Vitamin D compounds for people with chronic kidney disease requiring dialysis (Review)

Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GFM

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[Intervention Review]

Vitamin D compounds for people with chronic kidney disease requiring dialysis

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Editorial group: Cochrane Renal Group.
Publication status and date: New, published in Issue 4, 2009.
Review content assessed as up-to-date: 3 March 2008.

Citation: Palmer SC, McGregor DO, Craig JC, Elder G, Macaskill P, Strippoli GFM. Vitamin D compounds for people with chronic kidney disease requiring dialysis. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No.: CD005633. DOI: 10.1002/14651858.CD005633.pub2.

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ABSTRACT

Background

Clinical guidelines recommend vitamin D compounds to suppress serum parathyroid hormone (PTH) in chronic kidney disease (CKD), however treatment may be associated with increased serum phosphorus and calcium, which are associated with increased mortality in observational studies. Observational data also indicate vitamin D therapy may be independently associated with reduced mortality in CKD.

Objectives

We assessed the effects of vitamin D compounds on clinical, biochemical, and bone outcomes in people with CKD and receiving dialysis.

Search strategy

We searched The Cochrane Renal Group's specialised register, Cochrane's Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and reference lists of retrieved articles.

Selection criteria

Randomised controlled trials (RCTs) in subjects with CKD and requiring dialysis that assessed treatment with vitamin D compounds.

Data collection and analysis

Data was extracted by two authors. Results are summarised as risk ratios (RR) for dichotomous outcomes or mean differences (MD) for continuous outcomes, with 95% confidence intervals (CI).

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Main results

Sixty studies (2773 patients) were included. No formulation, route, or schedule of administration was associated with altered risks of death, bone pain, or parathyroidectomy. Marked heterogeneity in reporting of outcomes resulted in few data available for formal meta-analysis. Compared with placebo, vitamin D compounds lowered serum PTH at the expense of increasing serum phosphorus. Trends toward increased hypercalcaemia and serum calcium did not reach statistical significance but may be clinically relevant. Newer vitamin D compounds (paricalcitol, maxacalcitol, doxercalciferol) lowered PTH compared with placebo, with increased risks of hypercalcaemia, although inadequate data were available for serum phosphorus. Intravenous vitamin D may lower PTH compared with oral treatment, and be associated with lower serum phosphorus and calcium levels, although limitations in the available studies precludes a conclusive statement of treatment efficacy. Few studies were available for intermittent versus daily and intraperitoneal versus oral administration or directly comparative studies of newer versus established vitamin D compounds.

Authors' conclusions

We confirm that vitamin D compounds suppress PTH in people with CKD and requiring dialysis although treatment is associated with clinical elevations in serum phosphorus and calcium. All studies were inadequately powered to assess the effect of vitamin D on clinical outcomes and until such studies are conducted the relative importance of changes in serum PTH, phosphorus and calcium resulting from vitamin D therapy remain unknown. Observational data showing vitamin D compounds may be associated with improved survival in CKD need to be confirmed or refuted in specifically designed RCTs.

PLAIN LANGUAGE SUMMARY

Vitamin D compounds for people with chronic kidney disease requiring dialysis

People with reduced kidney function (chronic kidney disease; CKD) develop changes in circulating blood levels of calcium and phosphorus. The kidney gradually loses the ability to remove phosphorus from the blood and cannot activate adequate amounts of vitamin D, to maintain normal levels of calcium. The parathyroid gland senses these changes and compensates to increase calcium by elevating production and release of parathyroid hormone. These metabolic changes alter bone metabolism to release calcium and accordingly lead to bone abnormalities including altered bone production. Consequently bone deformation, bone pain, and altered risks of fracture may occur.

Treatment for these mineral changes in CKD include replacing activated vitamin D to suppress parathyroid hormone release. Earlier activated vitamin D preparations (calcitriol and alfacalcidol) were associated with increased circulating calcium and phosphorus levels through their direct action on the vitamin D receptor. Newer agents have since been developed that similarly suppress parathyroid hormone but may limit increases in calcium and phosphorus. Avoidance of increased calcium and phosphorus is considered important as these minerals may activate calcification in arteries and tissues, potentially leading to heart disease and tissue damage.

We identified 60 studies of vitamin D preparations in people with CKD and requiring dialysis involving 2773 people. No studies were designed to understand the effect of vitamin D therapy on risks of death. Vitamin D agents suppress PTH significantly compared with no treatment, however also increase both circulating calcium and phosphorus levels. Intravenous vitamin D may lower PTH more than oral vitamin D. Few studies directly compare newer vitamin D therapies with earlier (and presently more common treatment options; calcitriol and alfacalcidol); newer treatment options therefore cannot be recommended as superior to established treatments.

In the future, new studies will required to know if vitamin D effects on parathyroid function improve survival, bone pain, and need for parathyroid removal by surgery. It is possible that vitamin D compounds are beneficial to patients regardless of their effects on parathyroid hormone. This can only be adequately evaluated by conducting specific studies that are large enough to be sure of any treatment differences.

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BACKGROUND

Description of the condition

All stages of chronic kidney disease (CKD) (*see* Table 1- *Stages of chronic kidney disease (KDOQI))* are associated with significantly reduced survival Weiner 2004. Large scale observational data now show the altered metabolism of calcium and phosphorus in people with CKD contributes to adverse cardiovascular and mortality outcomes (Block 2004; Ganesh 2001). The most frequent pattern of biochemical changes which occur early in CKD include increased serum phosphorus and parathyroid hormone (PTH) levels, while levels of serum calcium may be low, normal or elevated (Coen 2002). These abnormalities are associated with abnormal bone mineralization, increased bone fragility (Alem 2000; Piraino 1988), muscle weakness (Lazaro 1980), and vascular and soft tissue calcification (Di Leo 2003; Goldsmith 1997).

Table 1. Stages of chronic kidney disease (KDOQI)

CKD stage	GFR range
1	≥ 90 mL/min/1.73 m² with kidney damage for ≥3 months as defined by structural or functional abnormalities of the kidney
2	60-89 mL/min/1.73 m²
3	30-59 mL/min
4	15-29 mL/min
5	< 15 mL/min or dialysis

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Description of the intervention

Bone and soft tissue changes in CKD result from the interaction between abnormalities of vitamin D metabolism and parathyroid gland activity (*see* Figure 1– *Mechanisms for abnormal mineral metabolism in chronic kidney disease*). The term vitamin D refers to the secosterols vitamin D_2 (ergocalciferol), vitamin D_3 (cholecalciferol), and the metabolites and derivatives of these molecules. Vitamin D_3 is produced primarily following conversion of 7-dehydrocholesterol in the skin with ultraviolet irradiation. Vitamin D_3 is not active and must be hydroxylated in the liver to produce the intermediate molecule, 25 hydroxyvitamin D_3. This is converted to active vitamin D_3 (called calcitriol *or* 1,25 dihydroxyvitamin D_3) in the normal kidney. Vitamin D_2 is derived from plant and fungal sources and must be activated in a similar way to vitamin D_3 to produce the active form, 1,25 dihydroxyergocalciferol. The crucial role of calcitriol deficiency in the genesis of abnormal bone, vascular, and tissue mineralization provides the rationale for its use for treating bone disease in CKD. Vitamin D maintains normal calcium homeostasis via the vitamin D receptor to increase intestinal calcium absorption and to modulate mineral mobilisation from bone.

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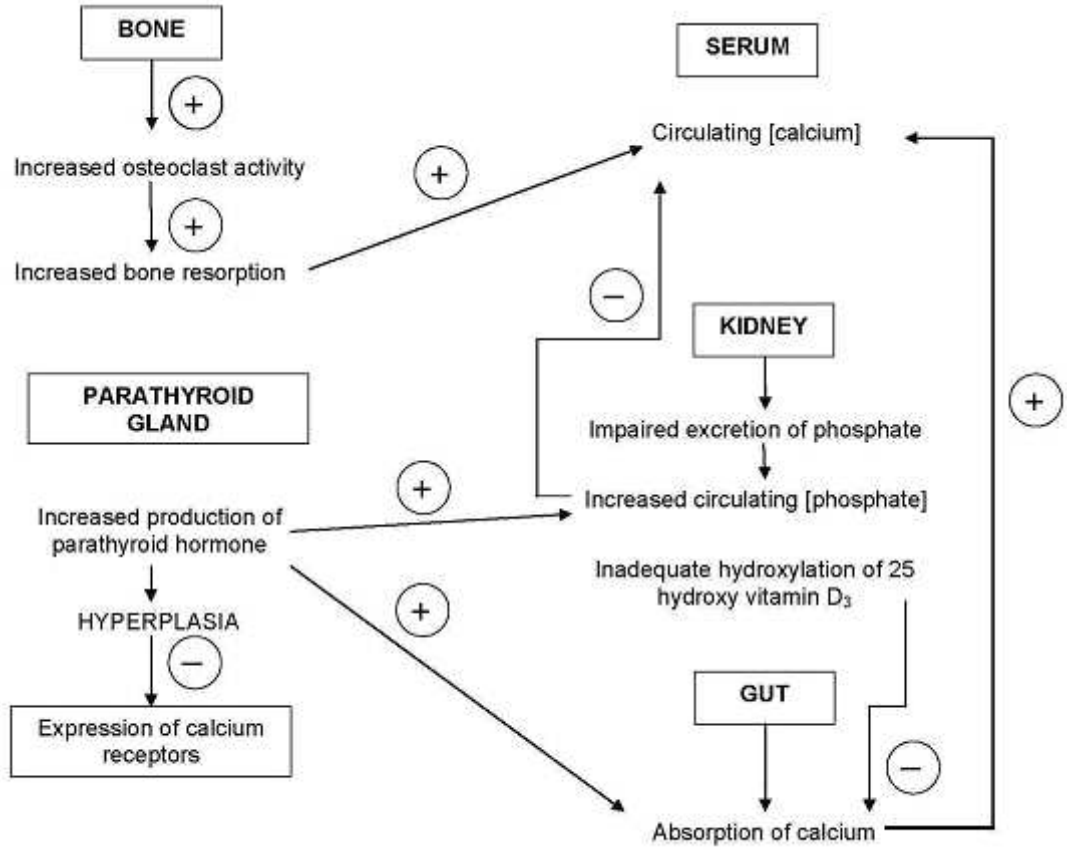
Figure 1. Mechanisms for abnormal mineral metabolism in chronic kidney disease



How the intervention might work

Interventions which are widely used to reduce complications of mineral metabolism in people with CKD include vitamin D compounds, calcium and non-calcium containing phosphate binders, and calcimimetic agents. Although vitamin D compounds reduce PTH levels, they may also increase calcium and phosphorus levels, which are associated with poorer cardiovascular and mortality outcomes (Block 1998; Block 2004; Ganesh 2001; Young 2005). Newer vitamin D compounds (maxacalcitol (22-oxacalcitriol), doxercalciferol, paricalcitol, and falecalcitriol) have been developed to provide similar or superior dose-equivalent suppression of PTH in experimental or small clinical studies, without increasing calcium and phosphorus levels to the same extent. This allows a potential for improved survival when compared with established vitamin D compounds (calcitriol or alfacalcidol) (Hirata 2003; Slatopolsky 2003; Teng 2003).

Why it is important to do this review

Given the potential opposing effects of vitamin D (improving serum PTH but increasing serum calcium and phosphorus), we evaluated available randomised controlled studies (RCTs) to assess the safety and efficacy of vitamin D compounds on biochemical, bone, and cardiovascular outcomes in people with CKD requiring dialysis together with a summary of optimal schedules and routes of administration.

OBJECTIVES

- To assess the benefits and harms of vitamin D compounds in people requiring dialysis (all-cause mortality, fracture, bone pain, stature, muscle weakness, parathyroidectomy, slipped femoral epiphyses, genu valgum).

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- To evaluate the effect of vitamin D compounds on surrogate outcomes of mineral metabolism (hypercalcaemia, hyperphosphataemia, serum calcium, phosphorus, PTH, alkaline phosphatase, bone mineral density, bone histomorphometry, periosteal erosions, vascular calcification).

Firstly, the review examined studies of vitamin D compounds (newer or established) with placebo/no treatment or direct comparative studies of newer versus established vitamin D compounds. Secondly the review explored comparisons of different routes of vitamin D compounds (oral, subcutaneous (SC), intraperitoneal (IP), intravenous (IV)) or schedules (differing doses, intermittent versus daily).

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of vitamin D compounds to manage CKD mineral and bone disorder were included. All RCTs and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) were included.

Types of participants

Adults and children with CKD requiring dialysis (CKD stage 5) were included. Recipients of kidney transplants and not receiving dialysis were excluded.

Types of interventions

Studies randomising participants to any form of vitamin D compound were included. Vitamin D compounds included:

Established vitamin D compounds

- vitamin D_3 (cholecalciferol)
- vitamin D_2 (calciferol)
- 1α -hydroxyvitamin D_3 (alfacalcidol)
- 25α-hydroxyvitamin D_3
- 24,25 dihydroxyvitamin D_3
- 1,25 dihydroxyvitamin D_3 (calcitriol)
- dihydrotachysterol

Newer vitamin D compounds

- maxacalcitol (22-oxacalcitriol, OCT)
- doxercalciferol (1α-hydroxyvitamin D_2)
- falecalcitriol (26,27-hexa-fluorocalcitriol)
- paricalcitol (19-nor-1,25-dihydroxyvitamin D_2)

Comparisons were made between:

- Vitamin D compounds versus placebo/no treatment
  - Subgroups
    - Established vitamin D compounds
    - Newer vitamin D compounds
- Vitamin D versus vitamin D compounds
  - Subgroups
    - Active vitamin D compounds versus vitamin D_3
    - Calcitriol versus other established vitamin D compounds
    - Newer versus established vitamin D compounds
- Any routes of treatment (oral versus IV, IP or SC)
- Differing schedules of treatment (intermittent versus continuous (daily))
- Differing doses of vitamin D compounds
  - Subgroups
    - Differing frequencies
    - Differing doses
    - Morning versus evening dosing

Any other co-administered treatment such as phosphate binders, calcimimetics, the adjustment of dialysate calcium, anti-bone resorption agents and dietary manipulation of calcium or phosphate were allowed in the included studies, but the randomised intervention was required to be vitamin D compounds.
Studies of other pharmacological or non-pharmacological interventions for CKD mineral and bone disorders (e.g. calcimimetics Strippoli 2006, phosphate binders Navaneethan 2006, kidney transplant recipients Palmer 2007a) are the subject of separate Cochrane reviews or protocols. Studies of vitamin D compounds for people with other stages of CKD are reported in New Reference. Studies of treatment for bone disease in children will be summarised in a Cochrane review by Geary 2009.

Types of outcome measures

- Mortality (all-cause)
- Fracture
- Development or resolution of bone pain
- Development or resolution of muscle dysfunction
- Parathyroidectomy.

Paediatric outcomes also included:

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- Genu valgum
- Slipped upper femoral epiphyses
- Stature

Surrogate outcomes included:

- Periosteal erosions
- Vascular calcification
- Bone mineral density
- Reduction of PTH concentration ≥ 30% or 50% of baseline PTH level
- Hypercalcaemia (≥10.5 mg/dL (2.63 mmol/L))
- Hyperphosphataemia (≥ 5.2 mg/dL (1.7 mmol/L))
- Elevated calcium × phosphorus product (> 75 mg^2/dL^2)
- Discontinuation from therapy due to hypercalcaemia (≥ 10.5 mg/dL (2.63 mmol/L))
- End of treatment serum PTH, calcium, phosphorus, or alkaline phosphatase concentrations
- Adverse events (excluding hypercalcaemia, hyperphosphataemia, raised calcium × phosphorus product, altered biochemical values)

Search methods for identification of studies

Relevant studies were obtained from the following resources without language restriction (see Appendix 1 *Electronic search strategies*).

1. The Cochrane Renal Group's specialised register and the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library.* CENTRAL and the Renal Group's specialised register contain the handsearched results of conference proceedings from general and specialty meetings. This is an ongoing activity across the Cochrane Collaboration and is both retrospective and prospective (Master List 2009). Therefore, we did not specifically search conference proceedings. Please refer to The Cochrane Renal Group's Module in *The Cochrane Library* for the most up-to-date list of conference proceedings (Renal Group 2009).
2. MEDLINE using the optimally sensitive strategy developed for the Cochrane Collaboration for the identification of RCTs (Dickersin 1994) with a specific strategy for vitamin D compounds in CKD.
3. EMBASE using a search strategy developed for the Cochrane Collaboration for the identification of RCTs (Lefebvre 1996) together with a specific search strategy for vitamin D compounds in CKD.
4. Reference lists of nephrology text books, review articles and relevant studies.

Data collection and analysis

Selection of studies

Titles and abstracts were screened by (SP) who discarded studies that were not applicable, however studies and reviews that might include relevant information were retained initially. Two authors assessed retrieved abstracts and, if necessary, the full text to determine which studies satisfied the inclusion criteria. This process favoured over inclusion in order to select all appropriate studies. Any disagreements with article selection was resolved through discussion.

Data extraction and management

Data were extracted by two authors from eligible studies. Participant characteristics (number, age, gender, dialysis type), intervention (type of vitamin D compound, schedule or dose of treatment), and primary and secondary outcomes were recorded. In the event of the data being published more than once, the most complete data were extracted from all sources, and used in the analyses only once. Studies reported in non-English language journals were translated before assessment. Any further information required from the original author was requested in written correspondence and any relevant information obtained in this manner was included in the review.

Assessment of risk of bias in included studies

The quality of studies was assessed without blinding to authorship or journal. Discrepancies in extraction were resolved by discussion. The quality items assessed were:

- allocation concealment,
- blinding of investigators, participants, outcome assessors and data assessors
- intention-to-treat analysis, and
- completeness to follow-up.

Results for each quality item was recorded separately. See Appendix 2 for quality assessment criteria.

Measures of treatment effect

For dichotomous outcomes (all-cause mortality, fracture, bone pain, muscle dysfunction, parathyroidectomy, vascular calcification, periosteal erosion, reduction of PTH concentration, hypercalcaemia, hyperphosphataemia, elevation of calcium × phosphorus product, genu valgum, slipped upper femoral epiphyses) results were expressed as risk ratios (RR) with 95% confidence intervals (CI). Where continuous scales of measurement were used to assess the effects of treatment (serum PTH, calcium, phosphorus and alkaline phosphatase concentrations, BMD, stature) the mean difference (MD) was used.

