SDS at 12 months.

Study or subgroup	Intermittent N	Intermittent Mean(SD)	Daily N	Daily Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Schmitt 2003	12	-0 (0.5)	12	-0.2 (0.3)		0.13[-0.22,0.48]

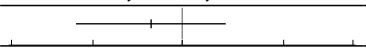


Analysis 2.2. Comparison 2 Intermittent versus daily oral calcitriol, Outcome 2 Fall in PTH.

Study or subgroup	Intermittent N	Intermittent Mean(SD)	Daily N	Daily Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.2.1 8 weeks						
Ardissino 2000	30	13.7 (46.7)	29	19.2 (57.8)		-5.5[-32.37,21.37]
2.2.2 12 months						
Schmitt 2003	12	58 (26)	12	64 (22)		-6[-25.27,13.27]

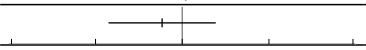
Analysis 2.3. Comparison 2 Intermittent versus daily oral calcitriol, Outcome 3 Number with fall in PTH at 8 weeks.

Study or subgroup	Intermittent n/N	Daily n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ardissino 2000	21/30	23/29		0.88[0.65,1.19]



Analysis 2.4. Comparison 2 Intermittent versus daily oral calcitriol, Outcome 4 Mean integrated PTH at 12 months.

Study or subgroup	Intermittent N	Intermittent Mean(SD)	Daily N	Daily Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Schmitt 2003	12	285 (213)	12	343 (171)		-58[-212.55,96.55]

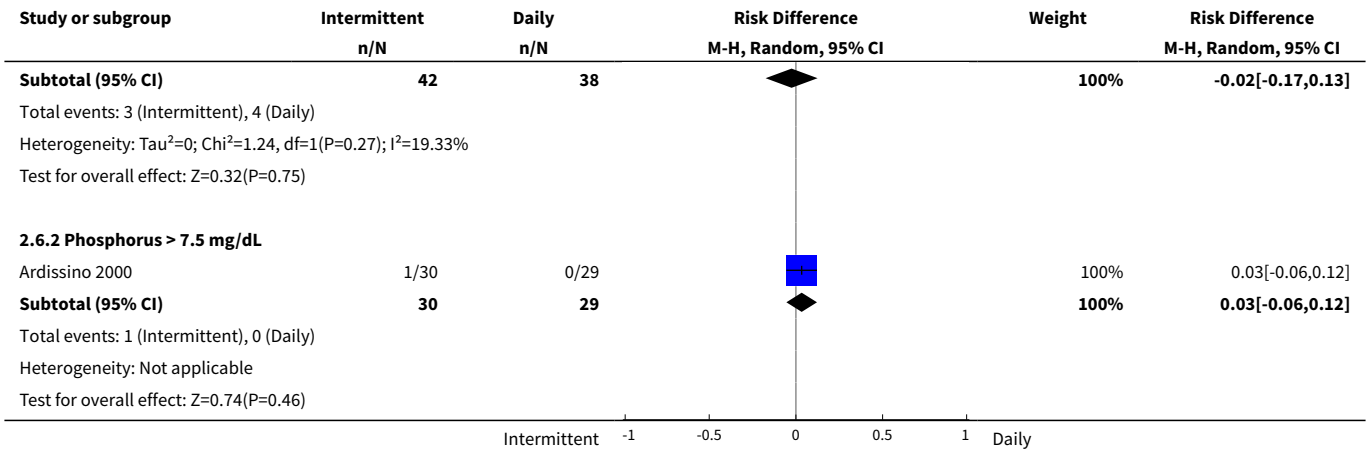


Analysis 2.5. Comparison 2 Intermittent versus daily oral calcitriol, Outcome 5 Kidney function.

Study or subgroup	Intermittent N	Intermittent Mean(SD)	Daily N	Daily Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.5.1 Final CrCl at 8 weeks [mL/min/1.73 m2]						
Ardissino 2000	30	22.1 (13.3)	29	21.6 (11)		0.5[-5.72,6.72]
2.5.2 Change in CrCl at 12 months [mL/min/1.73 m2]						
Schmitt 2003	12	-1.6 (4)	12	-3.1 (4.8)		1.5[-2.04,5.04]

Analysis 2.6. Comparison 2 Intermittent versus daily oral calcitriol, Outcome 6 Adverse events.

Study or subgroup	Intermittent n/N	Daily n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
2.6.1 Calcium > 11.5 mg/dL					
Ardissino 2000	1/30	1/29		85.68%	-0[-0.09,0.09]
Klaus 1995	2/12	3/9		14.32%	-0.17[-0.54,0.21]



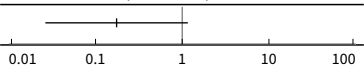
Comparison 3. Vitamin D preparations versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abnormal bone histology	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Elevated PTH	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 PTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Number with 30% fall in PTH on two occasions	2	76	Risk Ratio (M-H, Random, 95% CI)	2.75 [1.39, 5.47]
5 Change in PTH with IV calcitriol	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Hypercalcaemia	4	103	Risk Difference (M-H, Random, 95% CI)	0.08 [-0.08, 0.24]
7 Calcium-phosphorus product > 7.5 mg^2/dL^2	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected
8 Phosphorus > 6.5 mg/dL	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected
9 Change in biochemical values	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 Calcium [mg/dL]	2	76	Mean Difference (IV, Random, 95% CI)	0.10 [-0.45, 0.65]
9.2 Calcium-phosphorus product [mg^2/dL^2]	2	76	Mean Difference (IV, Random, 95% CI)	0.45 [-7.94, 8.83]
9.3 Phosphorus [mg/dL]	2	76	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.66, 0.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.4 Bone ALP [µg/L]	1	41	Mean Difference (IV, Random, 95% CI)	-47.7 [-88.54, -6.86]

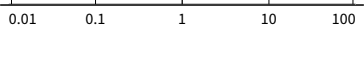
Analysis 3.1. Comparison 3 Vitamin D preparations versus placebo/no treatment, Outcome 1 Abnormal bone histology.

Study or subgroup	Vitamin D preparations n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Eke 1983	1/8	5/7		0.18[0.03,1.16]



Analysis 3.2. Comparison 3 Vitamin D preparations versus placebo/no treatment, Outcome 2 Elevated PTH.

Study or subgroup	Vitamin D preparations n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Watson 1988	1/6	6/6		0.23[0.06,0.97]

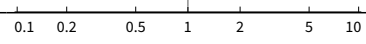


Analysis 3.3. Comparison 3 Vitamin D preparations versus placebo/no treatment, Outcome 3 PTH.

Study or subgroup	Vitamin D preparations N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Watson 1988	6	18 (14.7)	6	73 (31.8)		-55[-83.03,-26.97]

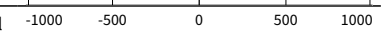
Analysis 3.4. Comparison 3 Vitamin D preparations versus placebo/no treatment, Outcome 4 Number with 30% fall in PTH on two occasions.