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Assessment of heterogeneity

Heterogeneity was analysed using a Chi² test on n-1 degrees of freedom with an α of 0.05 used for statistical significance, and with the I² statistic (Higgins 2003). I² values of 25%, 50%, and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

Insufficient RCTs comparing the same intervention were identified to examine for publication bias using a funnel plot (Egger 1997).

Data synthesis

Data were pooled using the random effects model. Fixed effect estimates were also calculated for comparison to ensure robustness of the model chosen and susceptibility to outliers.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of ongoing studies.

Results of the search

From 1455 citations, 149 underwent full text review. Full text review excluded a further 48 citations as they were not randomised, were review articles, defined outcomes unrelated to bone disease, were case reports/letters, or were pharmacokinetic studies. Sixteen studies reported RCTs of vitamin D compounds in people with other stages of CKD, which are reported in a separate systematic reviews (Palmer 2007a; Palmer 2009). Seventy eight publications reporting 60 studies (2773 patients) were included in this review. Most studies were small, with nine studies enrolling more than 75 patients and only 27 studies including more than 30 patients. Two ongoing studies of vitamin D compounds for people requiring dialysis were identified from studies registries (NCT00257920; NCT00397475) and will be assessed upon publication.

Included studies

Population characteristics

- Six studies enrolled paediatric patients (Greenbaum 2005; Greenbaum 2007; Jones 1994; Klaus 1995; Salusky 1998; Watson 1989).
- Seven studies enrolled patients on peritoneal dialysis (PD) (Gadallah 2000; Jones 1994; Liou 1995; Moe 1998; Qiu 2003; Salusky 1998; Watson 1989).
- Fifty studies enrolled patients on haemodialysis (HD) (Akiba 1998; Akizawa 2004; Bacchini 1997; Baker 1986; Berl 1980; Borazan 2003; Buccianti 1981; Caravaca 1995; Coen 1982; Delmez 2000; Deuber 2003; Djukanovic 1994; El-Reshaid 1997; Fischer 1993; Fournier 1993; Frazao 2000; Gallieni 2000; Greenbaum 2005; Greenbaum 2007; Haddad 2004; Hayashi 2004; Herrmann 1994; Indridason 2000; Khajehdehi 2003; Kihara 2004; Koshikawa 2002; Lee 1994; Levin 1995; Levine 1996; Liou 1994; Llach 1998; Martin 1998; Martin 2001; Martinez 1996; Maxwell 1978; Memmos 1981; Mitsopoulos 2006; Mochizuki 2007; Moe 2001; Moriniere 1985; Pecovnik-Balon 1995; Popovtzer 1992; Quarles 1994; Sanchez Perales 1999; Sprague 2003; Tarrass 2006; Tsuruoka 2003; Turk 2002; van der Merwe 1990; Zisman 2005).
- Two studies used both dialysis types (Gonzalez 2003; Varghese 1992).
- For one study the dialysis modality could not be ascertained (Klaus 1995).

Interventions

Vitamin D compound versus placebo (18 studies)

- Seven studies (485 patients) used calcitriol (Baker 1986; Delmez 2000; Greenbaum 2005; Khajehdehi 2003; Koshikawa 2002; Memmos 1981; Pecovnik-Balon 1995).
- Two studies (39 patients) used alfacalcidol (Moriniere 1985; Watson 1989).
- One study (12 patients) used 24, 25 dihydroxyvitamin D_3 (Varghese 1992).
- One study (176 patients) used maxacalcitol (Akizawa 2004).
- One study (138 patients) used doxercalciferol (Frazao 2000).
- Six studies (447 patients) used paricalcitol (Gonzalez 2003; Greenbaum 2007; Llach 1998; Martin 1998; Moe 2001; Qiu 2003).

Vitamin D compound versus vitamin D compound (13 studies)

Thirteen studies compared vitamin D "head-to-head" with another vitamin D compound.

Active vitamin D compound versus vitamin D_3 (2 studies)

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- Two studies (53 patients) compared calcitriol with vitamin D_3 (Berl 1980; Maxwell 1978).

Calcitriol versus another established vitamin D compound (3 studies)

- Two studies (70 patients) compared calcitriol with alfacalcidol (Deuber 2003; El-Reshaid 1997).
- One study (31 patients) compared calcitriol with 25-hydroxyvitamin D_3 (Buccianti 1981).

Established vitamin D compound versus newer vitamin D compound (6 studies)

- Three studies (130 patients) administered maxacalcitol versus calcitriol (Hayashi 2004; Kihara 2004; Mochizuki 2007),
- One study (263 patients) compared paricalcitol versus calcitriol (Sprague 2003).
- One study (21 patients) compared falecalcitriol with alfacalcidol (Akiba 1998).

Other "head-to-head" comparisons (3 studies)

- Two studies (44 patients) compared alfacalcidol and 24,25 dihydroxycholecalciferol with alfacalcidol alone (Djukanovic 1994; Popovtzer 1992).
- One study (15 patients) compared calcitriol and 25-hydroxycholecalciferol with calcitriol alone (Coen 1982)

Vitamin D compound versus calcium (1 study)

- One study (47 patients) used calcium as a comparator intervention (Fournier 1993).

Routes of vitamin D administration (16 studies)

Sixteen studies assessed different routes of administration of vitamin D compounds, all using the oral route as the comparator.

- Twelve studies (720 patients) assessed IV vitamin D (Bacchini 1997; Borazan 2003; Caravaca 1995; Fischer 1993; Haddad 2004; Indridason 2000; Lee 1994; Levin 1995; Levine 1996; Liou 1994; Quarles 1994; Turk 2002).
- Three studies (74 patients) assessed IP use (Gadallah 2000; Jones 1994; Salusky 1998).
- One study (6 patients) analysed SC dosing (Liou 1995).

Vitamin D dosing schedules (12 studies)

Twelve small studies compared different dosing schedules.

- Five studies (140 patients) compared daily with intermittent treatment (Herrmann 1994; Klaus 1995; Moe 1998; Tarrass 2006; van der Merwe 1990).
- Three studies (57 patients) compared differing frequencies of calcitriol,
    - once a week versus three times a week (Martinez 1996; Sanchez Perales 1999) or
    - twice a week versus three times a week (Gallieni 2000)
- One study (13 patients) compared morning with evening administration of vitamin D_3 (Tsuruoka 2003).
- Three studies (195 patients) were direct comparisons of different doses of doxercalciferol (Zisman 2005) or paricalcitol (Martin 2001; Mitsopoulos 2006).

Risk of bias in included studies

Allocation

Allocation concealment was adequately reported in five studies (Frazao 2000; Hayashi 2004; Indridason 2000; Quarles 1994; Watson 1989), inadequate in five (Delmez 2000; Fischer 1993; Gadallah 2000; Memmos 1981; Turk 2002), and unclear in the remaining 50 studies.

Blinding

Blinding of participants and investigators was reported in 18 studies (Akizawa 2004; Baker 1986; Berl 1980; Frazao 2000; Gonzalez 2003; Greenbaum 2005; Greenbaum 2007; Koshikawa 2002; Llach 1998; Martin 1998; Martin 2001; Maxwell 1978; Memmos 1981; Mitsopoulos 2006; Moe 2001; Qiu 2003; Quarles 1994; Sprague 2003).
Ten studies reported blinding of outcome assessors (Berl 1980; Indridason 2000; Jones 1994; Koshikawa 2002; Martin 1998; Martin 2001; Memmos 1981; Moriniere 1985; Quarles 1994; Watson 1989).

Incomplete outcome data

- Nineteen studies reported no patient was lost to follow-up (Bacchini 1997; Borazan 2003; Coen 1982; Delmez 2000; Djukanovic 1994; El-Reshaid 1997; Frazao 2000; Greenbaum 2007; Jones 1994; Lee 1994; Liou 1994; Martin 2001; Moriniere 1985; Quarles 1994; Salusky 1998; Sanchez Perales 1999; Tarrass 2006; Varghese 1992; Watson 1989).
- Completeness of follow-up was not ascertained in 11 studies (Berl 1980; Deuber 2003; Gonzalez 2003; Khajehdehi

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2003; Kihara 2004; Klaus 1995; Llach 1998; Liou 1995; Maxwell 1978; Pecovnik-Balon 1995; Zisman 2005).

- Incomplete follow-up was reported in the remaining studies, including
  - fewer than 20% in 17 studies (Akiba 1998; Akizawa 2004; Fischer 1993; Fournier 1993; Gallieni 2000; Haddad 2004; Indridason 2000; Levine 1996; Martinez 1996; Mitsopoulos 2006; Moe 1998; Moe 2001; Qiu 2003; Sprague 2003; Turk 2002; van der Merwe 1990),
  - 20% to 40% in eight studies (Caravaca 1995; Greenbaum 2005; Hayashi 2004; Koshikawa 2002; Levin 1995; Mochizuki 2007; Popovtzer 1992; Tsuruoka 2003),
  - and > 40% in the remaining six studies (Baker 1986; Buccianti 1981; Gadallah 2000; Herrmann 1994; Martin 1998; Memmos 1981).

Selective reporting

Sixteen studies were considered to have analysed their results on an ITT basis (Akizawa 2004; Borazan 2003; Fischer 1993; Gallieni 2000; Greenbaum 2007; Jones 1994; Lee 1994; Llach 1998; Martin 1998; Martin 2001; Mitsopoulos 2006; Moriniere 1985; Watson 1989; van der Merwe 1990; Sprague 2003; Tarrass 2006).

Other potential sources of bias

Twenty-two studies disclosed funding from pharmaceutical companies (Akiba 1998; Berl 1980; Frazao 2000; Greenbaum 2005; Greenbaum 2007; Gonzalez 2003; Haddad 2004; Indridason 2000; Jones 1994; Lee 1994; Levin 1995; Levine 1996; Liou 1994; Martin 1998; Martin 2001; Maxwell 1978; Moe 2001; Qiu 2003; Quarles 1994; Sprague 2003; Watson 1989; Zisman 2005).
Of the eight studies reporting efficacy as a reduction in serum PTH (> 30% or > 50%) (Akizawa 2004; Gonzalez 2003; Greenbaum 2005; Greenbaum 2007; Llach 1998; Martin 1998; Qiu 2003; Sprague 2003), six were funded or authored by Abbott Laboratories and examined paricalcitol or IV calcitriol. The remaining two studies that reported absolute PTH suppression (Akizawa 2004; Llach 1998) had no disclosures available regarding funding in the study reports.

Effects of interventions

Despite 60 studies included in this review, data were reported heterogeneously and frequently not available for meta-analysis. A summary of the efficacy and adverse event data extractable for meta-analysis is presented in Table 2. Data that were not extractable are provided in descriptive format.

Table 2. Summary of extractable data for meta-analysis

Comparison (studies)	Studies	Patients	Studies with efficacy data extractable for meta-analysis	Studies with adverse event data available	Studies/meta-analysis (range)
Vitamin D versus placebo (18)					
All studies combined	18	1297	14	8	1-7
Established vitamin D	10	850	7	5	1-4
Newer vitamin D	8	447	7	3	1-6
Vitamin D versus vitamin D compound (13)					
Active vitamin D versus vitamin D_3	2	53	1	2	1-2
Calcitriol versus another established vitamin D	3	101	1	2	1-2
Established versus newer vitamin D	5	414	2	3	1-2

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Table 2. Summary of extractable data for meta-analysis (*Continued*)

Other comparisons	3	59	Meta-analysis not possible		
Vitamin D versus calcium (1)					
All studies combined	1	47	Meta-analysis not possible		
IV **versus oral vitamin D (12)**					
All studies combined	12	720	8	8	1-6
Intraperitoneal versus oral vitamin D (3)					
All studies combined	3	74	Meta-analysis not possible		
Subcutaneous versus oral vitamin D (1)					
All studies combined	1	6	Meta-analysis not possible		
Intermittent versus daily vitamin D (5)					
All studies combined	5	140	1	4	1-4
Differing dosing schedules (7)					
Differing frequency	3	57	Meta-analysis not possible		
Differing doses	3	195	Meta-analysis not possible		
Morning versus evening dosing	1	13	Meta-analysis not possible		

Vitamin D compounds versus placebo/no treatment

Eighteen studies compared vitamin D compounds with placebo or no treatment.

Mortality

Five studies reported mortality. Memmos 1981 reported three deaths in each treatment arm and Moe 2001 reported one death in the vitamin D group. The three other studies reported that no deaths occurred during treatment (Greenbaum 2005; Khajehdehi 2003; Llach 1998). No difference in mortality was observed between active vitamin D treatment and placebo/no treatment (Analysis 1.1, 5 studies (233 patients): RR 1.34, 95% CI, 0.34 to 5.24).

Fracture

Two patients experienced one or more fractures in Baker 1986. Three other studies (Delmez 2000; Martin 1998; Watson 1989) reported no fracture events (Analysis 1.2, 4 studies (181 patients): RR 1.00, 95% CI 0.06 to 15.41).

Development of bone pain

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Two studies reported one patient developing bone pain in the no treatment arm (Llach 1998; Moriniere 1985). Two other studies reported no patients developing bone pain (Delmez 2000; Memmos 1981) (Analysis 1.3, 4 studies (109 patients): RR 0.29, 95% CI 0.03 to 2.63).

Stature

Memmos 1981 reported four patients in the placebo arm lost height during the two year study of calcitriol.

Parathyroidectomy

Two early studies reported 10 parathyroidectomy events during treatment with established vitamin D compounds (Baker 1986; Memmos 1981). No difference was observed between treatment groups (Analysis 1.4, 2 studies (133 patients): RR 0.82, 95% CI 0.05 to 12.47). No data were available for newer vitamin D compounds.

Subperiosteal erosions

Three studies reported radiology data extractable for analysis (Baker 1986; Memmos 1981; Watson 1989). No difference was observed between treatment groups for development of subperiosteal erosions (Analysis 1.5, 3 studies (120 patients): RR 0.41, 95% CI 0.07 to 2.38).

Memmos 1981 reported resolution of subperiosteal lesions in 5/11 subjects receiving calcitriol (Analysis 1.6, 1 study (22 patients): RR 11.00, 95% CI 0.68 to 177.72). No data were extractable for newer vitamin D compounds.

Vascular calcification

Two studies (Baker 1986; Moriniere 1985) reported development of vascular calcification. No difference was observed between vitamin D treatment and placebo/no treatment (Analysis 1.7, 2 studies (103 patients): RR 1.09, 95% CI 0.45 to 2.67). Baker 1986 reported progression of vascular calcification in 9/38 patients in the calcitriol group and in 17/38 patients in the placebo group (Analysis 1.8, 1 study (76 patients): RR 0.53, 95% CI 0.27 to 1.04). No extractable data were available for newer vitamin D compounds.

Bone histomorphometry

One study (patients undergoing sequential bone biopsy) reported bone histomorphometry (Baker 1986). Vitamin D treatment was associated with lower incidence of osteitis fibrosa (Analysis 1.9, 1 study (17 patients): RR 0.11, 95% CI 0.01 to 1.36) and higher risk of osteomalacia (Analysis 1.10, 1 study (13 patients): RR 23.80, 95% CI 0.89 to 633.53) these did not reach statistical significance. No data were available for newer vitamin D agents. One further study examined bone histomorphometry comparing vitamin D compounds with placebo. Watson 1989 (10 patients undergoing sequential bone biopsy) reported reduction in osteoid index and seam width in children receiving alfacalcidol for six months.

Parathyroid hormone

End of treatment serum PTH was significantly lower with vitamin D treatment compared with placebo (Analysis 1.11, 6 studies (212 patients): MD -196.05 pg/mL, 95% CI -298.43 to -93.66 (MD -22.3 pmol/L, 95% CI -34.0 to -10.7)) (Delmez 2000; Martin 1998; Memmos 1981; Moe 2001; Moriniere 1985; Watson 1989). There was significant heterogeneity in this analysis (I^2 = 65%) in part due to a higher end of treatment serum PTH in the vitamin D group in Moriniere 1985. At baseline in this study the vitamin D group had a higher serum PTH concentration than the no treatment group. No heterogeneity was observed when the effects of newer vitamin D compounds versus placebo on serum PTH was analysed in isolation.

Seven studies reported efficacy of PTH suppression as the achievement of PTH reduction $\geq$ 30% from baseline (Akizawa 2004; Gonzalez 2003; Greenbaum 2005; Greenbaum 2007; Llach 1998; Martin 1998; Qiu 2003). Vitamin D treatment was associated with a significantly higher incidence of PTH suppression (Analysis 1.12, 7 studies (361 patients): RR 5.90, 95% CI 3.17 to 10.96). Moderate heterogeneity in this analysis (I^2 = 41%) was likely due to combining the results of newer with established vitamin D compounds. Heterogeneity was lowered when the comparison of newer vitamin D versus placebo was considered separately (I^2 = 21%).

No data were extractable for the outcome of reduction in parathyroid hormone level by 50%.

Six of the eighteen studies reported effects of treatment on serum PTH that were not in a format extractable for meta-analysis (end of treatment serum PTH with estimate of variance or reduction in PTH from baseline $\geq$ 30% or $\geq$ 50%):

- Baker 1986 reported a significant reduction in serum PTH in the calcitriol group compared with placebo.
- Varghese 1992 reported results in a crossover study, comparing 24,25 hydroxyvitamin D_3 with no treatment. Serum PTH was significantly lower following three months of 24,25 hydroxyvitamin D_3 treatment compared with placebo.
- Pecovnik-Balon 1995 reported that no difference was observed between calcitriol and no treatment groups at the end of a year of treatment for serum PTH
- Frazao 2000 reported changes in serum PTH after 16 weeks of open-label doxercalciferol treatment. Following switch to placebo, serum PTH values returned to baseline values during eight weeks of the study. Serum PTH values remained significantly suppressed with doxercalciferol treatment (8 weeks).
- Koshikawa 2002 reported a dose-dependent decrease in serum PTH across 12 weeks of treatment with IV calcitriol whereas no change was observed in the no treatment group.

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- Khajehdehi 2003 reported that oral pulse calcitriol was associated with significant reductions in serum PTH following three months of treatment.