Study or subgroup	Vitamin D preparations n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Greenbaum 2005	11/21	5/26		59.93%	2.72[1.12,6.61]
Greenbaum 2007	9/15	3/14		40.07%	2.8[0.95,8.28]
Total (95% CI)	**36**	**40**		**100%**	**2.75[1.39,5.47]**
Total events: 20 (Vitamin D preparations), 8 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.97); I²=0%					
Test for overall effect: Z=2.89(P=0)					



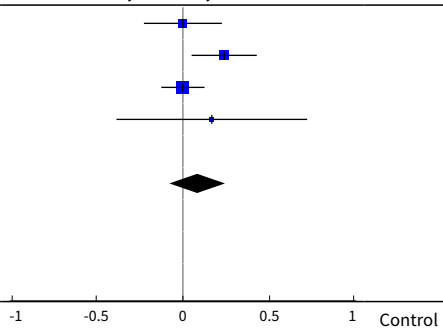
Analysis 3.5. Comparison 3 Vitamin D preparations versus placebo/ no treatment, Outcome 5 Change in PTH with IV calcitriol.

Study or subgroup	IV calcitriol		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Greenbaum 2005	21	-193 (637)	26	10 (347)		-203[-506.34,100.34]



Analysis 3.6. Comparison 3 Vitamin D preparations versus placebo/no treatment, Outcome 6 Hypercalcaemia.

Study or subgroup	Vitamin D preparations	Control	Risk Difference	Weight	Risk Difference
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Eke 1983	0/8	0/7		25.11%	0[-0.22,0.22]
Greenbaum 2005	5/21	0/26		29.49%	0.24[0.05,0.43]
Greenbaum 2007	0/15	0/14		38.14%	0[-0.12,0.12]
Watson 1988	3/6	2/6		7.26%	0.17[-0.38,0.72]
Total (95% CI)	**50**	**53**		**100%**	**0.08[-0.08,0.24]**
Total events: 8 (Vitamin D preparations), 2 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=6.62, df=3(P=0.09); I^2=54.65%					
Test for overall effect: Z=1.01(P=0.31)					

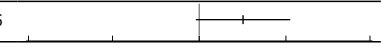


Analysis 3.7. Comparison 3 Vitamin D preparations versus placebo/ no treatment, Outcome 7 Calcium-phosphorus product > 7.5 mg^2/dL^2.

Study or subgroup	Vitamin D preparations	Control	Risk Difference	Risk Difference
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Greenbaum 2005	8/21	1/26		0.34[0.12,0.56]

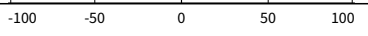
Analysis 3.8. Comparison 3 Vitamin D preparations versus placebo/no treatment, Outcome 8 Phosphorus > 6.5 mg/dL.

Study or subgroup	Vitamin D preparations	Control	Risk Difference	Risk Difference
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Greenbaum 2005	15/21	12/26		0.25[-0.02,0.52]



Analysis 3.9. Comparison 3 Vitamin D preparations versus placebo/no treatment, Outcome 9 Change in biochemical values.

Study or subgroup	Vitamin D preparations N	Mean(SD)	Control N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.9.1 Calcium [mg/dL]							
Greenbaum 2005	21	0.4 (0.6)	26	0.1 (0.7)		65.37%	0.3[-0.06,0.66]
Greenbaum 2007	15	0 (1)	14	0.3 (1)		34.63%	-0.29[-1.03,0.45]
Subtotal ***	**36**		**40**			**100%**	**0.1[-0.45,0.65]**
Heterogeneity: Tau^2=0.09; Chi^2=1.99, df=1(P=0.16); I^2=49.79%							
Test for overall effect: Z=0.34(P=0.73)							
3.9.2 Calcium-phosphorus product [mg2/dL2]							
Greenbaum 2005	21	4.7 (12.4)	26	0.6 (14.8)		57.81%	4.1[-3.68,11.88]
Greenbaum 2007	15	-1.3 (14.1)	14	3.2 (14.1)		42.19%	-4.56[-14.83,5.71]
Subtotal ***	**36**		**40**			**100%**	**0.45[-7.94,8.83]**
Heterogeneity: Tau^2=15.9; Chi^2=1.74, df=1(P=0.19); I^2=42.39%							
Test for overall effect: Z=0.1(P=0.92)							
3.9.3 Phosphorus [mg/dL]							
Greenbaum 2005	21	0.2 (1.3)	26	0 (1.7)		56.62%	0.23[-0.63,1.09]
Greenbaum 2007	15	-0.1 (1.4)	14	0.2 (1.4)		43.38%	-0.33[-1.31,0.65]
Subtotal ***	**36**		**40**			**100%**	**-0.01[-0.66,0.63]**
Heterogeneity: Tau^2=0; Chi^2=0.71, df=1(P=0.4); I^2=0%							
Test for overall effect: Z=0.04(P=0.97)							
3.9.4 Bone ALP [µg/L]							
Greenbaum 2005	19	-4.5 (67)	22	43.2 (66)		100%	-47.7[-88.54,-6.86]
Subtotal ***	**19**		**22**			**100%**	**-47.7[-88.54,-6.86]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.29(P=0.02)							



Vitamin D preparations Control

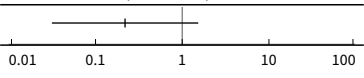
Comparison 4. Calcitriol versus ergocalciferol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Height velocity ≥ expected	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Improved bone histology	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 PTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Hypercalcaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Biochemical values	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Calcium [mmol/L]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Phosphorus [mmol/L]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 ALP [U/L]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

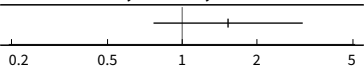
Analysis 4.1. Comparison 4 Calcitriol versus ergocalciferol, Outcome 1 Height velocity ≥ expected.

Study or subgroup	Calcitriol n/N	Ergocalciferol n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hodson 1985	1/8	4/7		0.22[0.03,1.53]



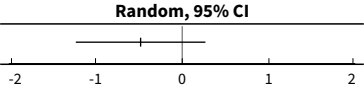
Analysis 4.2. Comparison 4 Calcitriol versus ergocalciferol, Outcome 2 Improved bone histology.

Study or subgroup	Calcitriol n/N	Ergocalciferol n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hodson 1985	7/8	4/7		1.53[0.77,3.06]



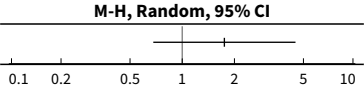
Analysis 4.3. Comparison 4 Calcitriol versus ergocalciferol, Outcome 3 PTH.

Study or subgroup	Calcitriol N	Calcitriol Mean(SD)	Ergocalciferol N	Ergocalciferol Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Hodson 1985	6	0.9 (0.4)	7	1.4 (0.9)		-0.48[-1.23,0.27]



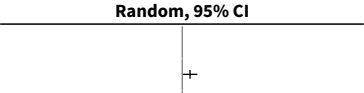
Analysis 4.4. Comparison 4 Calcitriol versus ergocalciferol, Outcome 4 Hypercalcaemia.

Study or subgroup	Calcitriol n/N	Ergocalciferol n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hodson 1985	6/8	3/7		1.75[0.68,4.5]



Analysis 4.5. Comparison 4 Calcitriol versus ergocalciferol, Outcome 5 Biochemical values.

Study or subgroup	Calcitriol N	Calcitriol Mean(SD)	Ergocalciferol N	Ergocalciferol Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
4.5.1 Calcium [mmol/L]						
Hodson 1985	6	2.6 (0.1)	7	2.5 (0.2)		0.18[0.01,0.35]
4.5.2 Phosphorus [mmol/L]						



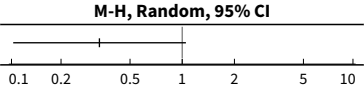
Study or subgroup	Calcitriol N	Calcitriol Mean(SD)	Ergocalciferol N	Ergocalciferol Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Hodson 1985	6	1.6 (0.3)	7	1.9 (0.5)		-0.34[-0.76,0.08]
4.5.3 ALP [U/L]						
Hodson 1985	6	169 (58)	7	208 (84)		-39[-116.63,38.63]

Comparison 5. Ergocalciferol versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number developing hyperparathyroidism	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 PTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Calcium	2	60	Mean Difference (IV, Random, 95% CI)	0.26 [-0.28, 0.81]
4 Phosphorus	2	60	Mean Difference (IV, Random, 95% CI)	-0.29 [-0.96, 0.39]
5 End 1.25(OH)D3 levels	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

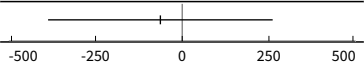
Analysis 5.1. Comparison 5 Ergocalciferol versus placebo/no treatment, Outcome 1 Number developing hyperparathyroidism.

Study or subgroup	Ergocalciferol n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Shroff 2012	3/20	9/20		0.33[0.11,1.05]



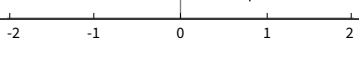
Analysis 5.2. Comparison 5 Ergocalciferol versus placebo/no treatment, Outcome 2 PTH.

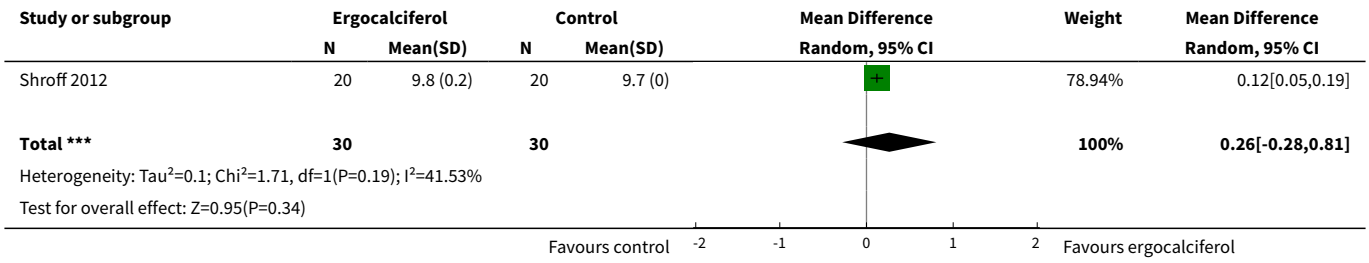
Study or subgroup	Ergocalciferol N	Ergocalciferol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Rianthavorn 2013	10	392 (409)	10	455 (325)		-63[-386.78,260.78]



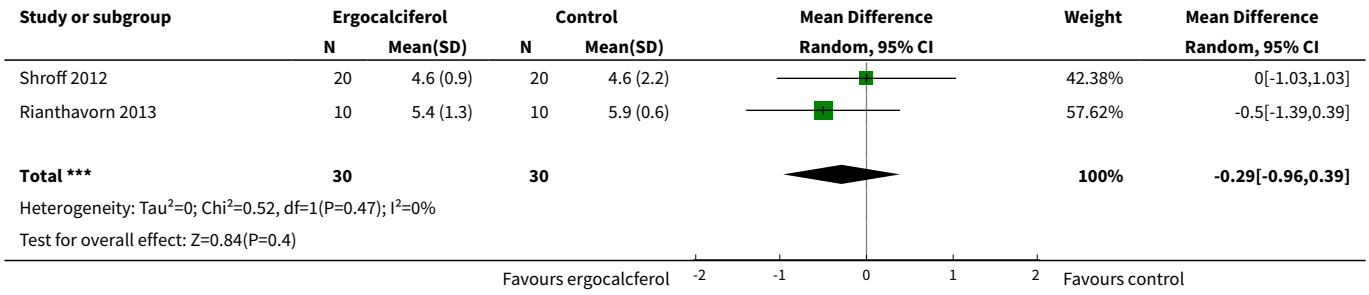
Analysis 5.3. Comparison 5 Ergocalciferol versus placebo/no treatment, Outcome 3 Calcium.

Study or subgroup	Ergocalciferol N	Ergocalciferol Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Rianthavorn 2013	10	9.8 (1)	10	9 (1.3)		21.06%	0.8[-0.22,1.82]

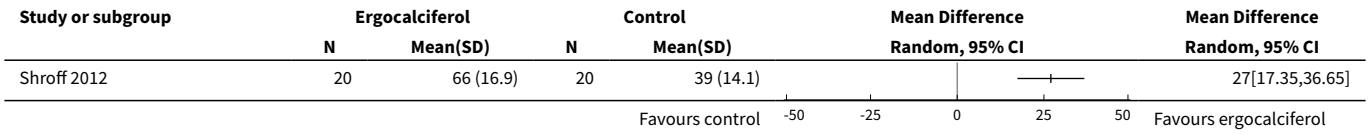




Analysis 5.4. Comparison 5 Ergocalciferol versus placebo/no treatment, Outcome 4 Phosphorus.



Analysis 5.5. Comparison 5 Ergocalciferol versus placebo/no treatment, Outcome 5 End 1.25(OH)D3 levels.

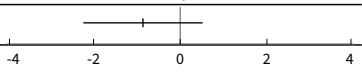


Comparison 6. Calcium carbonate versus aluminium hydroxide

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Height SDS	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Abnormal bone biopsy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Bone aluminium	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 PTH	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 ALP	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Hypercalcaemia	1		Risk Difference (M-H, Random, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Calcium carbonate versus aluminium hydroxide, Outcome 1 Height SDS.

Study or subgroup	Calcium carbonate N	Calcium carbonate Mean(SD)	Aluminium hydroxide N	Aluminium hydroxide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Salusky 1991	10	-2.8 (1.6)	7	-1.9 (1.3)		-0.86[-2.24,0.52]



Analysis 6.2. Comparison 6 Calcium carbonate versus aluminium hydroxide, Outcome 2 Abnormal bone biopsy.

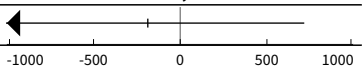
Study or subgroup	Calcium carbonate n/N	Aluminium hydroxide n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Salusky 1991	3/10	6/7		0.35[0.13,0.95]

Analysis 6.3. Comparison 6 Calcium carbonate versus aluminium hydroxide, Outcome 3 Bone aluminium.

Study or subgroup	Calcium carbonate N	Calcium carbonate Mean(SD)	Aluminium hydroxide N	Aluminium hydroxide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Salusky 1991	10	9 (9.5)	7	10 (13)		-1[-12.29,10.29]

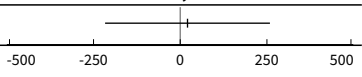
Analysis 6.4. Comparison 6 Calcium carbonate versus aluminium hydroxide, Outcome 4 PTH.