Established vitamin D compounds versus placebo

Serum PTH was lowered with established vitamin D compounds compared with placebo (Analysis 1.11.1, 4 studies (104 patients): MD -220.54 pg/mL, 95% CI -473.63 to 32.55 (MD -25.1 pmol/L, 95% CI -54.0 to 3.7)) (Delmez 2000; Memmos 1981; Moriniere 1985; Watson 1989) although this was not statistically significant. Exclusion of Moriniere 1985 (in which the vitamin D group had a higher serum PTH concentration at baseline) resulted in a significant reduction in serum PTH in the remaining studies (3 studies (77 patients): MD -217.75 pg/mL, 95% CI -308.49 to -127.01 (MD 24.8 pmol/L, 95% CI -35.2 to 14.5)).
Greenbaum 2005 reported PTH suppression of ≥ 30% from baseline, reporting 11/21 events in the vitamin D arm and 5/26 events in the control arm (Analysis 1.12.1: RR 2.72, 95% CI 1.12 to 6.61).

Newer vitamin D compounds versus placebo

Serum PTH was lowered with newer vitamin D compounds in the two studies that reported end of treatment serum PTH (Analysis 1.11.2, 2 studies (212 patients): MD -183.88 pg/mL, 95% CI -217.88 to -149.89) (MD -21.0 pmol/L, 95% CI -24.8 to -17.1)) with narrow confidence intervals (Martin 1998; Moe 2001).
Six studies reported achievement of serum PTH suppression ≥ 30% from baseline. Newer vitamin D therapy was more likely to achieve this outcome than no treatment (Analysis 1.12.2, 6 studies (314 patients): RR 7.05, 95% CI 3.82 to 13.04) (Akizawa 2004; Gonzalez 2003; Greenbaum 2007; Llach 1998; Martin 1998; Qiu 2003). Low heterogeneity (I^2 = 21%) was evident in this analysis.

Phosphorus

Two studies reported end of treatment serum phosphorus (Martin 1998; Moriniere 1985). Vitamin D therapy was associated with a significant increase in serum phosphorus (Analysis 1.13, 2 studies (105 patients): MD 0.70 mg/dL, 95% CI 0.08 to 1.33 (MD 0.23 mmol/L, 95% CI 0.03 to 0.43)).
Two studies reported one or more episodes of hyperphosphataemia (Greenbaum 2005; Watson 1989) showing a trend toward increasing hyperphosphataemia events with vitamin D treatment (Analysis 1.14, 2 studies (59 patients): RR 1.57, 95% CI 0.97 to 2.54). No extractable data were available for newer vitamin D compounds.
Fourteen of 18 studies reported effects of treatment on serum phosphorus that were not in a format extractable for meta-analysis (end of treatment serum phosphorus with estimate of variance or hyperphosphataemia):

- Memmos 1981 reported no difference in proportions of patients receiving calcitriol and placebo who showed a rise or fall in serum phosphorus during the study.
- Watson 1989 reported no difference between groups across six months of alfacalcidol treatment for serum phosphorus (paediatric study in PD).
- Varghese 1992 reported no difference in serum phosphorus levels after 24,25 hydroxyvitamin D_3 treatment (3 months) compared with placebo.
- Pecovnik-Balon 1995 reported a significant increase in serum phosphorus at the end of treatment in the calcitriol group.
- Llach 1998 reported no significant change in serum phosphorus from baseline values in either the paricalcitol or no treatment groups.
- Delmez 2000 reported no difference between calcitriol and no treatment groups during 52 weeks of treatment.
- Frazao 2000 reported no difference in serum phosphorus between groups at end of treatment with maxacalcitol versus placebo.
- Moe 2001 reported no difference in serum phosphorus levels between IV paricalcitol and no treatment groups across 12 weeks treatment.
- Koshikawa 2002 reported no changes in serum phosphorus in either IV calcitriol or no treatment groups across the 12 week study.
- Khajehdehi 2003 reported no difference in serum phosphorus levels between pulse oral calcitriol and no treatment groups across three months of treatment.
- Gonzalez 2003 reported no difference in incidence of hyperphosphataemia between oral paricalcitol and no treatment groups (12 week studies) in individuals with baseline serum PTH > 1000 pg/mL). Data were pooled from three placebo controlled RCTs.
- Akizawa 2004 reported serum phosphorus increased significantly during 12 weeks of maxacalcitol treatment compared with placebo.
- Greenbaum 2005 reported the absolute change from mean baseline to final value of serum phosphorus finding an increase across 12 weeks of IV calcitriol treatment in children although the increase was not statistically different from the no treatment group.
- Greenbaum 2007 reported no difference in mean absolute change in serum phosphorus between paricalcitol and placebo groups at end of treatment.

Two studies did not report treatment effects on serum phosphorus (Baker 1986; Qiu 2003).

Calcium

Two studies reported end of treatment serum calcium in a format extractable for meta-analysis (Martin 1998; Moriniere 1985). Vitamin D therapy was not associated with a significant increase in

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serum calcium (Analysis 1.15, 2 studies (105 patients): MD 0.36 mg/dL, 95% CI -0.26 to 0.98 (MD 0.09 mmol/L, 95% CI, -0.07 to 0.25)). One study reported this outcome for established vitamin D compounds Moriniere 1985 and one for newer vitamin D compounds Martin 1998.

Five studies reported one or more episodes of hypercalcaemia (Akizawa 2004; Delmez 2000; Greenbaum 2005; Llach 1998; Watson 1989) showing a trend toward increasing hypercalcaemia events with vitamin D treatment (Analysis 1.16, 5 studies (182 patients): RR 3.80, 95% CI 0.90 to 16.12). There was moderate heterogeneity in this analysis (I^2 = 58%) likely because newer vitamin D compounds were more frequently associated with hypercalcaemia (100% of 30 events in vitamin D group) than established compounds (73% of 15 events). It was therefore appropriate to consider established vitamin D compounds and newer vitamin D compounds separately in this analysis.

Hypercalcaemia events were not more likely with established vitamin D compounds (Delmez 2000; Greenbaum 2005; Watson 1989) (Analysis 1.16.1, 3 studies (74 patients): RR, 1.96, 95% CI 0.62 to 6.22) possibly because patients were more likely to be withdrawn from studies due to hypercalcaemia (Baker 1986; Watson 1989) (Analysis 1.17.1, 2 studies (88 patients): RR 3.66, 95% CI 0.96 to 14.03)). Low heterogeneity was observed.

By contrast, in two studies (Akizawa 2004; Llach 1998) newer vitamin D compounds were more likely to result in one or more episodes of hypercalcaemia (Analysis 1.16.2, 2 studies (108 patients): RR 11.97, 95% CI 1.48 to 96.58) although confidence intervals were wide indicating imprecision around the point estimate. Low heterogeneity was observed. Two studies of newer vitamin D compounds reported withdrawal from the study due to hypercalcaemia (all in the active treatment group) (Akizawa 2004; Llach 1998) showing no difference between treatment groups (Analysis 1.17.2, 2 studies (108 patients): RR 5.61, 95% CI 0.74 to 42.45).

Nine of 18 studies reported effects of treatment on serum calcium that were not in a format extractable for meta-analysis (end of treatment serum calcium with estimate of variance, one of more episodes of hypercalcaemia or withdrawal of treatment due to hypercalcaemia):

- Memmos 1981 reported that 17/27 patients receiving calcitriol experienced a rise in serum calcium in the first year of the study and 13/17 patients still receiving calcitriol had increases in serum calcium in the second year of the study. No patients receiving placebo had increased serum calcium.
- Varghese 1992 reported no difference in serum calcium (total or ionised) levels after 24,25 hydroxyvitamin D_3 treatment (3 months) compared with placebo.
- Pecovnik-Balon 1995 reported a significant increase in serum calcium during the course of treatment (1 year) in the calcitriol group.
- Frazao 2000 reported significantly higher serum calcium levels at end of treatment with maxacalcitol.
- Moe 2001 reported the change in serum calcium was significantly greater in the paricalcitol group compared with the placebo group.
- Koshikawa 2002 reported significant increases in serum calcium over 12 weeks of treatment in the calcitriol group. No change was observed in the placebo group.
- Gonzalez 2003 reported no difference in incidence of hypercalcaemia between oral paricalcitol and no treatment groups (12 week studies) in individuals with baseline serum PTH > 1000 pg/mL). Data were pooled from three placebo controlled RCTs.
- Khajehdehi 2003 reported significant increases in serum calcium across three months of pulse oral calcitriol compared with no treatment.
- Greenbaum 2007 reported no difference in mean change in serum calcium between paricalcitol and placebo groups at end of treatment.

Qiu 2003 did not report treatment effects on serum calcium.

Elevated calcium x phosphorus product

One study reported one or more episodes of elevated calcium x phosphorus product Greenbaum 2005 (Analysis 1.18, 1 study (88 patients): RR 9.90, 95% CI 1.34 to 73.02).

Alkaline phosphatase (ALP)

Vitamin D treatment was associated with lowering of serum alkaline phosphatase (ALP) in three studies (Martin 1998; Moe 2001; Moriniere 1985) (Analysis 1.19, 3 studies (135 patients): MD -27.35 U/L, 95% CI -50.69 to -4.01). There was no heterogeneity in this analysis. One study of established vitamin D compounds reported this outcome (Moriniere 1985). Two studies of newer vitamin D compounds resulted in lowering of serum ALP by -27.35 U/L (95% CI -50.69 to -4.01) (Martin 1998; Moe 2001).

Five studies reported serum alkaline phosphatase in a format not extractable for meta-analysis:

- Pecovnik-Balon 1995 reported no difference between calcitriol and placebo groups for end of treatment ALP concentrations.
- Koshikawa 2002 reported decreased ALP concentrations in the calcitriol group with no changes in the no treatment group.
- Khajehdehi 2003 reported significant lowering of serum ALP across three months of oral pulse calcitriol.
- Greenbaum 2005 reported change from mean baseline to final value finding an significant decrease in serum ALP across 12 weeks of IV calcitriol treatment in children.

Adverse events

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Established vitamin D compounds

Two studies did not report adverse events (Moriniere 1985; Pecovnik-Balon 1995), seven reported that no adverse events related to medication occurred (Baker 1986; Delmez 2000; Greenbaum 2005; Khajehdehi 2003; Memmos 1981; Varghese 1992; Watson 1989) and one reported possible adverse events occurred. Koshikawa 2002 reported hypercalcaemia-related effects of insomnia, pruritus, feelings of irritation, conjunctival congestion, and eosinophilia in an unknown number of patients (uncertain treatment allocation) during treatment with IV calcitriol or no treatment.

Newer vitamin D compounds

Four studies did not report adverse events (Frazao 2000; Gonzalez 2003; (abstract report only); Martin 1998; Qiu 2003 (abstract report only)), no study reported no adverse events related to medication occurred, and four reported possible adverse events occurred.

- Llach 1998 reported a pruritic rash in (1 patient - paricalcitol), dry cough (1 patient - paricalcitol, 1 patient placebo), intermittent headache (1 patient - placebo), and rib pain (1 patient - placebo).
- Moe 2001 reported three patients in each group (paricalcitol and placebo) experienced one or more episodes of infection during the study.
- Akizawa 2004 reported pruritus with concurrent hypercalcaemia (serum calcium $\geq$ 11.5 mg/dL (2.88 mmol/L)) in 1/26 placebo patients and 4/47 patients receiving the highest dose of maxacalcitol, and 2/47 cases of elevated creatinine phosphokinase in the highest dose of maxacalcitol group.
- Greenbaum 2007 reported widely diverse adverse events in 10/15 patients in the paricalcitol group and 6/14 patients in the placebo group.

Vitamin D compound versus other vitamin D compound

Thirteen studies compared vitamin D compounds and the comparisons were;

1. Active vitamin D compound versus vitamin D_3
2. Calcitriol versus established vitamin D compound
3. Established versus newer vitamin D compound.

Combining these categories together for meta-analysis resulted in high heterogeneity (I^2 = 50-100%) and therefore the results are presented for individual subgroups only.

Mortality

Studies of newer versus established compounds were the only ones to report mortality events. Hayashi 2004 reported 2/41 deaths in patients receiving maxacalcitol and 1/41 deaths in patients receiving calcitriol over 12 months of treatment. Akiba 1998 reported no deaths in either arm during treatment with falecalcitriol or alfacalcidol. No difference was observed between newer versus established vitamin D compounds for mortality (Analysis 2.1, 2 studies (94 patients): RR 2.00, 95% CI 0.19 to 21.21).

Fracture

One study (Hayashi 2004) reported no patients experienced a fracture during treatment.

Bone pain

Berl 1980 noted that in three patients with severe symptomatic bone disease, calcitriol treatment was associated with improved bone pain, muscle strength, whereas one symptomatic patient treated with vitamin D_3 showed no improvement. Popovtzer 1992 reported 7/14 patients receiving alfacalcidol and 24,25 dihydroxyvitamin D_3 had improved bone pain and 1/9 patients with bone pain receiving alfacalcidol alone had improved bone pain.

Bone histomorphometry

- In addition to reporting the number of patients with improved bone histology comparing calcitriol with vitamin D_3, Berl 1980 also analysed calcium and mineral content in 13 patients. Treatment with vitamin D_3 was associated with significant reductions in bone calcium and mineral content whereas for subjects treated with calcitriol, these parameters did not change.
- Buccianti 1981 performed bone histomorphometry before and after treatment in 6/17 subjects receiving calcitriol and 13/24 subjects receiving 25-hydroxyvitamin D_3. Calcitriol therapy (6 months) was associated with significantly decreased osteoid index. 25-hydroxyvitamin D_3 was associated with a marked decrease in osteoid index and mean lacunar surface.
- Coen 1982 reported bone histomorphometry before and after 6-12 months treatment with calcitriol (9 patients) or calcitriol and 25-hydroxyvitamin D_3 combined (6 patients). Calcitriol was associated with significant reductions in osteoid volume and osteoid surface. Combined therapy resulted in more marked reductions in these parameters.
- Popovtzer 1992 reported reductions in lower bone turnover with combined 24,25 dihydroxyvitamin D_3/alfacalcidol therapy but not alfacalcidol alone. Marrow fibrosis was similar between groups at the end of treatment.
- El-Reshaid 1997 reported a crossover study design. Data were not extractable for patients after the first period of treatment.

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Parathyroid hormone

No data were available comparing activated vitamin D compound with vitamin D_3. One study of calcitriol versus another active vitamin D compound (25-hydroxycholecalciferol) (Buccianti 1981) reported greater PTH suppression with calcitriol (Analysis 2.5.2, 1 study (41 patients): -MD, -210.0 pg/mL, 95% CI -244.5 to -175.5 (MD -23.9 pmol/L, 95% CI -27.9 to -20.0)). One study of established versus newer vitamin D compounds reported no difference between groups (Hayashi 2004) (Analysis 2.5.3, 1 study (73 patients): - MD 19.0 pg/mL, 95% CI -96.2 to 134.2 (MD 2.2 pmol/L, 95% CI -11.0 to 15.3)).
Eight of the 13 studies reported effects of treatment on serum PTH that were not in a format extractable for meta-analysis (end of treatment serum PTH with estimate of variance or reduction in PTH from baseline ≥ 30% or ≥ 50%).

- Berl 1980 reported that elevated PTH values at baseline were not reduced in patients receiving vitamin D_3 but were significantly decreased in patients receiving calcitriol
- Coen 1982 reported end of treatment serum PTH in mU/mL, and showed significant PTH suppression with both calcitriol and combined treatment with calcitriol and 25-hydroxyvitamin D_3.
- Popovtzer 1992 measured serum PTH in subjects receiving either alfacalcidol or alfacalcidol/24,25 dihydroxyvitamin D_3 combined. Problems with sample handling meant data were not available.
- El-Reshaid 1997 reported a crossover study design. Data were not extractable for patients after the first period of treatment.
- Akiba 1998 reported significantly greater suppression of PTH with falecalcitriol compared with alfacalcidol.
- Deuber 2003 did not report effects of treatment on serum PTH according to treatment assignation.
- Kihara 2004 did not report effects of treatment on serum PTH according to treatment assignation.
- Mochizuki 2007 reported a crossover study design. Data were not extractable for patients after the first period of treatment.

Phosphorus

In a single study of established versus newer vitamin D compounds, no difference was observed between treatment groups for serum phosphorus (Hayashi 2004) (Analysis 2.6.3, 1 study (73 patients): MD -0.31 mg/dL, 95% CI -1.05 to 0.43 (MD -0.10 mmol/L, 95% CI -0.34 to 0.14)). In this study, 30/38 patients receiving calcitriol and 30/35 patients receiving maxacalcitol experienced one or more episodes of hyperphosphataemia (Analysis 2.7.3, 1 study (73 patients): RR 1.09, 95% CI 0.88 to 1.34). No data were available to compare active vitamin D compounds with vitamin D_3.

Seven of 13 studies reported effects of treatment on serum phosphorus that were not in a format extractable for meta-analysis (end of treatment serum phosphorus with estimate of variance or hyperphosphataemia):

- Berl 1980 reported no difference in serum phosphorus levels between calcitriol and vitamin D_3 groups which was not accounted for by differences in phosphorus binder therapy.
- Coen 1982 reported no significant changes in serum phosphorus levels during 6-12 months of calcitriol or combined calcitriol/25-hydroxyvitamin D_3 therapy.
- Popovtzer 1992 reported phosphorus outcomes in figure format only.
- Djukanovic 1994 reported "control" of hyperphosphataemia in both groups (alfacalcidol/calcitriol versus alfacalcidol alone) using phosphate binding agents.
- Akiba 1998 reported significantly lower serum phosphorus with falecalcitriol compared with alfacalcidol.
- Kihara 2004 did not report effects of treatment on serum phosphorus according to treatment assignation.
- Mochizuki 2007 reported a crossover study design. Data were not extractable for patients after the first period of treatment.

Calcium

Serum calcium was significantly higher at end of treatment with calcitriol compared with vitamin D_3 in Berl 1980 (Analysis 2.8.1, 1 study (31 patients): MD 0.85 mg/dL, 95% CI 0.35 to 1.35 (MD 0.21 mmol/L, 95% CI 0.09 to 0.34)). No difference in end of treatment serum calcium was observed between established and newer vitamin D compounds in Hayashi 2004 (Analysis 2.8.3, 1 study (73 patients): MD 0.30 mg/dL, 95% CI -0.11 to 0.71 (MD 0.08 mmol/L, 95% CI -0.03 to 0.18)).
Seven of 13 studies reported effects of treatment on serum calcium that were not in a format extractable for meta-analysis (end of treatment serum calcium with estimate of variance, one of more episodes of hypercalcaemia or withdrawal of treatment due to hypercalcaemia):

- Coen 1982 reported increases in serum calcium with calcitriol and calcitriol/25-hydroxyvitamin D_3 combined therapy.
- Djukanovic 1994 reported serum calcium levels were not different during therapy comparing alfacalcidol/calcitriol versus alfacalcidol alone
- El-Reshaid 1997 reported a crossover study design. Data were not extractable for patients after the first period of treatment.
- Akiba 1998 reported no difference in the change in serum calcium levels comparing falecalcitriol with alfacalcidol
- Sprague 2003 reported the combined outcome of hypercalcaemia and/or elevated calcium x phosphorus product at

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least once during treatment finding no difference between groups treated with paricalcitol or calcitriol.

- Kihara 2004 did not report effects of treatment on serum calcium according to treatment assignation.
- Mochizuki 2007 reported a crossover study design. Data were not extractable for patients after the first period of treatment.

Alkaline phosphatase

Six of 13 studies reported effects of treatment on serum alkaline phosphatase (ALP) that were not in a format extractable for meta-analysis (end of treatment serum ALP with estimate of variance):

- Maxwell 1978 reported that calcitriol lowered serum ALP compared with vitamin D_3
- Berl 1980 reported no difference in serum ALP levels between calcitriol and vitamin D_3 groups.
- Buccianti 1981 reported end of treatment serum ALP in mmol/mL, showing significant reductions in ALP during treatment with calcitriol (17 patients) and 25-hydroxyvitamin D_3 (24 patients).
- Coen 1982 reported no change in serum ALP levels with 6-12 months of calcitriol or combined calcitriol/25-hydroxyvitamin D_3 therapy.
- Djukanovic 1994 reported serum ALP levels were similar comparing alfacalcidol/calcitriol versus alfacalcidol alone.
- El-Reshaid 1997 reported a crossover study design. Data were not extractable for patients after the first period of treatment.

Adverse events

Active vitamin D compound versus vitamin D_3

Maxwell 1978 reported four patients (calcitriol (2)) developed electrocardiographic abnormalities during treatment. Elevated liver enzymes occurred in four patients receiving vitamin D_3 and two receiving calcitriol. Two patients receiving vitamin D_3 experienced rising hepatitis B titres. Berl 1980 did not reported any adverse events.

Calcitriol versus established vitamin D compound

Buccianti 1981 and Deuber 2003 did not report adverse events. El-Reshaid 1997 reported that no major adverse events occurred during three months of therapy with either alfacalcidol or calcitriol.

Established versus newer vitamin D compound

Three studies did not report adverse events (Hayashi 2004; Kihara 2004; Sprague 2003), one study reported than no adverse events related to medication occurred (Mochizuki 2007), and one reported possible adverse events occurred. Akiba 1998 reported one patient of 13 experiencing arthralgia with hyperphosphataemia during treatment with falecalcitriol.

Other comparisons

Coen 1982; Popovtzer 1992; Djukanovic 1994 did not report adverse events.

IV versus oral vitamin D compounds

Twelve studies compared IV versus oral vitamin D compounds.

Mortality

Data for patient centred outcomes comparing IV and oral vitamin D compounds were absent or extremely limited. Turk 2002 (28 patients) reported a single death during treatment.

Fracture

Fischer 1993 reported no episodes of fracture in 10 patients during treatment.

Bone mineral density

Turk 2002 reported the end of treatment bone mineral density at the femoral neck (Analysis 3.3, 1 study (27 patients): MD 0.01 g/cm², 95% CI -0.04 to 0.06) and lumbar spine (Analysis 3.4, 1 study (27 patients): MD -0.03 g/cm², 95% CI -0.10 to 0.04) with no difference between the two routes of administration.

Parathyroid hormone

IV vitamin D resulted in lower PTH levels (Analysis 3.5, 8 studies (171 patients): MD -76.20 pg/mL, 95% CI -150.92 to -1.48 (MD 8.7 pmol/L, 95% CI -17.2 to -0.17)) (Bacchini 1997; Borazan 2003; Caravaca 1995; Fischer 1993; Indridason 2000; Levine 1996; Liou 1994; Turk 2002). There was high-level heterogeneity in this analysis (I^2 = 78%) in part due to higher end of treatment PTH levels in the IV group at the end of treatment in Fischer 1993, compared with lower levels in the remaining studies. The authors reported higher PTH levels at baseline in the patients receiving IV calcitriol in this study that might account for this observation. In addition, Liou 1994 reported significant PTH suppression with IV administration more than oral treatment, although in this study the IV dose administered was higher than the oral dose. Removal of Liou 1994 from the analysis resulted in finding no difference between groups for end of treatment PTH (7 studies (161

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patients): MD -50.36 pg/mL, 95% CI -122.26 to 21.54 (MD -5.74 pmol/L, 95% CI -13.9 to 2.45); I^2 = 74%). The meta-analysis retained high-level heterogeneity even excluding both Fischer 1993 and Liou 1994 (I^2 = 64%) suggesting caution is required to interpret the effect of IV vitamin D on PTH lowering. Multiple other causes of heterogeneity were possible including patient mix, dose of treatment, and severity of hyperparathyroidism at baseline, however it is not possible to discern the cause of heterogeneity in this analysis.

Four of the 12 studies reported effects of treatment on serum PTH that were not in a format extractable for meta-analysis (end of treatment serum PTH with estimate of variance or reduction in PTH from baseline ≥ 30% or ≥ 50%):

- Lee 1994 reported a crossover study design. Data were not extractable for patients after the first period of treatment
- Quarles 1994 reported no difference in end of treatment PTH between oral and calcitriol groups.
- Levin 1995 reported 50% of patients in the IV group achieving a reduction in PTH > 50% from baseline versus 36% in the oral group. The number of patients in each group was not reported.
- Haddad 2004 did not report an estimate of variance. No difference was observed for end of treatment PTH between IV and oral calcitriol, in subjects with PTH at baseline between 250-500 pg/mL, or subjects with baseline PTH > 500 pg/mL.

Phosphorus

End of treatment serum phosphorus was lower with IV versus oral vitamin D treatment (Analysis 3.6, 5 studies (112 patients): MD -0.30 mg/dL, 95% CI -0.58 to -0.03 (MD -0.09 mmol/L, 95% CI -0.19 to -0.01)) (Bacchini 1997; Caravaca 1995; Fischer 1993; Indridason 2000; Turk 2002). Incidence of hyperphosphataemia (Analysis 3.7, 5 studies (102 patients): RR 0.98, 95% CI 0.65 to 1.48)) was not different between IV and oral vitamin D treatment (Bacchini 1997; Caravaca 1995; Haddad 2004; Indridason 2000; Quarles 1994).

Five of 12 studies reported effects of treatment on serum phosphorus that were not in a format extractable for meta-analysis (end of treatment serum phosphorus with estimate of variance or hyperphosphataemia):

- Lee 1994 reported a crossover study design. Data were not extractable for patients after the first period of treatment.
- Liou 1994 reported a crossover study design. Data were not extractable for patients after the first period of treatment.
- Levin 1995 reported no difference in end of treatment serum phosphorus between IV and oral vitamin D treatment.
- Levine 1996 reported no difference between groups for phosphorus levels during treatment.
- Borazan 2003 reported no significant increase in serum phosphorus at the end of treatment for either IV versus oral vitamin D treatment.

Calcium

End of treatment serum calcium was no different between IV and oral vitamin D treatment (Analysis 3.8, 6 studies (146 patients): MD 0.17 mg/dL, 95% CI -0.31 to 0.65 (MD 0.04 mmol/L, 95% CI -0.08 to 0.16)) (Bacchini 1997; Borazan 2003; Caravaca 1995; Fischer 1993; Indridason 2000; Turk 2002). However, there was high-level heterogeneity (I^2 = 64%) in this analysis. Exclusion of Borazan 2003 with significantly lower end of treatment calcium in the oral group (a discrepant result compared with the other studies) eliminated heterogeneity in the analysis and suggested a trend toward lower serum calcium with IV vitamin D therapy (5 studies (112 patients): MD -0.15 mg/dL, 95% CI -0.38 to 0.08 (MD -0.04 mmol/L, 95% CI -0.25 to 0.02)).

The risk of hypercalcaemia (Analysis 3.9, 6 studies (128 patients): RR 1.08, 95% CI 0.75 to 1.56) was not different between IV and oral vitamin D groups (Bacchini 1997; Borazan 2003; Fischer 1993; Haddad 2004; Indridason 2000; Quarles 1994). There was minimal heterogeneity in this analysis.

Four of 12 studies reported effects of treatment on serum calcium that were not in a format extractable for meta-analysis (end of treatment serum calcium with estimate of variance, one of more episodes of hypercalcaemia or withdrawal of treatment due to hypercalcaemia):

- Lee 1994 reported a crossover study design. Data were not extractable for patients after the first period of treatment
- Liou 1994 reported a crossover study design. Data were not extractable for patients after the first period of treatment
- Levin 1995 reported no difference in end of treatment serum calcium between IV and oral vitamin D treatment
- Levine 1996 reported significant increases in serum calcium during IV vitamin D treatment compared with oral treatment

Alkaline phosphatase

Alkaline phosphatase (Analysis 3.10, 4 studies (116 patients): MD 3.43 U/L, 95% CI -50.11 to 56.95) was not different between treatment groups (Borazan 2003; Caravaca 1995; Indridason 2000; Turk 2002).

Adverse events

Nine studies did not report adverse events (Bacchini 1997; Borazan 2003; Fischer 1993; Haddad 2004; Lee 1994; Levin 1995; Levine 1996; Quarles 1994; Turk 2002), one study reported that no adverse events related to medication occurred (Liou 1994), and two studies reported possible adverse events occurred. Caravaca 1995 reported intensification of pruritis in one patient (unknown treatment assignation) and Indridason 2000 reported 1/20 patients was intolerant of oral calcitriol due to an upset stomach.

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IP versus oral vitamin D compounds

Three studies compared IP versus oral vitamin D compounds.

Patient-centred outcomes

Data were absent for the comparison between the IP and oral routes of vitamin D compound administration for mortality, fracture, parathyroidectomy, or bone pain. Each biochemical outcome available contained only one study. Jones 1994 was a crossover study design of oral versus IP calcitriol in nine children and data were not available for the end of the first phase of treatment. Salusky 1998 reported significantly decreased height (Z-score) in children receiving IP calcitriol (compared with growth rates occurring in the year before the study). No change in growth velocity was observed in the children receiving oral vitamin D. Loss of height was associated with development of osteomalacia, and possibly associated with IP calcitriol due to the larger doses received by this group.

Bone histomorphometry

No significant difference for improvement in bone histomorphometry was identified between IP and oral treatment groups (Analysis 4.1, 1 study (8 patients): RR 7.33, 95% CI 0.54 to 99.13) (Gadallah 2000) although wide confidence intervals indicate considerable imprecision about the point estimate. Salusky 1998 reported 12 months lower bone formation rates with oral or IP calcitriol. No difference was observed between groups.

Parathyroid hormone

End of treatment PTH was not different between oral and intraperitoneal vitamin D compound (Analysis 4.2, 1 study (34 patients): MD -24.40 pg/mL, 95% CI -58.74 to 9.94 (MD -2.78 pmol/L, 95% CI -6.70 to 1.13)) (Gadallah 2000).

Phosphorus

No difference in risk of hyperphosphataemia was observed between treatment groups (Analysis 4.3, 1 study (33 patients): RR 0.71, 95% CI 0.14 to 3.70) (Salusky 1998). No data were extractable for meta-analysis of serum phosphorus in any study. Gadallah 2000 reported significantly higher serum phosphorus at follow-up in the group receiving oral calcitriol compared with IP calcitriol.

Calcium

No difference between IP and oral vitamin D administration was found for risk of hypercalcaemia (Analysis 4.4, 1 study (33 patients): RR 1.06, 95% CI 0.53 to 2.15) (Salusky 1998). Jones 1994 reported no hypercalcaemic events in either phase of an oral versus IP calcitriol study in nine children. No data were extractable for end of treatment serum calcium. Gadallah 2000 reported serum calcium was not different at follow-up comparing oral with IP calcitriol.

Adverse events

Two studies did not report adverse events (Gadallah 2000; Salusky 1998). Jones 1994 reported two episodes of peritonitis in each treatment assignation through both arms of the crossover study.

SC versus oral vitamin D compounds

A single study (six patients) analysed SC dosing (Liou 1995). Meta-analysis was not possible.

Intermittent versus daily vitamin D compounds

Five studies reported outcomes for intermittent versus daily vitamin D therapy (Herrmann 1994; Klaus 1995; Moe 1998; Tarrass 2006; van der Merwe 1990).

Patient-centred outcomes

No data were available for mortality, fracture, bone pain, or parathyroidectomy comparing intermittent and daily administration schedules. Moe 1998 reported that no fracture occurred during a study of daily versus pulse calcitriol.

Bone histomorphometry

Five of 18 patients underwent bone biopsy before and after treatment with intermittent or daily calcitriol (24 weeks) (Moe 1998). No comparative analyses were possible however the authors reported quantitative improvement in all five biopsies.

Bone densitometry

Moe 1998 reported no difference in bone densitometry of hip, spine and radius between groups across intermittent and daily calcitriol therapy.

Parathyroid hormone

Moe 1998 reported end of treatment serum PTH extractable for analysis. No difference was observed between groups (Analysis 5.2, 1 study (18 patients): MD -3.30 pg/mL, 95% CI -30.36 to 23.76 (MD -0.4 pmol/L, 95% CI -3.5 to 2.7)).

Four of the five studies reported effects of treatment on serum PTH that were not in a format extractable for meta-analysis (end of treatment serum PTH with estimate of variance or reduction in PTH from baseline $\geq$ 30% or $\geq$ 50%):

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- van der Merwe 1990 reported PTH suppression with both intermittent and daily calcitriol administration with no difference between groups at the end of treatment. PTH was reported as end of treatment mean with range.
- Herrmann 1994 used a target of PTH suppression < 10 pmol/L (< 114 pg/mL) as an outcome. They reported 11/21 patients (52%) in the intermittent group and 18/24 patients (75%) in the continuous group achieving this target. No statistical difference was observed between groups.
- Klaus 1995 reported significant reductions in end of treatment serum PTH. No difference was observed between groups for this outcome.
- Tarrass 2006 reported a progressive decline in serum PTH across treatment with intermittent or continuous alfacalcidol. No difference was observed between groups.

Phosphorus

No difference was observed between intermittent and daily vitamin D treatment with regard to risk of hyperphosphataemia (Analysis 5.3, 3 studies (97 patients): RR 1.74, 95% CI 0.44 to 6.79) (Herrmann 1994; Moe 1998; Tarrass 2006).
Moe 1998 reported end of treatment phosphorus (Analysis 5.4, 1 study (18 patients): MD 0.49 mg/dL, 95% CI -0.79 to 1.77 (MD 0.16 mmol/L, 95% CI -0.24 to 0.57)) observing no difference between treatment groups.
van der Merwe 1990 reported effects of treatment on serum phosphorus that were not in a format extractable for meta-analysis (end of treatment serum phosphorus with estimate of variance or hyperphosphataemia). They reported no differences between intermittent and daily calcitriol administration for end of treatment serum phosphorus.

Calcium

No difference was observed between intermittent and daily vitamin D treatment with regard to risk of hypercalcaemia (Analysis 5.5, 4 studies (118 patients): RR 1.15, 95% CI 0.36 to 3.69) (Herrmann 1994; Klaus 1995; Moe 1998; Tarrass 2006).
Moe 1998 reported end of treatment calcium (Analysis 5.6, 1 study (18 patients): MD -0.24 mg/dL, 95% CI -1.28 to 0.80 (MD 0.06 mmol/L, 95% CI -0.32 to 0.40)) observing no difference between treatment groups.
One study reported effects of treatment on serum calcium that were not in a format extractable for meta-analysis (end of treatment serum calcium with estimate of variance, one of more episodes of hypercalcaemia or withdrawal of treatment due to hypercalcaemia):

- van der Merwe 1990 reported increases in the mean serum calcium in the treatment groups combined across 12 weeks of treatment with daily or intermittent calcitriol. No difference in end of treatment serum calcium was observed between treatment groups.

Alkaline phosphatase

No extractable data were available for this outcome. van der Merwe 1990 reported descriptively that no differences between intermittent and daily calcitriol administration for end of treatment serum alkaline phosphatase.

Adverse events

Four studies did not report adverse events (Herrmann 1994; Klaus 1995; Moe 1998; Tarrass 2006). One study reported possible adverse events. van der Merwe 1990 reported gastric fullness in 1/10 patients receiving intermittent therapy.

Differing dosing schedules

The remaining seven studies analysed differing doses of the same vitamin D compound (Martin 2001; Mitsopoulos 2006; Zisman 2005), differing weekly frequencies (Gallieni 2000; Martinez 1996; Sanchez Perales 1999) or morning versus evening dosing (Tsuruoka 2003).
Three small studies of short duration ($\leq$ 12 weeks) compared different doses of paricalcitol (PTH/80 μg versus 0.04 μg/kg thrice weekly (Martin 2001); PTH/80 μg versus PTH/120 μg thrice weekly (Mitsopoulos 2006)) or doxercalciferol (35%, 50% or 65% of previous paricalcitol dose thrice weekly) (Zisman 2005). Three studies compared differing frequencies of calcitriol; once a week versus three times weekly (Martinez 1996; Sanchez Perales 1999); or twice a week versus three times weekly (Gallieni 2000). One study compared morning with evening administration of vitamin D_3 (Tsuruoka 2003).
As few studies were available with heterogeneous comparisons, meta-analysis was not possible. For completeness, outcomes are provided descriptively where they were reported.

Patient-centred outcomes

One study reported one death in the higher dose group of paricalcitol in three months follow-up (Mitsopoulos 2006). No other data were available for bone pain, fracture, or parathyroidectomy.

Parathyroid hormone

- Martin 2001 (125 patients) reported that 72% of patients receiving paricalcitol according to PTH level (PTH/80) achieved reductions in serum PTH > 30% from baseline across 12 weeks of therapy compared with 66% of patients dosed according to body weight. No statistical analysis was provided.