Study or subgroup	Calcium carbonate N	Calcium carbonate Mean(SD)	Aluminium hydroxide N	Aluminium hydroxide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Salusky 1991	10	731 (1062)	7	918 (833)		-187[-1089.25,715.25]



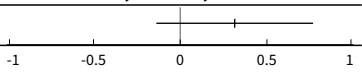
Analysis 6.5. Comparison 6 Calcium carbonate versus aluminium hydroxide, Outcome 5 ALP.

Study or subgroup	Calcium carbonate N	Calcium carbonate Mean(SD)	Aluminium hydroxide N	Aluminium hydroxide Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Salusky 1991	10	259 (231)	7	238 (256)		21[-216.62,258.62]



Analysis 6.6. Comparison 6 Calcium carbonate versus aluminium hydroxide, Outcome 6 Hypercalcaemia.

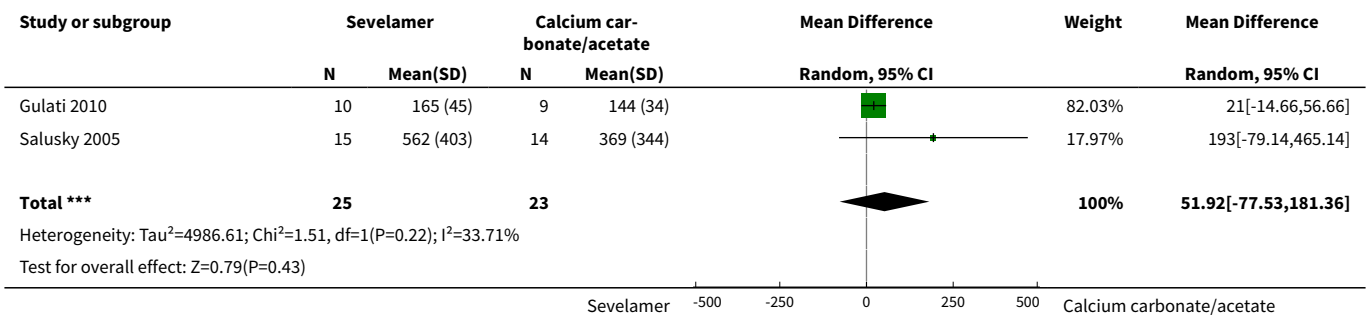
Study or subgroup	Calcium carbonate n/N	Aluminium hydroxide n/N	Risk Difference M-H, Random, 95% CI	Risk Difference M-H, Random, 95% CI
Salusky 1991	6/10	2/7		0.31[-0.14,0.77]



Comparison 7. Sevelamer versus calcium-containing phosphate binders

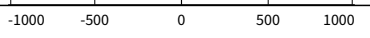
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 PTH	2	48	Mean Difference (IV, Random, 95% CI)	51.92 [-77.53, 181.36]
2 ALP	2	48	Mean Difference (IV, Random, 95% CI)	90.48 [-139.38, 320.35]
3 Calcium-phosphorus product	2	48	Mean Difference (IV, Random, 95% CI)	-1.12 [-5.88, 3.64]
4 Calcium	2	48	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.16, 0.36]
5 Phosphorus	2	48	Mean Difference (IV, Random, 95% CI)	0.17 [-0.37, 0.71]
6 Bone histomorphometry	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Bone formation rate [$\mu m^3/mm^2/d$]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Fall in bone formation rate [%]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Eroded perimeter [%]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.4 Osteoid area [%]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.5 Osteoid perimeter [%]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.6 Osteoid seam width [µm]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6.7 Bone area [%]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 7.1. Comparison 7 Sevelamer versus calcium-containing phosphate binders, Outcome 1 PTH.



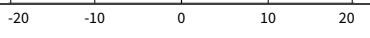
Analysis 7.2. Comparison 7 Sevelamer versus calcium-containing phosphate binders, Outcome 2 ALP.

Study or subgroup	Sevelamer		Calcium carbonate/acetate		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Gulati 2010	10	1352 (500)	9	1018 (557)		18.83%	334[-143.97,811.97]
Salusky 2005	15	254 (155)	14	220 (157)		81.17%	34[-79.65,147.65]
Total ***	**25**		**23**			**100%**	**90.48[-139.38,320.35]**
Heterogeneity: Tau²=13582.79; Chi²=1.43, df=1(P=0.23); I²=30.18%							
Test for overall effect: Z=0.77(P=0.44)							



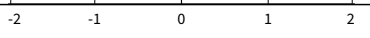
Analysis 7.3. Comparison 7 Sevelamer versus calcium-containing phosphate binders, Outcome 3 Calcium-phosphorus product.

Study or subgroup	Sevelamer		Calcium carbonate/acetate		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Gulati 2010	10	51.2 (8.4)	9	49.4 (12.9)		23.09%	1.8[-8.11,11.71]
Salusky 2005	15	51 (7.4)	14	53 (7.5)		76.91%	-2[-7.43,3.43]
Total ***	**25**		**23**			**100%**	**-1.12[-5.88,3.64]**
Heterogeneity: Tau²=0; Chi²=0.43, df=1(P=0.51); I²=0%							
Test for overall effect: Z=0.46(P=0.64)							



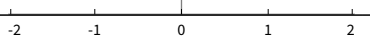
Analysis 7.4. Comparison 7 Sevelamer versus calcium-containing phosphate binders, Outcome 4 Calcium.

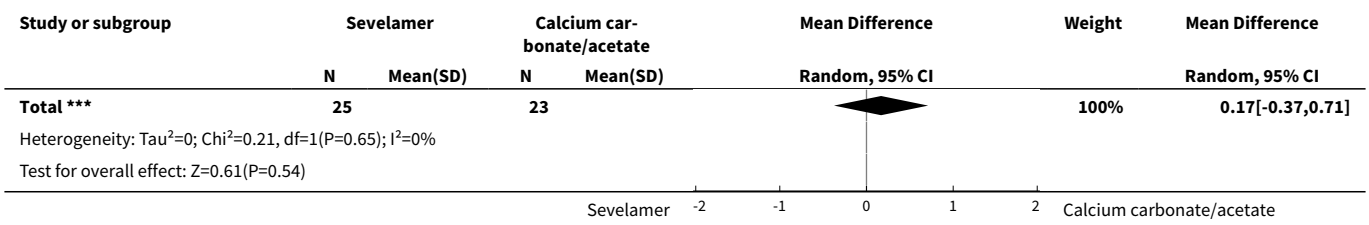
Study or subgroup	Sevelamer		Calcium carbonate/acetate		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Gulati 2010	10	8.6 (1)	9	8.5 (1)		37.44%	0.1[-0.8,1]
Salusky 2005	15	8.9 (0.8)	14	9.6 (0.4)		62.56%	-0.7[-1.14,-0.26]
Total ***	**25**		**23**			**100%**	**-0.4[-1.16,0.36]**
Heterogeneity: Tau²=0.19; Chi²=2.45, df=1(P=0.12); I²=59.15%							
Test for overall effect: Z=1.03(P=0.3)							