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- Mitsopoulos 2006 (43 patients) reported no difference in number of patients achieving PTH suppression > 30% from baseline between treatment groups (paricalcitol PTH/80 (78%) versus PTH/120 (71%)).
- Martinez 1996 (13 patients) reported similar PTH suppression with calcitriol dosed either once or thrice weekly.
- Sanchez Perales 1999 (22 patients) reported greater PTH suppression with calcitriol administered once weekly (3 µg) versus thrice weekly (1 µg).
- Gallieni 2000 (22 patients) reported similar reductions in serum PTH comparing IV calcitriol administered either twice or thrice weekly.
- Tsuruoka 2003 (13 patients) reported significantly greater PTH suppression with evening vitamin D_3 dosing compared with morning dosing.

Phosphorus

- Mitsopoulos 2006 reported that change in serum phosphorus was similar between groups treated with paricalcitol dosed according to baseline PTH (PTH/80 versus PTH/120).
- Martinez 1996 reported fewer episodes of hyperphosphataemia with once weekly versus thrice weekly calcitriol dosing (statistical analysis not provided).
- Sanchez Perales 1999 reported no difference in end of treatment serum phosphorus comparing calcitriol administered once weekly (3 µg) versus thrice weekly (1 µg).
- Gallieni 2000 reported similar end of treatment serum phosphorus comparing IV calcitriol administered either twice or thrice weekly.

Calcium

- Martin 2001 reported no episodes of hypercalcaemia in patients treated for 12 weeks with paricalcitol dosed either according to body weight or baseline PTH.
- Mitsopoulos 2006 reported statistically similar incidences of hypercalcaemia in treatment groups using paricalcitol dosed according to baseline PTH (PTH/80 versus PTH/120).
- Martinez 1996 reported fewer episodes of hypercalcaemia with once weekly versus thrice weekly calcitriol dosing (statistical analysis not provided).
- Sanchez Perales 1999 reported no difference in end of treatment serum calcium comparing calcitriol administered once weekly (3 µg) versus thrice weekly (1 µg).
- Gallieni 2000 reported similar end of treatment serum calcium comparing IV calcitriol administered either twice or thrice weekly.
- Tsuruoka 2003 reported more hypercalcaemia with morning vitamin D_3 compared with evening dosing.

Adverse events

- Mitsopoulos 2006 reported an allergic reaction in 1/22 patients the higher paricalcitol dose group.
- No data were available for genu valgum or slipped upper femoral epiphyses

DISCUSSION

Summary of main results

The review confirms the efficacy of vitamin D compounds to reduce serum PTH in people with CKD and requiring dialysis. Vitamin D compounds while lowering serum PTH when compared with placebo were associated with increased risks of hypercalcaemia and hyperphosphataemia. Although these outcomes were reported in few studies in extractable format and the findings did not reach statistical significance, they may be clinically relevant. Established vitamin D compounds (calcitriol, alfacalcidol, or 24,25 dihydroxycholecalciferol) suppressed PTH compared with placebo although few data were available for treatment effects on serum calcium or phosphorus. Subjects receiving established vitamin D compounds were not more likely to experience hypercalcaemia and more likely to be withdrawn from therapy due to this outcome. Newer vitamin D compounds (designed to suppress PTH with lower calcaemic and phosphataemic action that earlier vitamin D compounds) also suppressed serum PTH but were associated with more hypercalcaemia than placebo. No data were available for hyperphosphataemia and a single study had data extractable for end of treatment calcium and phosphorus.

No efficacy data were extractable from two studies comparing an active vitamin D compound with vitamin D_3. Single studies reported the effect of calcitriol versus another established vitamin D compound or established versus newer vitamin D compounds on serum PTH; meta-analysis was not possible.

IV vitamin D administration resulted in lower PTH concentrations and was associated with lower serum phosphorus, and a trend toward lower serum calcium levels, although exclusion of a study that administered higher vitamin D doses to the IV group resulted in no difference between oral and IV vitamin D compounds for suppressing PTH. High-level heterogeneity in the analysis for IV versus oral vitamin D compounds on both serum PTH and calcium suggest caution is needed in the interpretation of these results.

Meta-analysis was not possible to evaluate the effects of either intraperitoneal or subcutaneous versus oral vitamin D administration or for intermittent versus daily administration on serum PTH suppression.

Marked differences in methods of reporting bone histomorphometry combined with the number of differing treatment compar-

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isons and the small proportion of patients consenting to undergo bone biopsy resulted in few data available for these outcomes.

Overall completeness and applicability of evidence

This meta-analysis analyses the total available evidence for vitamin D compounds in CKD for people requiring dialysis. We have published a companion intervention review in this issue of the Cochrane Library of RCTs evaluating *Vitamin D compounds for people with chronic kidney disease and not requiring dialysis* (Palmer 2009).The results in that review and the present analysis are striking for the paucity of data for both clinical and biochemical outcomes.

While 60 RCTs examined vitamin D compounds in people with CKD requiring dialysis, meta-analysis was severely limited by the number of differing comparisons and the heterogeneity in reporting of outcomes, particularly serum PTH and bone histomorphometry. Effects of vitamin D compounds on biochemical outcomes including PTH were available in few small studies, resulting in considerable imprecision for point estimates of treatment effects. Most importantly, all studies were not designed to examine the effect of vitamin D treatment on mortality and none were powered to understand the effect of treatment on other important clinical outcomes, including resolution of bone pain, change in stature, risk of fracture, or need for parathyroidectomy.

Many of the studies were designed and conducted before observational studies in the 1990's found consistent associations between abnormalities of bone and mineral metabolism (serum calcium, phosphorus, and PTH), with increased risks for cardiovascular and all-cause mortality (Block 2004; Ganesh 2001). Studies of vitamin D compounds in CKD since have also not kept apace with findings linking calcium and phosphorus with adverse mortality outcomes, and, to date, no study of vitamin D compounds has been powered to examine mortality and cardiovascular endpoints in CKD. This is especially important given that vitamin D treatment may be associated with increased serum calcium and phosphorus and it is necessary to understand the relative importance of treatment effects on serum PTH, phosphorus and calcium on outcomes during vitamin D therapy. Indeed, studies identified in major clinical studies registries that are currently being conducted are also not powered to examine treatment effects for clinical outcomes in CKD and requiring dialysis.

Only one study reported efficacy data directly comparing newer with established vitamin D compounds. The relative efficacies of newer and established vitamin D compounds for PTH suppression and risks of hypercalcaemia or hyperphosphataemia remain unknown. IV administration of vitamin D was superior to oral administration for PTH suppression but with the removal of Liou 1994 from the analysis (which prescribed a higher dose of vitamin D to the IV group), the difference in PTH concentration was not different between IV and oral administration.

Quality of the evidence

Included studies were commonly reported incompletely and of poor quality, although this may reflect pre-2001 CONSORT (Consolidated Standards of Reporting Trials) practices (www.consort-statement.org). Allocation concealment was adequate in only 5/60 (8%) studies. Eighteen studies reported blinding of participants and investigators while 10 reported blinding of outcome assessors. Fourteen studies reported loss of follow-up or exclusion from data analysis exceeding 20% and in 11 studies completeness to follow-up was not clear. Absence of allocation concealment, blinding and ITT analysis tends to lead to an overestimate of the observed treatment effects. Many studies were too small to detect any differences between treatments even if differences did exist, particularly for bone histology outcomes. Only nine studies enrolled more than 75 patients and 27 studies included more than 30 patients. Most studies provided outcome data qualitatively as normal or not statistically different without providing the numeric results with an estimate of variance.

Potential biases in the review process

The review is greatly limited by insufficient extractable data for all outcomes (clinical, bone, and biochemical outcomes) increasing bias toward studies that reported these outcomes in an extractable format.

This was most apparent when considering the effect of vitamin D compounds to suppress parathyroid hormone. Fewer than one-third (19/60 studies) reported serum PTH at the end of treatment and due to the heterogeneity of treatment comparisons this resulted in eight or fewer studies in each meta-analysis for this outcome. Increasingly, the efficacy of newer vitamin D compounds (particularly paricalcitol) is measured as a percentage reduction in baseline PTH. This appears an initiative driven by study conduct or direct study funding by pharmaceutical companies. These PTH outcomes were consistently more extractable as they did not rely on an estimate of variance for inclusion. As these data were more available for meta-analysis than end of treatment PTH, they likely have biased the results of this review to favour the outcomes reported in these studies. This change in reporting of serum PTH also precludes the direct comparison of these newer studies (predominantly of paricalcitol) with older studies that examine calcitriol and alfacalcidol.

Further, when data were reported in descriptive format only (and therefore not extractable) the descriptive results frequently reported no difference between treatment comparisons. This would suggest that inclusion of extractable data only in the present meta-analyses might bias the analyses toward finding a difference between two treatment groups where no true difference exists (overestimating the treatment effect). Consistency in reporting of biochemical outcomes in all future would reduce this bias.

The principle adverse effects of clinical concern for vitamin D

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compounds are hypercalcaemia and hyperphosphataemia. However, these were reported as either one or more episodes of hypercalcaemia/hyperphosphataemia or end of treatment serum values. Due to the number of differing treatment comparisons and this variability in reporting, meta-analyses for treatment effects on hypercalcaemia all contained six or fewer studies and hyperphosphataemia included five or fewer studies, reducing the strength of conclusions that can be drawn from the review.

In future research, consistency of outcome reporting would greatly enhance comparability between studies and treatment effects for clinicians and consumers. Dual reporting of serum PTH, phosphorus and calcium as dichotomous variables (suppression below baseline, hypercalcaemia, hyperphosphataemia) and end of treatment values would also assist comparability particularly between studies from differing eras.

Agreements and disagreements with other studies or reviews

Observational studies support an association between vitamin D therapy and improved clinical outcomes in adults with CKD (Dobrez 2004; Kalantar-Zadeh 2006; Lee 2007; Shoji 2004; Teng 2003; Teng 2005; Tentori 2006). In four retrospective studies, treatment with a vitamin D compound (alfacalcidol, doxercalciferol, paricalcitol, or calcitriol) was associated with a reduced unadjusted hazard for death compared with no treatment in 117,068 patients receiving dialysis (Lee 2007; Shoji 2004; Teng 2005; Tentori 2006). Furthermore, the administration of doxercalciferol or paricalcitol was reported to reduce risk of death or hospitalisation in people receiving HD when compared with calcitriol (3 studies, 86,573 patients) (Dobrez 2004; Teng 2003; Tentori 2006). While observational studies have inherent limitations through unmeasured confounders (e.g. baseline co morbid conditions, nutritional status, or concomitant therapy) and selection bias, these large scale studies suggest a clinical advantage for vitamin D therapy in CKD that demands exploration through adequately powered RCTs.

We found no evidence of superiority of newer vitamin D compounds over established vitamin D compounds for any outcome, when these agents were compared directly in RCTs. Our findings are consistent with the National Kidney Foundation KDOQI Clinical Practice Guidelines for bone metabolism and disease in CKD (NKF-Guidelines 2003), suggesting patients treated with HD or PD and elevated serum PTH should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol) however, we cannot conclude whether newer vitamin D analogs are superior in terms of clinical outcomes or with regard to serum phosphorus and calcium levels compared with calcitriol and alfacalcidol. Our findings also support current CARI guidelines for CKD stage 5, published in 2006 (Elder 2006) and the Canadian Society of Nephrology guidelines (http://www.csnscn.ca/) which indicate that there is insufficient evidence to recommend the use of newer vitamin D analogs (see Table 3 – *Current guidelines for the use of vitamin D Compounds in chronic kidney disease* for a summary of the current guidelines*)*.

Table 3. Current guidelines for the use of vitamin D compounds in chronic kidney disease

Guideline	Country	Year	Recommendation
Kidney Disease Outcomes Quality Initiative	USA	2003	Patients treated with HD or PD with serum levels of intact PTH levels > 300 pg/mL) (33.0 pmol/L) should receive an active vitamin D sterol (such as calcitriol, alfacalcidol, paricalcitol, or doxercalciferol) to reduce the serum levels of PTH to a target range of 150-300 pg/mL (16.5-33.0 pmol/L). (EVIDENCE) The intermittent, IV administration of calcitriol is more effective than daily oral calcitriol in lowering serum PTH levels. (EVIDENCE) In patients with corrected serum calcium and/or phosphorus levels above the target range, a study of alternative vitamin D analogs, such as paricalcitol or doxercalciferol may be warranted. (OPINION) When either HD or PD patients are treated with active vitamin D sterols, management should integrate the changes in serum calcium, serum phosphorus, and plasma PTH.
Caring for Australasians with Renal Impairment	Australasia	2006	Oral calcitriol (intermittent or pulsed) is effective at lowering parathyroid hormone levels in patients on PD (Level II evidence). Vitamin D and its analogs, either given orally daily, orally intermittently, or intravenously are effective at lowering PTH levels in patients on HD (Level

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Table 3. Current guidelines for the use of vitamin D compounds in chronic kidney disease (*Continued*)

			I/II evidence). Oral calcitriol is effective for the prevention or treatment of hyperparathyroidism in most patients on HD or PD. IV calcitriol may be more effective at lowering PTH levels and be less likely to cause hypercalcaemia but the lack of well-designed studies of sufficient size prevents a more definitive statement. Vitamin D analogs are effective at lowering PTH but clinical studies proving their effectiveness with fewer side-effects prevents are either lacking or not definitive. On the basis of current evidence there is little reason to recommend their use over oral or IV calcitriol.
British Renal Society	UK	2007	The relative importance of hyperparathyroidism as a risk factor for premature vascular disease is difficult to determine from observational studies and no informative RCTs exist. There is no doubt that a serum PTH concentration over 4 times the normal limit is associated with increased risk of significant bone disease and should therefore be avoided by medical (or if necessary surgical) management of hyperparathyroidism. In the absence of firm evidence, individual clinicians should decide on the degree to which hyperparathyroidism should be corrects and how this should be achieved.
European Best Practice Guidelines (EBPG)	Europe	2002	No guideline
Europe -- expert panel (including members from Fresenius Medical Care) (not EBPG)	Europe	2001	PTH above 9-18 pmol/L (78-156 pg/mL) may well be treated with small daily doses of active vitamin D. IV pulse administration does not have any advantage over oral route. No evidence from direct comparative studies to show any superiority of maxacalcitol, doxercalciferol, or paricalcitol over calcitriol or alfacalcidol.
Canadian Society of Nephrology	Canada	2006	Avoid intact PTH (iPTH) levels < 100 pg/mL (10.6 pmol/L (Grade C); iPTH levels > 500 pg/mL (53 pmol/L) should be treated if accompanied by symptoms or clinical signs of hyperparathyroidism. Vitamin D analogs should be used in conjunction with a specialist. There is insufficient evidence to recommend use of novel vitamin D analogs (grade D, opinion)

HD - haemodialysis; PD - peritoneal dialysis

We were unable to find sufficient data for the optimal route or schedule of administration of vitamin D compounds. IV administration of vitamin D was superior to oral administration for PTH suppression and maintaining phosphorus levels but with the removal of Liou 1994 from the analysis (which prescribed a higher dose of vitamin D to the IV group compared with the oral group), the difference in PTH concentration was not different between IV and oral administration. Due to the significant limitations of the presently available studies, our findings do not support the KDOQI Clinical Practice Guidelines for people receiving dialysis (NKF-Guidelines 2003) in recommending that IV administration of calcitriol is more effective than daily oral calcitriol in lowering serum PTH levels.

In conclusion, based upon contemporary epidemiological standards for assessing the validity of interventions, vitamin D compounds remain of unproven clinical efficacy in people with CKD requiring dialysis. While vitamin D treatment suppresses serum PTH, the clinical consequences of this intervention are unknown. This is despite 60 RCTs in CKD conducted over 30 years. Biochemical and experimental data suggest that effects of vitamin D compounds may have opposing influences on mortality in this

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high risk population, but have been assessed in fewer than 3,000 people requiring dialysis and within studies that were not designed to assess the effects of treatment on clinical outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

- The effect of vitamin D compounds on mortality, stature, fracture or need for parathyroidectomy for people requiring dialysis is unknown.

- Newer vitamin D compounds cannot yet be regarded as superior to existing treatments. Inadequate data are available to determine their 'less calcaemic' or 'non calcaemic' status when compared with calcitriol or alfacalcidol.

- No recommendation regarding the efficacy of IV compared with equivalent oral vitamin D compounds can be made due to limitations of available study data.

Implications for research

- Understanding the effects of vitamin D compounds on clinical outcomes (hospital admissions, cardiovascular outcomes, fracture, bone pain, muscle weakness, and mortality) for people with CKD and receiving dialysis requires adequately powered RCTs.

- Recognition in observational studies that vitamin D therapy may be associated with lower mortality in people with CKD and requiring dialysis suggests that a fixed dose RCT of vitamin D should be considered (higher dose versus lower dose or a placebo-controlled study) with mortality as the primary outcome.

- Serum PTH must be validated as a surrogate marker for outcomes (bone and clinical) in CKD. RCTs should target differing levels of PTH and measure effects on clinical outcomes.

- Consistent reporting of outcomes (both patient-centred and biochemical) is necessary to ensure comparability of studies for clinicians and consumers. For evaluating efficacy of serum PTH suppression, studies should report the end of treatment PTH and not solely report an arbitrary measure such as two or more periods of > 30% reduction in serum PTH. If the more recent trend of reporting PTH suppression as either > 30% or > 50% below baseline continues, it must be validated as an outcome that is directly causal to improved clinical outcomes (including bone pain, need for parathyroidectomy, mortality, cardiovascular events).

- Given the expense but theoretically attractive profile of the newer vitamin D analogs (paricalcitol, maxacalcitol, doxercalciferol) future RCTs should prioritise directly comparing the efficacy of these agents against established vitamin D sterols (calcitriol, alfacalcidol) on mortality and patient centred outcomes.

ACKNOWLEDGEMENTS

- The authors thank the Cochrane Renal Group for their assistance and support with preparation of this review.

- Acknowledgement is made to the authors who kindly provided additional data for their studies, on request.

- We would like to thank Drs Jason Cota, Randall Faull, Elisabeth Hodson and Daniel Zehnder for their editorial advice during the preparation of this review.