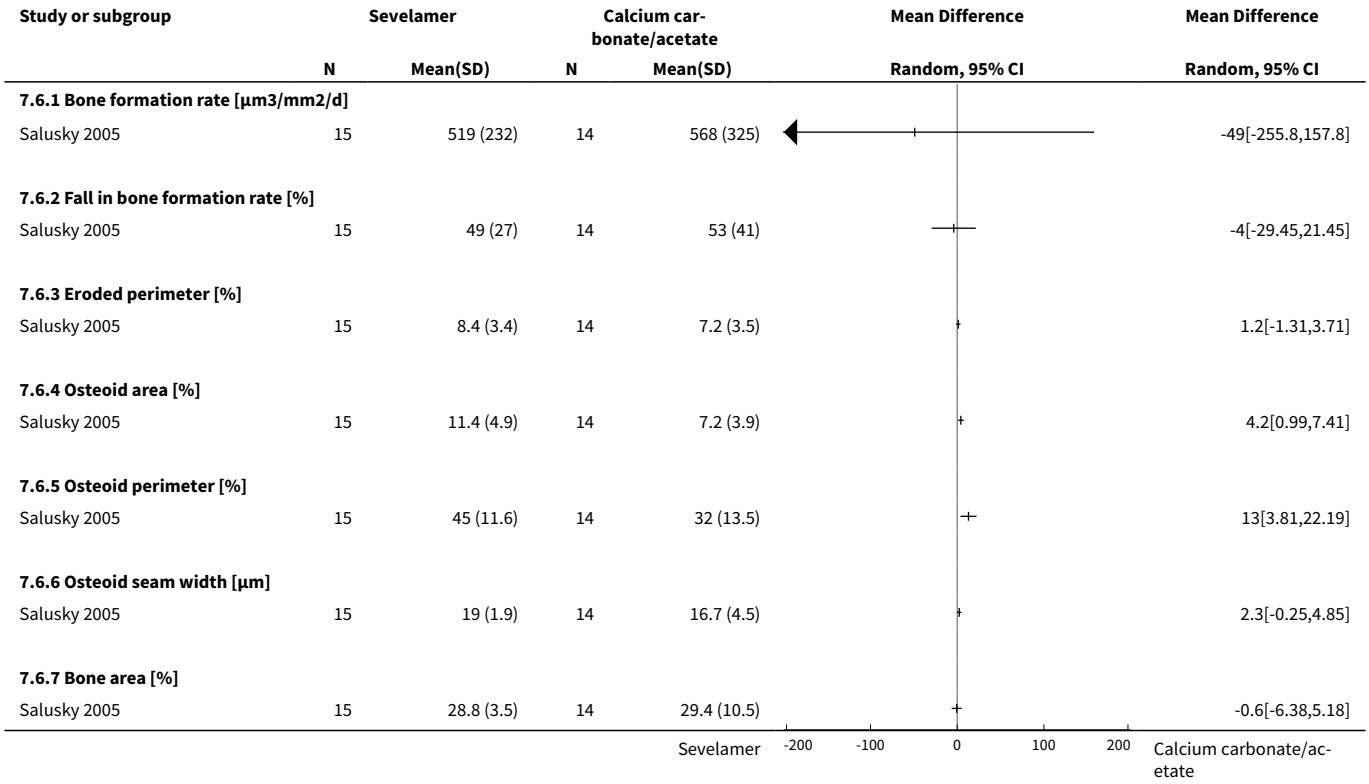
Analysis 7.5. Comparison 7 Sevelamer versus calcium-containing phosphate binders, Outcome 5 Phosphorus.

Study or subgroup	Sevelamer		Calcium carbonate/acetate		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Gulati 2010	10	6.2 (0.4)	9	5.8 (1.7)		22.79%	0.4[-0.74,1.54]
Salusky 2005	15	5.6 (1.2)	14	5.5 (0.4)		77.21%	0.1[-0.52,0.72]





Analysis 7.6. Comparison 7 Sevelamer versus calcium-containing phosphate binders, Outcome 6 Bone histomorphometry.



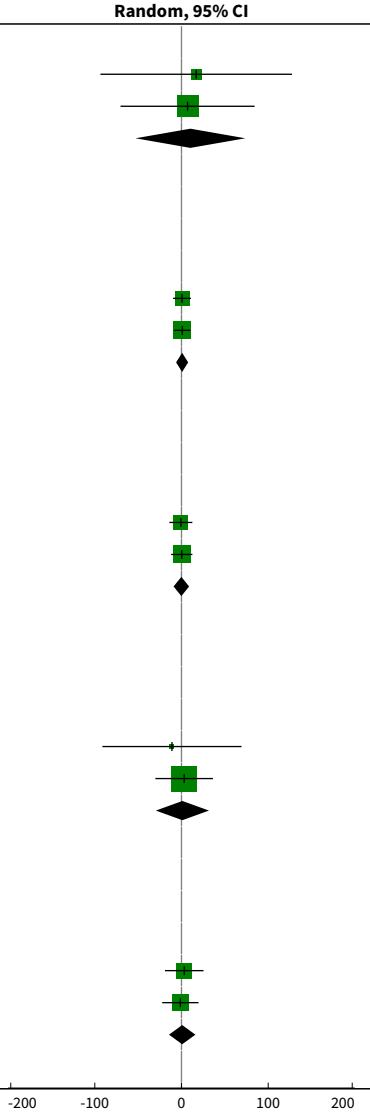
Comparison 8. Calcitriol versus doxercalciferol

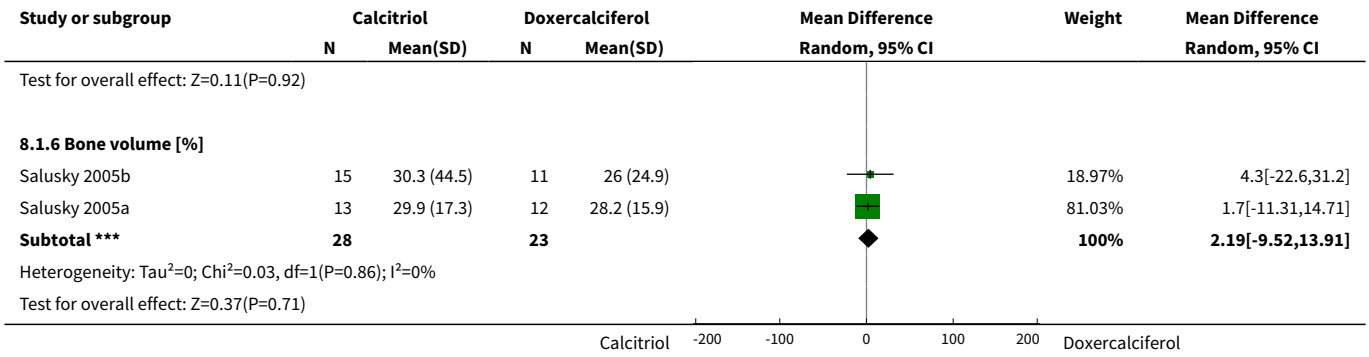
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Bone histomorphometry	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Bone formation rate [$\mu m^3/\mu m^2/d$]	2	51	Mean Difference (IV, Random, 95% CI)	10.29 [-53.07, 73.65]
1.2 Eroded bone surface [%]	2	51	Mean Difference (IV, Random, 95% CI)	0.76 [-6.19, 7.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Osteoid volume [%]	2	51	Mean Difference (IV, Random, 95% CI)	-0.16 [-9.16, 8.83]
1.4 Osteoid surface [%]	2	51	Mean Difference (IV, Random, 95% CI)	1.04 [-29.63, 31.71]
1.5 Osteoid maturation time [days]	2	51	Mean Difference (IV, Random, 95% CI)	0.82 [-14.41, 16.05]
1.6 Bone volume [%]	2	51	Mean Difference (IV, Random, 95% CI)	2.19 [-9.52, 13.91]

Analysis 8.1. Comparison 8 Calcitriol versus doxercalciferol, Outcome 1 Bone histomorphometry.

Study or subgroup	Calcitriol N	Calcitriol Mean(SD)	Doxercalciferol N	Doxercalciferol Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
8.1.1 Bone formation rate [µm3/µm2/d]							
Salusky 2005b	15	62 (201)	11	45 (73)		32.89%	17[-93.49,127.49]
Salusky 2005a	13	60 (97)	12	53 (100)		67.11%	7[-70.34,84.34]
Subtotal ***	**28**		**23**			**100%**	**10.29[-53.07,73.65]**
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%							
Test for overall effect: Z=0.32(P=0.75)							
8.1.2 Eroded bone surface [%]							
Salusky 2005a	13	7.9 (9.7)	12	7.3 (15.6)		45.7%	0.6[-9.68,10.88]
Salusky 2005b	15	8.6 (12.8)	11	7.7 (11.6)		54.3%	0.9[-8.53,10.33]
Subtotal ***	**28**		**23**			**100%**	**0.76[-6.19,7.71]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%							
Test for overall effect: Z=0.22(P=0.83)							
8.1.3 Osteoid volume [%]							
Salusky 2005b	15	8.2 (20.1)	11	8.9 (14.3)		46.25%	-0.7[-13.92,12.52]
Salusky 2005a	13	11.1 (19.8)	12	10.8 (10.4)		53.75%	0.3[-11.97,12.57]
Subtotal ***	**28**		**23**			**100%**	**-0.16[-9.16,8.83]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%							
Test for overall effect: Z=0.04(P=0.97)							
8.1.4 Osteoid surface [%]							
Salusky 2005b	15	43.8 (111.5)	11	54.8 (96.5)		14.62%	-11[-91.22,69.22]
Salusky 2005a	13	47.4 (55.9)	12	44.3 (23.6)		85.38%	3.1[-30.09,36.29]
Subtotal ***	**28**		**23**			**100%**	**1.04[-29.63,31.71]**
Heterogeneity: Tau^2=0; Chi^2=0.1, df=1(P=0.75); I^2=0%							
Test for overall effect: Z=0.07(P=0.95)							
8.1.5 Osteoid maturation time [days]							
Salusky 2005b	15	19.8 (31.8)	11	16.6 (25.9)		47.03%	3.2[-19.01,25.41]
Salusky 2005a	13	21.4 (14.4)	12	22.7 (34.3)		52.97%	-1.3[-22.23,19.63]
Subtotal ***	**28**		**23**			**100%**	**0.82[-14.41,16.05]**
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.77); I^2=0%							





ADDITIONAL TABLES

Table 1. Intraperitoneal versus oral calcitriol in children on peritoneal dialysis

Outcome	Jones 1994 [a]	Salusky 1998	Summary estimate[b]
Abnormal bone biopsy	Not reported	12/16[c] versus 12/17[d]	RR 1.06 (0.70 to 1.61)
Adynamic bone disease	Not reported	7/16 versus 5/17	RR 1.49 (0.59 to 3.74)
Osteitis fibrosa	Not reported	2/16 versus 6/17	RR 0.35 (0.08 to 1.51)
Mixed/mild disease	Not reported	3/16 versus 7/17	RR 0.46 (0.14 to 1.46)
Normal/reduced bone formation rate	Not reported	11/16 versus 11/17	RR 1.06 (0.66 to 1.72)
Bone formation rate ($\mu m^2/mm^2/d$)	Not reported	297 ± 472 versus 586 ± 973	MD -289.00 (-806.13 to 228.13)
PTH (pg/mL)	No significant difference	169 ± 228 versus 670 ± 400	MD -501.00 (-721.54 to -280.46)
Maximum serum calcium (mg/dL)	Not reported	10.4 ± 2 versus 9.7 ± 1.64	MD 0.70 (-0.55 to 1.95)
Hypercalcaemic patients	0/7 versus 0/7	8/16 versus 5/17	RD 0.21 (-0.12 to 0.53)
Hypophosphataemic patients	Not reported	2/16 versus 3/17	RD -0.05 (-0.29 to 0.19)
Peritonitis episodes/patient-month	1/ 11 versus 1/11	1/12 versus 1/10	RD 0.01 (-0.24 to 0.26)
Height SDS	-2.26 (-4.5 to -1.61) versus -2.33 (-4.27 to -1.43) (end)	Not reported	Not calculated

[a] Cross-over study
[b] Summary estimate (RR, RD, MD) and 95% CI; cross-over studies excluded
[c] Experimental intervention
[d] Comparative intervention
PTH - parathyroid hormone; SDS - standard deviation score

Table 2. Intermittent oral versus daily oral calcitriol

Outcome	Ardissino 2000	Klaus 1995	Schmitt 2003	Summary estimate [a]
% fall PTH	13.7 ± 46.7[b] versus 19.2 ± 57.8[c]	Not reported	58 ± 26 versus 64 ± 22	MD -5.83 (-21.49 to 9.83)
Number with fall in PTH	21/30 versus 23/29	"median PTH fell in both groups"	Not reported	RR 0.88 (0.65 to 1.19)
Mean integrated PTH (pg/mL)	Not reported	Not reported	285 ± 213 versus 343 ± 171	MD -58.00 (-212.55 to 96.55)
CrCl (mL/min/1.73 m^2)	22 ± 13 versus 22 ± 11(end)	Not reported	-1.6 ± 4.0 versus 3.1± 4.8 (change)	MD 0.50 (-5.72 to 6.72)
Change in height SDS	Not reported	Not reported	-0.05 ± 0.52 versus -0.18 ± 0.34	MD 0.13 (-0.22 to 0.48)
Hypercalcaemic patients	1/30 versus 1/29	2/12 versus 3/9	No difference in number of episodes	RD -0.02 (-0.17 to 0.13)
Hypophosphataemic patients	0/30 versus 1/29	Not reported	No difference in number of episodes	RD 0.03 (-0.06 to 0.12)

[a] Summary estimate (RR, RD, MD) and 95%
[b] Experimental intervention
[c] Comparative intervention
CrCl - creatinine clearance; PTH - parathyroid hormone; SDS - standard deviation score

Table 3. Vitamin D preparations versus placebo/no treatment

Outcomes	Eke 1983	Greenbaum 2005	Greenbaum 2007	Watson 1988	Summary estimate[a]
Number with abnormal bone histology	7/8[b] versus 2/7[c]	Not reported	Not reported	Reduced osteoid, bone formation and resorption in 1αOHD versus control	RR 0.17 (0.03 to 1.16)
PTH (pmol/L)	No difference	Not reported	Not reported	18 ± 15 versus 73 ± 32	MD -55.00 (-83.03 to -26.97)
Elevated PTH	Not reported	Not reported	Not reported	1/6 versus 6/6	RR 0.17 (0.03 to 1.00)
Number with 30% fall in PTH	Not reported	11/21 versus 5/26	9/15 versus 3/14	Not reported	RR 2.75 (1.39 to 5.47)
Change in PTH (pg/mL)	Not reported	-193 ± 637 versus 10 ± 347	-164 versus +238	Not reported	MD -203.00 (-506.34 to 100.34)
Hypercalcaemic patients	0/8 versus 0/7	5/21 versus 0/26	0/15 versus 0/14	3/6 versus 2/6	RD 0.08 (-0.08 to 0.24)
Ca x P > 7.5 mg^2/dL^2	Not reported	8/21 versus 1/26	Not reported	Not reported	RD 0.34 (0.12 to 0.56)