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* *Indicates the major publication for the study*

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CHARACTERISTICS OF STUDIES

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

Akiba 1998

Methods	• Setting/Design: Multicentre, crossover design • Time frame: July 1994 to March 1996 • Follow-up period: 6 months • Loss to follow-up: 16%
Participants	• Country: Japan • Secondary hyperparathyroidism (intact PTH 200-800 pg/mL (22-88 pmol/L) undergoing regular HD • Exclusions: Serum calcium outside range 9.0-10.5 mg/dL (2.25-2.63 mmol/L) **Newer vitamin D group** • Number: 13 • Age: 53.8 (2.7 SD) years • Sex (M/F): 6/7 **Established vitamin D group** • Number: 12 • Age: 51.2 (1.9 SD) years • Sex (M/F): 4/8
Interventions	**Newer vitamin D group** • Falecalcitriol: 0.15-3 µg/d orally for 24 weeks **Established vitamin D group** • Alfacalcidol: 0.25-0.5 µg/d orally for 24 weeks Cointerventions: NS
Outcomes	Extractable and relevant to this review • All-cause mortality • Hypercalcaemia (serum calcium > 10.5 mg/dL (2.63 mmol/L)) • Withdrawal from treatment due to hypercalcaemia (serum calcium > 10.5 mg/dL (2.63 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ 2 (treatment assignment NS) • **Stop or endpoint/s** ○ Post hoc: cerebral infarction (alfacalcidol, treatment period 1), arthralgia and uncontrolled serum phosphorus levels (falecalcitriol, treatment period 1), uncontrolled serum calcium levels and need for parathyroidectomy (alfacalcidol, treatment period 2) • **Additional data requested and/or received from authors** ○ Allocation concealment, number of fractures in each group, mean end of treatment PTH, calcium, phosphorus, and calcium x phosphorus concentrations • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 25 ○ Analysed: 21 ○ Per cent follow-up: 84

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Akiba 1998 (*Continued*)

	The study used a crossover design, with both interventions prescribed to each group randomly in reverse order, without washout period.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Central dynamic allocation method using serum calcium and iPTH concentrations during 8-week observation period and institution as stratification variables
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants or investigators. Blinding of outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	No	ITT not performed
Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

Akizawa 2004

Methods	• Setting/Design: Multicentre • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 16%
Participants	• Country: Japan • Age 20-75 years, stable on HD with secondary hyperparathyroidism (iPTH > 200 pg/mL (22pmol/L)); serum calcium 9.0-10.5 mg/dL (2.25-2.63 mmol/L), serum phosphorus > 7.0 mg/dL (2.3mmol/L) • Exclusions: Primary hyperparathyroidism; serious cardiac or hepatic disorders; malignant neoplasms; serious infectious diseases; specific conditions such as drug allergies or marked aluminium accumulation; pregnant or lactating women **Newer vitamin D group 1** • Number: 56 • Age: 49.4 (10.6 SD) years • Sex (M/F): 32/24 **Newer vitamin D group 2** • Number: 47 • Age: 50.0 (9.9 SD) years • Sex (M/F): 31/16 **Newer vitamin D group 3** • Number :47

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	• Age: 50.1 (10.6 SD) years • Sex (M/F): 28/19 **Placebo group** • Number: 26 • Age: 53.4 (10.7 SD) years • Sex (M/F): 14/12
Interventions	**Newer vitamin D group 1** • 22-oxacalcitriol: 5 μg IV thrice weekly **Newer vitamin D group 2** • 22-oxacalcitriol: 10 μg IV thrice weekly **Newer vitamin D group 3** • 22-oxacalcitriol: 15 μg IV thrice weekly **Placebo group** • Placebo IV thrice weekly (in identical vials) Cointerventions: Calcium carbonate or aluminium containing phosphate binders
Outcomes	Extractable and relevant to this review • Hypercalcaemia (> 11.5 mg/dL (2.88 mmol/L)) • Suppression of iPTH > 30% from baseline value
Notes	• **Exclusions post-randomisation but pre-intervention**: NS • **Stop or endpoint/s** ○ Discontinuation if corrected serum calcium concentration > 11.5 mg/dL (2.88 mmol/L) • **Additional data requested and/or received from authors** ○ Allocation concealment, blinding, compliance, fracture events during follow-up, per cent reduction iPTH > 30%, end of treatment iPTH, serum calcium, and serum phosphorus concentrations • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised:203 ○ Analysed: 176 ○ Per cent follow-up: 84%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Central dynamic allocation, stratified by iPTH concentration, corrected serum calcium level, age, and centre.
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants or investigators. Blinding of outcome assessors or data assessors not stated.

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Akizawa 2004 (*Continued*)

Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Bacchini 1997

Methods	• Setting/Design: Single centre • Time frame: NS • Follow-up period: 4 months • Loss to follow-up: 0%
Participants	• Country: Italy • HD, 18-66 years, iPTH 200-2 500 ng/mL (22-285 pmol/L) • Exclusions: Type 1 diabetes; prior parathyroidectomy; phenobarbital; phenytoin; glucocorticoids; inadequate dialysis; serum Al > 100 µg/L; serum ionised calcium > 5.52 mg/dL (1.38 mmol/L) **IV group** • Number: 10 • Age: 52.7 (19 SD) years • Sex (M/F): 5/5 **Oral group** • Number: 10 • Age: 50.6 (12 SD) years • Sex (M/F): 7/3
Interventions	**IV group** • Four-month washout without calcitriol. • IV calcitriol: 0.5 µg thrice weekly increased according to ionised calcium fortnightly for 16 weeks **Oral group** • Oral calcitriol: 0.5 µg thrice weekly increased according to ionised serum calcium fortnightly for 16 weeks Cointerventions: Alteration of dialysate calcium concentration and oral calcium carbonate
Outcomes	Extractable and relevant to this review • Hypercalcaemia (ionised calcium > 5.52 mg/dL (1.38 mmol/L)) • Hyperphosphataemia (> 5.26 mg/dL (> 1.70 mmol/L)) • End of treatment plasma PTH concentration • End of treatment serum calcium concentration • End of treatment phosphorus concentration
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ Nil

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Bacchini 1997 (*Continued*)

	• **Additional data requested and/or received from authors** ○ Allocation concealment, blinding methods, all-cause mortality and fracture events, mean end of treatment PTH concentration. • **Completeness of follow-up** ○ Eligible/considered for inclusion: 204 ○ Enrolled/randomised: 20 ○ Analysed: 20 ○ Per cent follow-up:100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Baker 1986

Methods	• Setting/Design: Two centre study • Time frame: March 1977 to January 1982 • Follow-up period: 5 years • Loss to follow-up: 46%
Participants	• Country: UK • Adults requiring HD without radiological or biochemical evidence of bone disease • Exclusions: Treatment with vitamin D derivative in previous 3 months; anticonvulsant or steroid therapy; previous parathyroidectomy **Established vitamin D group** • Number: 38 • Age: NS • Sex (M/F): NS **Placebo group** • Number: 38 • Age: NS • Sex (M/F): NS
Interventions	**Established vitamin D group** • Oral calcitriol: 0.25-1 µg/d

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Baker 1986 (*Continued*)

	Placebo group • Placebo Cointerventions: Aluminium containing phosphate binders, dialysis 15-24 hours/week, dialysate calcium concentration 6.6 mg/dL (1.65 mmol/L), daily dietary calcium intake 48-76 mg (12-19 mmol)
Outcomes	Extractable and relevant to this review • Fracture • Parathyroidectomy • Development of subperiosteal erosions • Development of vascular calcification • Progression of vascular calcification • Treatment-related toxicity • Withdrawal of treatment due to hypercalcaemia (11 mg/dL (2.75 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Immobilization, major surgery including transplantation (20), persistent hypercalcaemia (8), unacceptable side-effects • **Additional data requested and/or received from authors** ○ Method of randomisation and allocation concealment, all-cause mortality events, end of treatment PTH concentration • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 76 ○ Analysed (bone biopsy): 20 ○ Per cent follow-up: 9% remaining in study at 60 months

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated, stratified by time on dialysis, age, plasma alkaline phosphatase, the presence or absence of kidneys, and centre of care.
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants or investigators. Blinding of outcome assessors or data assessors not stated
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated.

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Berl 1980

Methods	• Setting/Design: Three dialysis centres • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: NS
Participants	• Country: USA • Regular HD, without regard for clinical or biochemical evidence for bone disease • Exclusions: Serum calcium > 10 mg/dL (2.5 mmol/L) or non compliance **Established vitamin D group 1** • Number: 16 • Age: 48 (3.4 SD) years • Sex (M/F): 8/8 **Established vitamin D group 2** • Number: 15 • Age: 45 (2.5 SD) years • Sex (M/F): 7/8
Interventions	**Established vitamin D group 1** • Oral calcitriol: 0.5-1.5 µg/d **Established vitamin D group 2** • Oral vitamin D: 400 IU/d Cointerventions: Stable dialysate calcium (6 mg/dL (1.5 mmol/L)), aluminium containing antacids to maintain serum phosphorus between 4.0-7.0 mg/dL (1.3-2.3 mmol/L)
Outcomes	Extractable and relevant to this review • Bone pain • Bone histomorphometry parameters • End of treatment serum calcium, phosphorus and alkaline phosphatase concentrations • Hypercalcaemia, (serum calcium > 11.5 mg/dL (2.88 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** • ITT analyses, all-cause mortality events, fracture events, end of treatment serum phosphorus concentrations • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 31 ○ Analysed: 28 ○ Per cent follow-up: 90%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computed-generated random sequence

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Berl 1980 (*Continued*)

Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Blinding of participants, investigators and outcomes assessors. Blinding of data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	No	Funded by pharmaceutical company

Borazan 2003

Methods	• Setting/Design: Two university centres • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 0%
Participants	• Country: Turkey • HD patients with secondary hyperparathyroidism • Exclusions: NS **Oral group** • Number: 18 • Age: 39.8 (13.4 SD) years • Sex (M/F): 9/9 **IV group** • Number: 16 • Age: 38.7 (14.3 SD) years • Sex (M/F): 7/9
Interventions	**Oral group** • Oral calcitriol: 0.5 µg/d **IV group** • IV calcitriol: 1 µg/thrice weekly Cointerventions: Dialysate calcium 6.8 mg/dL (1.7 mmol/L)
Outcomes	Extractable and relevant to this review • Episodes of hypercalcaemia (serum calcium > 11.5 mg/dL (2.88 mmol/L)) • End of treatment PTH concentration • End of treatment serum calcium, alkaline phosphatase concentration
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Nil • **Additional data requested and/or received from authors** ○ Method for randomisation, allocation concealment, blinding, or compliance

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Borazan 2003 (*Continued*)

	assessment, all-cause mortality and fracture events, end of serum phosphorus concentration. • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 34 ○ Analysed: 34 ○ Per cent follow-up 100% Ethics approval was not sought for study.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Buccianti 1981

Methods	• Setting/Design: University centre • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 29/48 lost to bone biopsy follow-up
Participants	• Country: Italy • Maintenance HD • Exclusions: NS **Established vitamin D group 1** • Number: 24 • Age: 48 years • Sex (M/F): 14/10 **Established vitamin D group 2** • Number: 24 • Age: 47 years • Sex (M/F): 17/7
Interventions	**Established vitamin D group 1** • Oral 25(OH)D3: 50 µg/d **Established vitamin D group 2** • Oral calcitriol: 0.5 µg/d

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Buccianti 1981 (*Continued*)

	Cointerventions: NS
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods for randomisation, allocation concealment, ITT analysis, and blinding, and number followed up. • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 65 ○ Analysed: 29/65 bone biopsy ○ Per cent follow-up: 100% (authors state patients who required dose adjustment were excluded; unclear whether excluded pre or post randomisation)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Caravaca 1995

Methods	• Setting/Design: Single regional university centre • Time frame: NS • Follow-up period: 2.5 months • Loss to follow-up: 24%
Participants	• Country: Spain • HD requiring, basal iPTH > 4 times normal range • Exclusions: NS **Intermittent group 1** • Number: 11 • Age: NS

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	• Sex (M/F): NS **Intermittent group 2** • Number: 8 • Age: NS • Sex (M/F): NS **Daily group** • Number: 7 • Age: NS • Sex (M/F): NS
Interventions	**Intermittent group 1** • IV calcitriol: 0.045 µg/wk **Intermittent group 2** • Oral calcitriol: 0.045 µg/wk **Daily group** • Oral calcitriol: 0.045 µg/wk Cointerventions: Calcium carbonate, calcium acetate, aluminium hydroxide
Outcomes	Extractable and relevant to this review • Hyperphosphataemia (serum phosphorus > 7 mg/dL (2.25 mmol/L)) • End of treatment serum calcium, phosphorus, PTH, alkaline phosphatase
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Post hoc: kidney transplantation (4), death (1), intensification of pruritus (1), clinical instability (1) • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, randomisation, blinding, compliance assessment, ITT analysis), death and fracture events. • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 31 ○ Analysed: 26 ○ Per cent follow-up: 84%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated, stratified according to PTH
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	No	Not performed

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Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Coen 1982

Methods	• Setting/Design: NS • Time frame: NS • Follow-up period: 6-12 months • Loss to follow-up: 0%
Participants	• Country: Italy • Regular HD • Exclusions: Serum calcium > 10 mg/dL (> 2.5 mmol/L) **Intermittent group** • Number: 16 • Age: 48 (3.4 SD) years • Sex (M/F): 8/8 **Daily group** • Number: 15 • Age: 45 (2.5 SD) years • Sex (M/F): 7/8
Interventions	**Intermittent group** • Oral calcitriol: 2.75 µg once weekly and 2.5 µg once weekly **Daily group** • Oral calcitriol: 0.75 µg daily Cointerventions: Calcium carbonate, calcium acetate, aluminium hydroxide
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, blinding, compliance), mortality and fracture events, and end of treatment serum PTH, calcium, and phosphorus concentrations. • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 15 ○ Analysed: NS ○ Per cent follow-up: NS

Risk of bias

Item	Authors' judgement	Description

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Coen 1982 (*Continued*)

Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Delmez 2000

Methods	• Setting/Design: Single university centre • Time frame: NS • Follow-up period: 12months • Loss to follow-up: 0%
Participants	• Country: USA • HD therapy < one year and lack of severe hyperparathyroidism, N-PTH level < 600 pg/mL (68 pmol/L) • Exclusions: Hypercalcaemia > 11 mg/dL (2.75 mmol/L) and hyperphosphataemia > 6.5 mg/dL (2 mmol/L), uncontrolled hypertension (blood pressure > 180/100), treatment with digoxin or prior parathyroidectomy **Established vitamin D group** • Number: 7 • Age: 57 (13 SD) years • Sex (M/F): 2/5 **No treatment group** • Number: 8 • Age: 53 (16 SD) years • Sex (M/F): 4/4
Interventions	**Established vitamin D group** • IV calcitriol: 2 µg after each dialysis. If hypercalcaemia occurred (calcium > 11mg/dL) the calcitriol dose was decreased to 1 µg/treatment, if hypercalcaemia reoccurred then the dose was reduced to 0.5 µg/treatment. **No treatment group** • No treatment Cointerventions: Calcium carbonate and aluminium hydroxide
Outcomes	Extractable and relevant to this review • Fracture at any site • Development of bone pain • Episodes of hypercalcaemia (calcium > 11mg/dL (2.75 mmol/L))

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Delmez 2000 (*Continued*)

Notes	• **Exclusions post-randomisation but pre-intervention** ○ 5 participants • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, blinding, compliance), death events, end of treatment serum PTH, calcium, and phosphorus concentrations. • **Completeness of follow-up** ○ Eligible/considered for inclusion: 20 ○ Enrolled/randomised: 15 ○ Analysed: 15 ○ Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	According to whether their patient number was even or odd.
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Deuber 2003

Methods	• Setting/Design: NS • Time frame: NS • Follow-up period: 36 months • Loss to follow-up: NS
Participants	• Country: Germany • HD therapy • Exclusions: NS **Established vitamin D group 1** • Number: 25 • Age: NS • Sex (M/F): NS **Established vitamin D group 2** • Number: 25 • Age: NS

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	• Sex (M/F): NS
Interventions	**Established vitamin D group 1** • Alfacalcidol: 3.8 ± 0.4 µg/wk **Established vitamin D group 2** • Calcitriol: 2.7 ± 0.5 µg/wk Cointerventions: NS
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ During 36 months of therapy 10 patients in alfacalcidol group and 16 in calcitriol group were switched to IV alfacalcidol (due to increased PTH concentrations) • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 50 ○ Analysed: NS ○ Percent followed: NS

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

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Djukanovic 1994

Methods	• Setting/Design: Single centre • Time frame: NS • Follow-up period: 24 weeks • Loss to follow-up: 0%
Participants	• Country: Yugoslavia • HD patients with PTH concentration > 3 times upper limit of normal • Exclusions: NS **Established vitamin D group 1** • Number: 10 • Age: 53 (9.6 SD) years • Sex (M/F): 4/6 **Established vitamin D group 2** • Number: 10 • Age: 54 (12.8 SD) years • Sex (M/F): 6/4
Interventions	**Established vitamin D group 1** • 1a-hydroxyvitamin D3: Commencing with 1 µg orally 3 times weekly in combination with 1,25 $(OH)_2$D3 10 µg/d. **Established vitamin D group 2** • 1-a-hydroxyvitamin D3: Commencing with 1 µg orally 3 times weekly Cointerventions: Calcium carbonate, aluminium hydroxide
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding, compliance assessment, ITT analyses), death and fracture events, hypercalcaemia events, end of treatment serum phosphorus and calcium concentrations • Completeness of follow-up ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 20 ○ Analysed: 20 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated

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Djukanovic 1994 (*Continued*)

Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

El-Reshaid 1997

Methods	• Setting/Design: Single university dialysis centre, crossover study design • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 0%
Participants	• Country: Kuwait • Maintenance HD for a minimum of one year • Exclusions: Diabetes mellitus; chronic infection; liver disease; malabsorption syndrome; autoimmune disease; immunosuppressive therapy; previous kidney transplantation or parathyroidectomy; patients receiving antiepileptic drugs or drugs known to interfere with hepatic enzymes. **Established vitamin D group 1** • Number: 10 • Age: 39 (12 SD) years • Sex (M/F): 8/2 **Established vitamin D group 2** • Number: 10 • Age: 40 (10 SD) years • Sex (M/F): 8/2
Interventions	**Established vitamin D group 1** • IV calcitriol: 1 µg dialysis treatment **Established vitamin D group 2** • IV 1-alpha OH vitamin D3: 1 µg/dialysis treatment Cointerventions: Calcium gluconate PO and other unspecified phosphate binders
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • Additional data requested and/or received from authors ○ Methods (randomisation, allocation concealment, blinding, assessment of compliance, ITT analyses), death and fracture events, end of treatment serum phosphorus, calcium and PTH concentrations (for first period of study).

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El-Reshaid 1997 (*Continued*)

	• **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 20 ○ Analysed: 20 ○ Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated, matched for age, gender, and dialysis vintage
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Fischer 1993

Methods	• Setting/Design: Single hospital centre, crossover study design • Time frame: NS • Follow-up period: 4 months • Loss to follow-up: 9%
Participants	• Country: Australia • Maintenance HD • Exclusions: NS **IV group** • Number: 6 • Age: NS • Sex (M/F): NS **Oral group** • Number: 5 • Age: NS • Sex (M/F): NS
Interventions	**IV group** • IV calcitriol: 2 µg thrice weekly **Oral group** • Oral calcitriol: 2 µg thrice weekly Cointerventions: Dialysate calcium reduction when hypercalcaemia occurred. No calcium containing phosphate binders were used.

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Fischer 1993 (*Continued*)

Outcomes	Extractable and relevant to this review • Fracture • Hypercalcaemia (serum calcium > 10.8 mg/dL (2.7 mmol/L)) • End of treatment serum calcium, phosphorus, PTH concentration
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, randomisation, blinding, ITT), fracture events, hypercalcaemia events, serum PTH, calcium, phosphorus concentrations (for end of first period of treatment) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised:11 ○ Analysed:10 ○ Per cent followed: 91%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Coin toss by nursing staff
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Unclear	No blinding of participants, investigators, outcome assessors or data assessors
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Fournier 1993

Methods	• Setting/Design: Single dialysis unit • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 13%
Participants	• Country: France • Requiring HD • Exclusions: NS **Established vitamin D group**

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Fournier 1993 (*Continued*)

	• Number: 23 • Age: 63 (11 SD) years • Sex (M/F): 11/12 **Calcium group** • Number: 24 • Age: 61.4 (12 SD) years • Sex (M/F): 13/11
Interventions	**Established vitamin D group** • IV 1-alpha-hydroxyvitamin D3: 1-4 μg thrice weekly **Calcium group** • Oral calcium carbonate: Titrated to plasma calcium and phosphorus, 25-hydroxyvitamin D3 Cointerventions: Magnesium hydroxide
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Exclusions after randomisation but before analyses** ○ Calcium group (1 patient, kidney transplant); 1-alpha-hydroxyvitamin D3 group (5 patients, 2 uncontrollable hyperphosphataemia, 1 cerebrovascular event, 2 deaths) • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors:** ○ Methods (allocation concealment, randomisation, blinding), fracture events, end of treatment PTH concentration • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 47 ○ Analysed: 41 ○ Per cent followed: 87%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated

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Fournier 1993 (*Continued*)

Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Frazao 2000

Methods	• Setting/Design: 18 HD units • Time frame: NS • Follow-up period: 2 months • Loss to follow-up: 0%
Participants	• Country: USA • 18-65 years; thrice weekly HD; HD > 6months; serum PTH > 250-500 pg/mL (28.5-55 pmol/L) and > 500 pg/mL (> 55 pmol/L) • Exclusions: Prior therapy with vitamin D analogues in doses exceeding 0.5 µg/d; prior parathyroidectomy; treatment in prior 6 months with medications that may interfere with vitamin D or bone homeostasis; serum calcium > 10.5 mg/dL (2.63 mmol/L); serum phosphorus > 7 mg/dL (2.26 mmol/L) **Newer vitamin D group** • Number: 71 • Age: 55 (12.4 SD) years • Sex (M/F): 35/36 **Placebo group** • Number: 67 • Age: 49 (14.9 SD) years • Sex (M/F): 33/34
Interventions	**Newer vitamin D group** • Oral doxercalciferol: 10 µg with each HD session 8 weeks, dose titrated to plasma iPTH 150-300 pg/mL (16.5-33 pmol/L) **Placebo group** • Placebo Cointerventions: Calcium carbonate, calcium acetate
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Exclusions post-randomisation, during treatment** ○ Doxercalciferol: 13 patients (3 protocol violations, 8 hyperphosphataemia (mean serum phosphorus > 6.9 mg/dL (2.23 mmol/L)), 1 cardiac death, 1 change in dialysis modality) ○ Placebo: 7 patients (3 protocol violations, 1 mean serum phosphorus > 6.9 mg/dL (2.23 mmol/L), 2 cardiac deaths, 1 parathyroidectomy) • **Stop or endpoint/s** ○ Treatment suspended temporarily if iPTH level fell below "target range (150-300 pg/mL (16.5-33 pmol/L)), serum calcium > 11.2 mg/dL (2.8 mmol/L), serum phosphorus > 8.0 mg/dL (2.58 mmol/L) or calcium x phosphorus product > 75.0.

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Frazao 2000 (*Continued*)

	• **Additional data requested and/or received from authors** ○ Allocation concealment, fracture events, end of treatment serum calcium and phosphorus concentrations, hypercalcaemia events during treatment. • **Completeness of follow-up** ○ Eligible/considered for inclusion: 211 ○ Enrolled/randomised:138 ○ Analysed: 99 ○ Per cent followed: 72%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Remote randomisation (centrally located, unaffiliated statistician, who used a randomisation code).
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	No	Funded by pharmaceutical company

Gadallah 2000

Methods	• Setting/Design: NS • Time frame: NS • Follow-up period: 48 months • Loss to follow-up: 55%
Participants	• Country: USA • Prevalent adults requiring CCPD • Exclusions: NS **IP group** • Number: 18 • Age: NS • Sex (M/F): NS **Oral group** • Number: 16 • Age: NS • Sex (M/F): NS

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Gadallah 2000 (*Continued*)

Interventions	**IP group** • IP calcitriol: 3-6 mg/wk in divided doses with 6 hour dwell time **Oral group** • Oral calcitriol: 3-6 mg/wk in divided doses Cointerventions: Adjustment of dialysate calcium
Outcomes	Extractable and relevant to this review • Improvement in bone histomorphometry • End of treatment PTH concentration
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised:76 ○ Analysed: 34 ○ Per cent followed: 45%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	According to date of entry into dialysis program
Allocation concealment?	No	Inadequate
Blinding? All outcomes	No	No blinding of participants, investigators, outcome assessors or data assessors.
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	Unclear	Not stated

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Gallieni 2000

Methods	• Setting/Design: 5 HD centres • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 4/22 (18%)
Participants	• Country: Italy • Dialysis treatment for at least 3 months; 3 times weekly; age >15 years; good compliance; phosphate binders = calcium carbonate or acetate; aluminium hydroxide <2 g/d; laboratory criteria including PTH level 400-900 pg/mL (44-100 pmol/L); calcium level 8.5-10.5 mg/dL (2.1-2.6 mmol/L) • Exclusions: Treatment with active vitamin D metabolites in the 4 weeks prior to the study; recent bone fracture; pregnancy; cancer; sarcoidosis; Paget's disease; parathyroidectomy; anticonvulsants or corticosteroids; severe hypertension (diastolic blood pressure > 110 mm Hg) **Thrice weekly group** • Number: 10 • Age: mean age NS • Sex (M/F): 4/6 **Twice weekly group** • Number: 12 • Age: mean age NS • Sex (M/F): 5/7
Interventions	**Thrice weekly group** • IV calcitriol: 3-6 µg/wk in three divided doses **Twice weekly group** • IV calcitriol IV 3-6 µg/wk in two divided doses Cointerventions: Aluminium-containing phosphate binders
Outcomes	Extractable and relevant to this review • Fracture • Hypercalcaemia (serum calcium > 10.8 mg/dL (2.7 mmol/L)) • End of treatment serum calcium, phosphorus, PTH concentrations
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Calcium x phosphorus product > 70 mg^2/dL^2 or calcium > 11.0 mg/dL (2.75 mmol/L) • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 22 ○ Analysed: 18 ○ Per cent follow-up: 82%
Risk of bias	

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Gallieni 2000 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants, investigators, outcome assessors or data assessors
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Gonzalez 2003

Methods	• Setting/Design: Multicentre studies (combined data from 3 pooled RCTs) • Time frame: NS • Follow-up period: 12 weeks • Loss to follow-up: NS
Participants	• Country: USA • CKD stage 5 with severe secondary hyperparathyroidism on dialysis • Exclusions: NS **Newer vitamin D group** • Number: 15 • Age: NS • Sex (M/F): NS **Placebo group** • Number: 11 • Age: NS • Sex (M/F): NS
Interventions	**Newer vitamin D group** • Paricalcitol (initial dose = iPTH/60) with maximum initial dose of 32 μg, titrated in 2 μg increments based on baseline calcium, calcium x phosphorus product, and iPTH **Placebo group** • Placebo Cointerventions: NS
Outcomes	Extractable and relevant to this review • Suppression of iPTH > 30% below baseline value
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s**

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Gonzalez 2003 (*Continued*)

	○ Efficacy end point: At least 2 consecutive ≥ 30% decrease in PTH from baseline • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 26 ○ Analysed: 26 ○ Per cent followed: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	No	Funded by Abbott Laboratories

Greenbaum 2005

Methods	• Setting/Design: Multicentre study • Time frame: During 1999 • Follow-up period: up to 12 weeks • Lost to follow-up: 19 (40%)
Participants	• Country: USA • Paediatric patients (2-18 years); on maintenance HD; serum calcium < 10.5 mg/dL (< 2.63 mmol/L); Ca X P< 70 mg^2/dL^2, two consecutive iPTH < 400 pg/mL (44 pmol/L) • Exclusions: Post pubescent; pregnant or nursing; allergy to calcitriol; concurrent growth hormone therapy; partial parathyroidectomy within previous year; AKI within 3 months; at risk of aluminium-related bone disease or required aluminium containing phosphate binder or sevelamer for > 3 weeks of the study **Established vitamin D group** • Number: 21 • Age: 15.3 (2.8 SD) years • Sex (M/F): 14/7 **Placebo group**

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Greenbaum 2005 (*Continued*)

	• Number: 26 • Age: 14.0 (3.8 SD) years • Sex (M/F): 17/9
Interventions	**Established vitamin D group** • Calcitriol: Initial dose based on plasma iPTH (iPTH < 500 pg/mL (55 pmol/L) initial dose 0.5 µg/d; iPTH 500-1000 pg/mL (55-110 pmol/L) initial dose 1 µg/d), iPTH > 1000 pg/mL (> 110 pmol/L) 1.5 µg/d **Placebo group** • Placebo Cointerventions: Calcium-containing phosphate binders
Outcomes	Extractable and relevant to this review • Hypercalcaemia (serum calcium > 10.5 mg/dL (2.63 mmol/L)) • Hyperphosphataemia (serum phosphorus > 6.5 mg/dL (2.1 mmol/L)) • Raised calcium x phosphorus product (> 75 mg^2/dL^2) • Suppression of iPTH > 30% below baseline value
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ Two consecutive PTH concentrations > 800 pg/mL (88 pmol/L) if this concentration represented an increase from baseline. • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion:72 ○ Enrolled/randomised: 47 ○ Analysed: 28 ○ Per cent followed: 59.6%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	No	Funded by Abbott Laboratories

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Greenbaum 2007

Methods	• Setting/Design: 11 sites • Time frame: 2002-2003 • Follow-up period: 12 weeks • Lost to follow-up: 0%
Participants	• Country: USA • Paediatric patients (2 to 20 years) undergoing maintenance HD therapy 3 times/wk for more than 1 month. • Exclusions: Pregnant or nursing; history of allergy to paricalcitol; underwent partial parathyroidectomy within 1 year or AKI within 3 months; at risk of aluminium-related bone disease; aluminium containing for longer than 3 weeks during 3 months before the study; active malignancy; HIV infection; clinically significant liver disease; recent history of drug or alcohol abuse; scheduled for kidney transplant within 16 weeks study initiation; investigational drug within 30 days; concurrent disease or condition that would prohibit completion of study; history poor compliance with diet, medication or HD; on maintenance calcitonin, glucocorticoid; other drug therapy that might affect indices of bone and mineral metabolism. **Newer vitamin D group** • Number: 15 • Age: 13.6 (4.8 SD) years • Sex (M/F): 13/2 **Placebo group** • Number: 14 • Age: 14.3 (4.1 SD) years • Sex (M/F): 9/5
Interventions	**Newer vitamin D group** • IV paricalcitol: 3 times/wk initial dose based on initial iPTH levels **Placebo group** • Placebo Cointerventions: Calcium carbonate, calcium acetate, sevelamer hydrochloride, and maintain dialysate calcium levels at 2.5 mEg/L (1.25 mmol/L)
Outcomes	Extractable and relevant to this review • Hypercalcaemia (one or more serum calcium level > 11.2 mg/dL (> 2.79 mmol/L)) • Reduction in PTH (two consecutive 30% decreases from baseline iPTH levels)
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ Discontinuation after 4 weeks treatment if they have 2 consecutive iPTH levels > 700 pg/mL (77 pmol/L) and if these levels represented an increase from baseline. • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: 46 ○ Enrolled/randomised: 29

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Greenbaum 2007 (*Continued*)

	○ Analysed: 29 ○ Completed treatment: 12 (41%) ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	No	Funded by Abbott Laboratories

Haddad 2004

Methods	• Setting/Design: Single dialysis centre • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 4/26 (15%)
Participants	• Country: Jordan • 18-65 years; thrice weekly HD; HD > 6months • Exclusions: Prior therapy with vitamin D analogues in doses exceeding 0.5 µg/d; prior parathyroidectomy; treatment in prior 6 months with medications that may interfere with vitamin D or bone homeostasis; serum calcium > 10.5 mg/dL (2.63 mmol/L); serum phosphorus > 7 mg/dL (2.26 mmol/L) **IV group** • Number: 12 • Age: NS • Sex (M/F): 5/7 **Oral group** • Number: 13 • Age: NS • Sex (M/F): 7/5
Interventions	**IV group** • IV alphacalcidol: 1-4µg thrice weekly titrated to serum calcium and phosphorus **Oral group** • Oral alphacalcidol: 1-4 µg thrice weekly titrated to serum calcium and phosphorus Cointerventions: NS

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Haddad 2004 (*Continued*)

Outcomes	Extractable and relevant to this review • Hypercalcaemia (serum calcium > 10.5 mg/dL (2.63 mmol/L)) • Hyperphosphataemia (serum phosphorus > 7.0 mg/dL (2.26 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (randomisation method, blinding, allocation concealment), end of treatment PTH, calcium, and phosphorus concentrations. • **Completeness of follow-up** ○ Eligible/considered for inclusion: 204 ○ Enrolled/randomised: 20 ○ Analysed: 20 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcomes assessors and data assessors not stated.
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

Hayashi 2004

Methods	• Setting/Design: Multicentre study • Time frame: NS • Follow-up period: 12 months • Loss to follow-up: 18/91 (20%)
Participants	• Country: Japan • 18 years or older; HD twice or thrice weekly and met the following criteria: ○ iPTH = 150 pg/mL (16.5 pmol/L), ○ predialysis adjusted serum calcium = 10.5 mg/dL (2.63 mmol/L), ○ no history of treatment with vitamin D preparations or at least 4 week washout period,

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	○ on dialysis for at least 12 months and stable clinical findings, ○ absence of severe liver disease. • Exclusions: NS **Newer vitamin D group** • Number: 38 • Age:55.7 (13.6 SD) years • Sex (M/F):33/ 5 **Established vitamin D group** • Number:35 • Age: 55.1 (11.2 SD) years • Sex (M/F): 25/10
Interventions	**Newer vitamin D group** • IV maxacalcitol: 10μg (for basal PTH > 500 pg/mL) or 5 μg (for basal iPTH < 500pg/mL) per dialysis session **Established vitamin D group** • IV calcitriol: 1 μg/dialysis session Cointerventions: Dialysate calcium, calcium carbonate
Outcomes	Extractable and relevant to this review • Fracture • Hypercalcaemia (adjusted calcium > 11.5 mg/dL (2.88 mmol/L)) • Hyperphosphataemia (serum phosphorus > 6.0 mg/dL (1.9 mmol/L)) • End of treatment serum calcium and phosphorus concentration • End of treatment iPTH concentration
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (blinding), fracture and mortality events, end of treatment serum calcium, phosphorus, and PTH concentrations • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 203 ○ Analysed: 176 ○ Per cent follow-up: 84%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Yes	Sealed envelopes
Blinding? All outcomes	Unclear	No blinding of participants, investigators, outcomes assessors or data assessors.