Table 3. Vitamin D preparations versus placebo/no treatment *(Continued)*

Phosphorus > 6.5 mg/dL x 2	Not reported	15/21 versus 12/26	Not reported	Not reported	RD 0.25 (-0.02 to 0.52)
Change in serum calcium (mg/dL)	No difference	0.38 ± 0.6 versus 0.08 ± 0.66	0.00 ± 1.01 versus 0.29 ± 1.01	No difference	MD -0.10 (-0.45 to 0.65)
Change in Ca x P (mg^2/dL^2)	Not reported	4.7 ± 12.4 versus 0.6 ± 14.8	-1.35 ± 14.1 versus 3.21 ± 14.1	Not reported	MD -0.45 (-7.94 to 8.83)
Change in serum phosphorus (mg/dL)	No difference	0.23 ± 1.33 versus 0.00 ± 1.68	-0.15 ± 1.35 versus 0.18 ± 1.35	No difference	MD -0.01 (-0.66 to 0.63)
Change in bone ALP (U/L)	No difference	-4.5 ± 67 versus 43.2 ± 66	Not reported	Not reported	MD -47.70 (-88.54 to -6.86)

[a] Summary estimate (RR, RD, MD) and 95% CI
[b] Experimental intervention
[c] Comparative intervention
ALP - alkaline phosphatase; Ca x P - calcium-phosphorus product; PTH - parathyroid hormone

Table 4. Calcitriol versus other active vitamin D preparations

Outcome	GFRD Study 1990	Hodson 1985	Salusky 2005a Doxercalciferol treatment	Salusky 2005b Calcitriol treatment	Summary estimate[a]
PTH (pg/mL)	Not reported	0.87 ± 0.44[b] versus 1.35 ± 0.89[c]	Graphical data only	Graphical data only	MD -0.48 (-1.23 to 0.27)
Number with Improved histology	Not reported	7/8 versus 4/7	Not reported	Not reported	RR 1.53 (0.77 to 3.06)
Height velocity ≥ expected	Positive growth scores with both treatments	1/8 versus 4/7	Not reported	Not reported	RR 0.22 (0.03 to 1.53)
Hypercalcaemic patients	No difference in number of episodes	6/8 versus 3/7	17 in sevelamer treated[b] versus 48 episodes in $CaCO_3$ treated[c]	17 in sevelamer treated[b] versus 48 episodes in $CaCO_3$ treated[c]	RR 1.75 (0.68 to 4.50)
GFR (mL/min/1.73 m^2)	Fell in both groups	Not reported	Peritoneal dialysis patients	Peritoneal dialysis patients	Not calculated
Calcium (mmol/L)	Not reported	2.63 ± 0.10 versus 2.45 ± 0.20	Graphical data only	Graphical data only	MD 0.18 (0.01 to 0.35)
Phosphorus (mmol/L)	Not reported	1.59 ± 0.30 versus 1.93 ± 0.47	Graphical data only	Graphical data only	MD -0.34 (-0.76 to 0.08)
ALP (U/L)	Not reported	169 ± 58 versus 208 ± 84	Graphical data only	Graphical data only	MD -39.00 (-116.63 to 38.63)

Table 4. Calcitriol versus other active vitamin D preparations *(Continued)*

Bone formation rate ($\mu m^3/\mu m^2$/d)	Not reported	Not reported	60 ± 97 versus 53 ± 100	62 ± 201 versus 45 ± 73	MD 10.29 (-53.07 to 73.65)
Osteoid volume (%)	Not reported	Not reported	11.1 ± 19.8 versus 10.8 ± 10.4	8.2 ± 20.1 versus 8.9 ± 14.3	MD -0.16 (-9.16 to 8.83)
Eroded bone surface (%)	Not reported	Not reported	7.9 ± 9.7 versus 7.3 ± 15.6	8.6 ± 12.8 versus 7.7 ± 11.6	MD 0.76 (-6.16 to 7.71)
Bone volume (%)	Not reported	Not reported	29.9 ± 17.3 versus 28.2 ± 15.9	30.3 ± 44.5 versus 26 ± 24.9	MD 2.19 (-9.12 to 13.91)

[a] Summary estimate (RR, RD, MD) and 95% CI
[b] Experimental intervention
[c] Comparative intervention
ALP - alkaline phosphatase; GFR - glomerular filtration rate; PTH - parathyroid hormone

Table 5. Calcium carbonate versus aluminium hydroxide

Outcome	Mak 1985 [a]	Salusky 1991	Summary estimate[b]
Abnormal bone biopsy	4 improved, 5 no change, 2 worse	3/10 versus 6/7	RR 0.35 (0.13 to 0.95)
Bone aluminium (mg/kg)	Not reported	9 ± 9.5 versus 10 ± 13	MD -1.00 (-12.29 to 10.29)
PTH levels (mL-eq/L)	Normalised with both treatments	731 ± 1062[c] versus 918 ± 833[d]	MD --187.00 (-1089.25 to 715.25)
ALP (IU/L)	Not reported	259 ± 231 versus 328 ± 256	MD 21.00 (-216.62 to 258.62)
Hypercalcaemic patients	Not reported	6/10 versus 2/7	RD 0.31 (-0.14 to 0.77)
GFR (mL/min/1.73 m^2)	21 (SE 4; beginning) versus 23 (SE 5; end)	Peritoneal dialysis patients	Not calculated
Height SDS	Not reported	-2.73 ± 1.55 versus -1.92 ± 1.33 (end)	MD -0.86 (-2.44 to 0.52)
Growth velocity SDS for chronological age	-0.82 (SE 0.31) increased to +0.31 (SE 0.39) P < 0.01	Not reported	Not calculated
Plasma aluminium (μ/dL)	3.0 ± 2.1 versus 9.0 ± 4.5	Not reported	Not calculated

[a] Cross-over study
[b] Summary estimate (RR, RD, MD) and 95% CI; cross-over studies excluded
[c] Experimental intervention
[d] Comparative intervention
ALP - alkaline phosphatase; GFR - glomerular filtration rate; PTH - parathyroid hormone; SDS - standard deviation score

Table 6. Sevelamer versus calcium carbonate or calcium acetate

Outcome	Gulati 2010	Pieper 2006 [a]	Salusky 2005	Summary estimate[b]

Table 6. Sevelamer versus calcium carbonate or calcium acetate *(Continued)*

PTH (pg/mL)	165 ± 45 versus 144 ± 34 (final)	-7 ± 196 versus -43 ± 270 (change)	562 ± 403[c] versus 369 ± 344[d] (final)	MD 51.92 (-77.53 to 181.36)
ALP (U/L)	1352 ± 500 versus1018 ± 557 (final)	70 ± 108 versus 34 ± 127 (change)	254 ± 155 versus 220 ± 157 (final)	MD 90.48 (-139.38 to 320.35)
Hypercalcaemic patients	0/10 versus 0/9	1/32 versus 6/30 periods of calcitriol	5 episodes versus 22 episodes	Not calculated
Ca x P (mg^2/dL^2)	51.2 ± 8.4 versus 49.4 ± 12.9	-1.37 ± 1.4 versus -1.12 ± 1.25 (change)	51 ± 7.4 versus 53 ± 7.5	MD -1.12 (-5.9 to 3.64)
Calcium (mg/dL)	8.6 ± 1 versus 8.5 ± 1	-0.2 ± 0.7 versus 0.4 ± 1.0 (change)	8.9 ± 0.8 versus 9.6 ± 0.4	MD -0.4 (-1.16 to -0.36)
Phosphorus (mg/dL)	6.2 ± 0.4 versus 5.8 ± 1.7	-1.5 ± 1.6 versus -1.7 ± 1.7 (change)	5.6 ± 1.2 versus 5.5 ± 0.4	MD 0.17 (-0.37 to 0.71)

[a] Cross-over study
[b] Summary estimate (RR, RD, MD) and 95% CI; cross-over studies excluded
[c] Experimental intervention
[d] Comparative intervention
ALP - alkaline phosphatase; Ca x P - calcium-phosphorus product; PTH - parathyroid hormone

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. (kidney disease or kidney failure or renal disease or renal failure):ti,ab,kw 2. renal insufficiency:ti,ab,kw 3. (CKD or CKF or CRD or CRF or CRI or ESKD or ESRD or ESKF or ESRF):ti,ab 4. renal next replacement next therap*:ti,ab,kw 5. (predialysis or dialysis):ti,ab,kw 6. (hemodialysis or haemodialysis):ti,ab,kw 7. (CAPD or CCPD or APD):ti,ab,kw 8. {or #1-#7} 9. bone disease*:ti,ab,kw 10.(osteo* or hyperparathyroid* or hyperphosphat*m*):ti,ab,kw 11.MeSH descriptor: [Bone Diseases] this term only 12.MeSH descriptor: [Bone Diseases, Metabolic] explode all trees 13.MeSH descriptor: [Hyperparathyroidism, Secondary] explode all trees 14.{or #9-#13} 15.{and #8, #14}
MEDLINE	1. Bone Diseases/ 2. exp Bone Diseases, Metabolic/ 3. exp Hyperparathyroidism, Secondary/ 4. bone disease$.tw.

(Continued)

5. (osteo$ or hyperparathyroid$ or hyperphosphat$).tw.
6. or/1-5
7. Renal Replacement Therapy/
8. exp Renal Dialysis/
9. (hemodialysis or haemodialysis).tw.
10. (hemofiltration or haemofiltration).tw.
11. (hemodiafiltration or haemodiafiltration).tw.
12. dialysis.tw.
13. (CAPD or CCPD or APD).tw.
14. Renal Insufficiency/
15. exp Renal Insufficiency, Chronic/
16. Kidney Diseases/
17. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
18. (ESRF or ESKF or ESRD or ESKD).tw.
19. (chronic kidney or chronic renal).tw.
20. (CKF or CKD or CRF or CRD).tw.
21. (predialysis or pre-dialysis).tw.
22. or/7-21
23. and/6,22

EMBASE

1. exp metabolic bone disease/
2. bone disease/
3. secondary hyperparathyroidism/
4. (osteo$ or hyperparathyroid$ or hyperphosphat$).tw.
5. bone disease$.tw.
6. or/1-5
7. exp Renal Replacement Therapy/
8. (hemodialysis or haemodialysis).tw.
9. (hemofiltration or haemofiltration).tw.
10. (hemodiafiltration or haemodiafiltration).tw.
11. dialysis.tw.
12. (CAPD or CCPD or APD).tw.
13. Kidney Disease/
14. Chronic Kidney Disease/
15. Kidney Failure/
16. Chronic Kidney Failure/
17. (chronic kidney or chronic renal).tw.
18. (CKF or CKD or CRF or CRD).tw.
19. (end-stage renal or end-stage kidney or endstage renal or endstage kidney).tw.
20. (ESRF or ESKF or ESRD or ESKD).tw.
21. (predialysis or pre-dialysis).tw.
22. or/7-21
23. exp Child/
24. exp newborn/
25. Adolescent/
26. child$.tw.
27. (pediatr$ or paediatr$).tw.
28. infant$.tw.
29. adolescen$.tw.
30. or/23-29
31. and/6,22,30

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Was there adequate sequence generation?	*Yes (low risk of bias):* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	No (high risk of bias): Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Was allocation adequately concealed?	*Yes (low risk of bias):* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	No (high risk of bias): Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Was knowledge of the allocated interventions adequately prevented during the study?	*Yes (low risk of bias):* No blinding, but the review authors judge that the outcome and the outcome measurement are not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken; either participants or some key study personnel were not blinded, but outcome assessment was blinded and the non-blinding of others unlikely to introduce bias.
	No (high risk of bias): No blinding or incomplete blinding, and the outcome or outcome measurement is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken; either participants or some key study personnel were not blinded, and the non-blinding of others likely to introduce bias.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'
Were incomplete outcome data adequately addressed?	*Yes (low risk of bias):* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	No (high risk of bias): Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis

(Continued)

	done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.
Are reports of the study free of suggestion of selective outcome reporting?	*Yes (low risk of bias):* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	No (high risk of bias): Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.
Was the study apparently free of other problems that could put it at a risk of bias?	*Yes (low risk of bias):* The study appears to be free of other sources of bias.
	No (high risk of bias): Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to permit judgement of 'Yes' or 'No'.

WHAT'S NEW

Date	Event	Description
2 November 2015	New citation required but conclusions have not changed	No change to conclusions
2 November 2015	New search has been performed	New search; 3 new studies included
8 September 2015	Amended	Search strategies revised

CONTRIBUTIONS OF AUTHORS

- Elisabeth M. Hodson: concept and design, data extraction, analysis and interpretation, writing the manuscript
- Deirdre Hahn: data extraction, analysis and interpretation, writing the manuscript
- Jonathan C. Craig: concept and design, interpretation of the data, writing the manuscript

DECLARATIONS OF INTEREST

- Elisabeth Hodson: I was the lead author on a study published in 1985 (Hodson 1985), which was eligible for and included in this review. Data extraction was carried out independently by Dr Geary and myself and all data included in the review was agreed on by both authors.
- Deirdre Hahn: none declared
- Jonathan Craig: none declared

INDEX TERMS

Medical Subject Headings (MeSH)

Aluminum Hydroxide [therapeutic use]; Bone Density Conservation Agents [*therapeutic use]; Bone Diseases, Metabolic [blood] [*drug therapy] [etiology]; Calcitriol [therapeutic use]; Calcium [blood]; Calcium Carbonate [therapeutic use]; Chronic Disease; Ergocalciferols [therapeutic use]; Kidney Diseases [*complications]; Parathyroid Hormone [blood]; Phosphorus [blood]; Polyamines [therapeutic use]; Randomized Controlled Trials as Topic; Sevelamer [therapeutic use]; Vitamin D [therapeutic use]

MeSH check words

Child; Humans