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Hayashi 2004 (*Continued*)

Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Herrmann 1994

Methods	• Setting/Design: 6 dialysis centres • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 84%
Participants	• Country: Germany • HD; persistent elevation of 1-84 iPTH (> 20 pmol/L) on 3 occasions; age > 16 years; normal vitamin D status; no corticosteroid or anticonvulsant treatment • Exclusions: Hypercalcaemia > 2.7 mmol/L (10.8 mg/dL) or hyperphosphataemia > 2.2 mmol/L (6.8 mg/dL) in three predialysis samples **Intermittent group** • Number: 21 • Age: 68.0 (range 25-81) years • Sex (M/F): 10/11 **Continuous group** • Number: 24 • Age: 64.5 (range 25-80) years • Sex (M/F): 15/9
Interventions	**Intermittent group** • Oral calcitriol: At the end of the first (2.75 µg) and last (2.5 µg) dialysis session/wk **Continuous group** • Oral calcitriol: 0.75 µg/d Cointerventions: Calcium carbonate, calcium acetate, aluminium hydroxide (one centre, protocol violation)
Outcomes	Extractable and relevant to this review • Hypercalcaemia (serum calcium > 10.8 mg/dL (2.7 mmol/L)) • Hyperphosphataemia (serum phosphorus > 6.8 mg/dL (2.2 mmol/L) on 3 occasions)
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ PTH < 91 pg/mL (10 pmol/L), serum calcium > 10.8 mg/dL (2.7 mmol/L) (single determination), or serum phosphorus 6.8 mg/dL (2.2 mmol/L) (3 determinations) • **Additional data requested and/or received from authors** ○ None

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Herrmann 1994 (*Continued*)

	• **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 47 ○ Analysed: 41 ○ Per cent followed: 87%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number generation
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators, outcomes assessors or data assessors not stated
Intention-to-treat analysis - was it performed?	Unclear	Not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Indridason 2000

Methods	• Setting/Design: 5 dialysis centres • Time frame: November 1994 to July 1996 • Follow-up period: 9 months • Loss to follow-up: 19%
Participants	• Country: USA • Patients initiating HD with a serum intact PTH between 150-600 pg/mL • Exclusions: Dialysis duration >1 year; < 18 years; pregnancy; HIV disease; aluminium toxicity; prior parathyroidectomy; serum calcium > 10.5 mg/dL (2.63 mmol/L) without calcium or calcitriol therapy; vitamin D therapy within previous 2 months; treatment with steroids; phenytoin or phenobarbital; serious coexisting disease; plans for transplant or transfer to other dialysis modality; KT/V < 1.0 or urea reduction ratio < 55%. **IV group** • Number: 19 • Age: 53.3 (3.3 SD) years • Sex (M/F): 13/6 **Oral group** • Number: 20 • Age: 54.6 (3.29 SD) years • Sex (M/F): 13/7 **Calcium group** • Number: 11

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Indridason 2000 (*Continued*)

	• Age: 60.1 (3.36 SD) years • Sex (M/F): 3/8
Interventions	**IV group** • IV calcitriol: 1 µg/dialysis session (3 µg/wk) increased by 1.5 µg/wk titrated to serum calcium **Oral group** • Oral calcitriol: 0.5 µg daily (3.5 µg/wk) increased 1.75 µg/wk titrated to serum calcium **Calcium group** • Oral calcium carbonate: 2.5 g increased titrated to serum calcium Cointerventions: Calcium carbonate, dietary advice, aluminium hydroxide
Outcomes	Extractable and relevant to this review • Hypercalcaemia (serum calcium > 10.5 mg/dL (2.63 mmol/L)) • Hyperphosphataemia (serum phosphorus > 6.5 mg/dL (2.1 mmol/L)) • End of treatment PTH concentration • End of treatment bone alkaline phosphatase concentration • End of treatment serum calcium and phosphorus concentration
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Randomisation methods, death and fracture events, episodes of hypercalcaemia • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 52 ○ Analysed: 42 ○ Per cent followed: 81%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Permuted block randomisation
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Blinding of outcome assessors.
Intention-to-treat analysis - was it performed?	No	Not performed

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Indridason 2000 (*Continued*)

Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

Jones 1994

Methods	• Setting/Design: Single university centre, crossover study design • Time frame: 3 months • Follow-up period: 3 months • Loss to follow-up: 0%
Participants	• Country: Canada • Paediatric study; CAPD or CCPD with an estimated GFR < 10 mL/min • Exclusions: NS **Oral group** • Number: NS • Age: NS • Sex (M/F): NS **IP group** • Number: NS • Age: NS • Sex (M/F): NS
Interventions	**Oral group** • Oral calcitriol: mean ± SD dose 8.4 ± 2.3 ng/kg/dose for 3 months **IP group** • IP calcitriol: mean ± SD dose 7.3 ± 1.7 ng/kg/dose for 3 months Cointerventions: Dietary phosphorus restriction, calcium carbonate, dialysate calcium concentration
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding, and ITT analyses), deaths and fracture events, hypercalcaemia events, end of treatment serum calcium, and phosphorus (at end of first 3 months of treatment, prior to cross over) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 7 ○ Analysed: 7 ○ Per cent follow-up: 100%
Risk of bias	

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Jones 1994 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stared
Blinding? All outcomes	Yes	Blinding of outcome assessors.
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funded by a pharmaceutical company

Khajehdehi 2003

Methods	• Setting/Design: Single dialysis centre • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: NS
Participants	• Country: Iran • Adults requiring HD • Exclusions: NS **Established vitamin D group** • Number: 32 • Age: NS • Sex (M/F): NS **Placebo group** • Number: 32 • Age: NS • Sex (M/F): NS
Interventions	**Established vitamin D group** • Oral calcitriol: Twice weekly **Placebo group** • Placebo Cointerventions: Calcium carbonate 4.5 g/d
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors**

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Khajehdehi 2003 (*Continued*)

	○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 32 ○ Analysed: NS ○ Per cent follow-up: NS

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Kihara 2004

Methods	• Setting/Design: Single dialysis centre • Time frame: 2001-2003 • Follow-up period: 80 weeks • Loss to follow-up: NS
Participants	• Country: Japan • Intact PTH > 300 pg/mL (33 pmol/L); maintenance HD; corrected calcium < 10.5 mg/dL (2.63 mmol/L); phosphorus concentration < 6.5 mg/dL (2.1 mmol/L) • Exclusions: History of parathyroidectomy; kidney transplant; use of medications known to affect bone metabolism such as glucocorticoids, phenytoin, cyclosporine; diseases that affect bone metabolism such as malignancies; liver disease; gastrointestinal disease; tuberculosis; acquired immunodeficiency; chronic alcoholism; drug addiction; HD related amyloidosis **Newer vitamin D group** • Number: NS • Age: NS • Sex (M/F): NS **Established vitamin D group** • Number: NS • Age: NS • Sex (M/F): NS

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Kihara 2004 (*Continued*)

Interventions	**Newer vitamin D group** • IV maxacalcitol: 0.5 µg thrice weekly **Established vitamin D group** • IV calcitriol: 0.5 µg thrice weekly Cointerventions: Calcium based phosphate binders
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 130 ○ Enrolled/randomised:17 ○ Analysed: NS ○ Per cent follow-up: NS

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Klaus 1995

Methods	• Setting/Design: University centre • Time frame: NS • Follow-up period: NS • Loss to follow-up: NS
Participants	• Country: Germany • Dialysis dependent children • Exclusions: NS

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Klaus 1995 (*Continued*)

	Daily group • Number: 9 • Age: NS • Sex (M/F): NS **Intermittent group** • Number: 12 • Age: NS • Sex (M/F): NS
Interventions	**Daily group** • Oral calcitriol: 0.5 µg/d **Intermittent group** • Oral calcitriol: 1 µg thrice weekly Cointerventions: Calcium-containing phosphate binder
Outcomes	Extractable and relevant to this review • Hypercalcaemia (serum calcium > 11.2 mg/dL (2.8 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Treatment stopped if iPTH < 91 pg/mL (10 pmol/L), serum calcium > 11.2 mg/dL (2.8 mmol/L) or serum phosphorus > 7.7 mg/dL (2.5 mmol/L) • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 21 ○ Analysed: NS ○ Per cent follow-up: NS

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants, investigators, outcome assessors or data assessors
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

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Koshikawa 2002

Methods	• Setting/Design: Multicentre • Time frame: NS • Follow-up period: 12 weeks • Loss to follow-up: 52/151 (34%)
Participants	• Country: Japan • Age 20-75 years; PTH to conform to either (i) carboxy-terminal > 5 ng/mL (ii) high-sensitive mid-terminal PTH > 20,000 pg/mL (iii) intact PTH > 150 pg/mL (16.5 pmol/L); predialysis adjusted calcium < 10 mg/dL (2.5 mg/dL); patients not receiving vitamin D preparations: stable clinical findings and dialysis > 3 months • Exclusions: Severe hepatic impairment; concurrent prescription of digitalis-containing preparations; pregnant or lactating women **Established vitamin D group 1** • Number: 43 • Age: 50.0 (10.4 SD) years • Sex (M/F): 23/20 **Established vitamin D group 2** • Number: 44 • Age: 51.4 (11.8 SD) years • Sex (M/F): 21/23 **Established vitamin D group 3** • Number: 43 • Age: 51.0 (11.6 SD) years • Sex (M/F): 32/11 **Placebo group** • Number: 21 • Age: 48.5 (12.5 SD) years • Sex (M/F): 12/9
Interventions	**Established vitamin D group 1** • IV calcitriol: 1 μg/dialysis **Established vitamin D group 2** • IV calcitriol: 1.5 μg/dialysis **Established vitamin D group 3** • IV calcitriol: 2 μg/dialysis **Placebo group** • Placebo Cointerventions: Calcium carbonate
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Hypercalcaemia (serum calcium > 11.5 mg/dL (2.88 mmol/L)), patients included in safety analyses • **Additional data requested and/or received from authors** ○ Methods (randomisation method, allocation concealment), fracture, mortality, and hypercalcaemia events, end of treatment serum calcium, phosphorus,

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Koshikawa 2002 (*Continued*)

	and PTH concentrations. • **Completeness of follow-up** ○ Eligible/considered for inclusion: 162 ○ Enrolled/randomised: 157 ○ Analysed: 151 ○ Per cent follow-up: 99 (66%)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Blinding of participants, investigators, outcomes assessors and data assessors
Intention-to-treat analysis - was it performed?	Unclear	Not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Lee 1994

Methods	• Setting/Design: Single dialysis centre, cross-over study • Time frame: NS • Follow-up period: 28 weeks • Loss to follow-up: 0%
Participants	• Country: New Zealand • maintenance HD with mild to moderate hyperparathyroidism (not defined) • Exclusions: Initial total serum calcium > 10.8 mg/dL (2.7 mmol/L); PTH < 90.1 pg/mL (10 pmol/L); phosphorus > 6.2mg/dL (2 mmol/L) **IV group** • Number: 8 • Age: NS • Sex (M/F): NS **Oral group** • Number: 8 • Age: NS • Sex (M/F): NS
Interventions	**IV group** • IV 1-alpha-hydroxyvitamin D3: 4 µg/thrice weekly for 6 weeks **Oral group** • Oral 1-alpha-hydroxyvitamin D3: 4 µg/thrice weekly for 6 weeks

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Lee 1994 (*Continued*)

	Cointerventions: All received aluminium hydroxide 1.2-4.2 g/d and/or calcium carbonate 2.5-11.25 g/d; use of phosphate binders was adjusted to maintain a predialysis plasma phosphate < 6.2 mg/dL
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding, intention-to treat analyses), episodes of hypercalcaemia or fracture, death, end of treatment serum calcium, phosphorus, and PTH, at the end of the first period of treatment. • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 16 ○ Analysed: 16 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants, investigators, outcomes assessors or data assessors
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

Levin 1995

Methods	• Setting/Design: 5 centres • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 22/76 (29%)
Participants	• Country: Canada • Medically stable paediatric patients (2-18 years) undergone CCPD for at least. For those begun on dialysis due to AKI a period of 6 months stabilization was required before subjects became eligible, bone biopsy evidence of secondary

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Levin 1995 (*Continued*)

	hyperparathyroidism or normal rates of bone formation. • Exclusions: Other skeletal lesions of renal bone disease such as adynamic lesions, osteomalacia or mixed lesions; noncompliance with medication; undergone parathyroidectomy in previous 12 months; received prednisone or other immunosuppressive agents while undergoing regular dialysis. **IV group** • Number: 16 • Age: 12.5 (4.4 SD) years • Sex (M/F): 9/7 **Oral group** • Number: 17 • Age: 13.2 (5.4 SD) years • Sex (M/F): 9/8
Interventions	**IV group** • IV calcitriol: 0.5 µg thrice weekly **Oral group** • Oral calcitriol: 2 µg thrice weekly Cointerventions: Calcium supplementation, standardised dialysate calcium
Outcomes	Extractable and relevant to this review • Suppression of iPTH concentration below 50% of baseline value
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 76 ○ Analysed: 54 ○ Per cent follow-up: 71%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated

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Levin 1995 (*Continued*)

Was the study free of potential bias from the funding source?	No	Funded by pharmaceutical company

Levine 1996

Methods	• Setting/Design: Single university centre/ open label RCT • Time frame: NS • Follow-up period: 24 weeks • Loss to follow-up: 3/18 (17%)
Participants	• Country: USA • Plasma total calcium level < 9.5 mg/dL (2.4 mmol/L); serum PTH level > 200 pg/mL (22 pmol/L); HD three times/week; calcium x phosphorus product < 70 mg^2/dL^2; age 18-70 years • Exclusions: NS **IV group** • Number: 9 • Age: 54.2 (10.3 SD) years • Sex (M/F): 9/0 **Oral group** • Number: 9 • Age: 55.7 (13.1 SD) years • Sex (M/F): 9/0
Interventions	**IV group** • IV calcitriol: 2 µg/dialysis titrated to serum calcium to maximum 12 µg/wk **Oral group** • Oral calcitriol: 2 µg/dialysis titrated to serum calcium to maximum 12 µg/wk Cointerventions: Dialysate calcium adjustment, calcium and aluminium-containing phosphate binders
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment), number of deaths or fracture events during treatment, end of treatment serum phosphorus, calcium, and PTH concentrations. • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 18 ○ Analysed: 15 ○ Per cent follow-up: 83%

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Levine 1996 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants, investigators, outcome assessors or data assessors
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

Liou 1994

Methods	• Setting/Design: Crossover study design • Time frame: NS • Follow-up period: 12 weeks • Loss to follow-up: 0%
Participants	• Country: Taiwan • Maintenance HD who had at least a ten-fold elevation of serum intact PTH and radiographic and/or histological evidence of secondary hyperparathyroidism • Exclusions: Use of vitamin D within 3 months prior to the study and use of anticonvulsants, steroids or other medications that may interfere with mineral metabolism **Intermittent group** • Number: 5 • Age: NS • Sex (M/F): NS **Daily group** • Number: 5 • Age: NS • Sex (M/F): NS
Interventions	**Intermittent group** • IV calcitriol: 0.5 µg thrice weekly **Daily group** • Calcitriol: 0.25 µg/d increased in increments to a maximum 1.5 µg/d Cointerventions: Aluminium-containing phosphate binders
Outcomes	Extractable and relevant to this review • Nil

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Liou 1994 (*Continued*)

Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding, ITT), fracture or mortality events, end of treatment serum phosphorus, calcium, PTH concentrations, and episodes of hypercalcaemia • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 10 ○ Analysed: 10 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

Liou 1995

Methods	• Setting/Design: Crossover study design • Time frame: NS • Follow-up period: 8 weeks • Loss to follow-up: NS
Participants	• Country: Taiwan • Patients receiving CAPD with secondary hyperparathyroidism (undefined) • Exclusions: NS **SC group** • Number: NS • Age: NS • Sex (M/F): NS **Oral group** • Number: NS • Age: NS

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Liou 1995 (*Continued*)

	• Sex (M/F): NS
Interventions	**SC group** • SC calcitriol: 2 µg thrice weekly **Oral group** • Oral calcitriol: 2 µg thrice weekly Cointerventions: NS
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 6 ○ Analysed: NS ○ Per cent follow-up: NS

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants or investigators. Blinding of outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

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Llach 1998

Methods	• Setting/Design: Multicentre multiple ascending dose study • Time frame: NS • Follow-up period: 16 weeks • Loss to follow-up: NS
Participants	• Country: USA • At least 18 years of age and undergoing HD; moderate to severe hyperparathyroidism defined as iPTH concentration > 300 pg/mL (33 pmol/L) • Exclusions: Allergy to vitamin D compounds; malignancy; liver disease; drug or alcohol abuse; or were at risk for aluminium-related bone disease **Newer vitamin D group** • Number: 22 • Age: 49 (15 SD) years • Sex (M/F): 12/10 **Placebo group** • Number: 13 • Age: 51 (18 SD) years • Sex (M/F): 6/7
Interventions	**Newer vitamin D group** • IV paricalcitol: 0.04 µg/kg thrice weekly for weeks with each successive group receiving 0.08 µg/kg, 0.16 µg/kg, or 0.24 µg/kg after the previous group had demonstrated safety at the previous dose level Placebo group **Placebo group** • IV Placebo thrice weekly Cointerventions: NS
Outcomes	Extractable and relevant to this review • Development of bone pain • Hypercalcaemia (serum calcium > 11.5 mg/dL (2.88 mmol/L)) • Withdrawal of treatment due to hypercalcaemia • Decrease in serum iPTH of at least 30% from maximum baseline
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ Hypercalcaemia (serum calcium > 11.5 mg/dL (2.88 mmol/L)) (3 in paricalcitol group), elevated calcium x phosphorus product (> 70) (3 in paricalcitol group), adverse events (mild persistent rash (1 in paricalcitol group)) • **Additional data requested and/or received from authors** ○ Methods (blinding, randomisation, allocation concealment, ITT analyses), mean end of treatment PTH, calcium, and phosphorus concentrations. • **Completeness of follow-up** ○ Eligible/considered for inclusion: 71 ○ Enrolled/randomised: 35 ○ Analysed: 100% ○ Per cent follow-up: 100%
Risk of bias	

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Llach 1998 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Unclear	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Martin 1998

Methods	• Setting/Design: 11 dialysis centres, dose-escalating multicentre studies (pooled data from 3 identical studies) • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 49%
Participants	• Country: USA • HD patients with intact PTH > 400 pg/mL (44 pmol/L), normalised serum calcium between 8.0 and 10.0 mg/dL (2.0 and 2.5 mmol/L) and calcium phosphorus product < 75 mg^2/dL^2 • Exclusions: NS **Newer vitamin D group** • Number: 40 • Age: 54 (14 SD) years • Sex (M/F): 21/19 **Placebo group** • Number: 38 • Age: 54 (16 SD) years • Sex (M/F): 121/9
Interventions	**Newer vitamin D group** • IV paricalcitol: 0.04 µg/kg thrice weekly titrated to plasma PTH, incremented by 0.04 µg/kg at 2 weekly intervals if decline in PTH less than 30% of baseline, calcium < 11.5mg/dL, and calcium phosphorus product < 75 mg^2/dL^2. The dose of the drug was reduced by one level if PTH became less than 100 pg/mL (11 pmol/L) or if hypercalcaemia (serum calcium > 11.5 mg/dL (2.88 mmol/L)) occurred or an elevated calcium phosphate product occurred (< 75 mg^2/dL^2) **Placebo group** • IV placebo thrice weekly Cointerventions: Calcium carbonate and calcium acetate based phosphate binders

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Martin 1998 (*Continued*)

Outcomes	Extractable and relevant to this review • Fracture • Decrease in PTH by > 30% from baseline • End of treatment PTH concentration • End of treatment serum calcium concentration • End of treatment serum phosphorus concentration • End of treatment alkaline phosphatase concentration
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding), events during follow-up (fracture) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 78 ○ Analysed: 40 ○ Per cent follow-up: 51%

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer randomisation
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Blinding of participants, investigators, outcomes assessors and data assessors
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funded by Abbott Laboratories

Martin 2001

Methods	• Setting/Design: Multicentre • Time frame: NS • Follow-up period: 12 weeks • Loss to follow-up: 0%
Participants	• Country: USA • Age ≥ 18 years; on maintenance dialysis therapy for at least one month; non-pregnant and non lactating and use appropriate birth control; PTH level > 300 pg/mL

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	(33 pmol/L); calcium level of 8.0-10.5 mg/dL (2.0-2.63 mmol/L) and calcium x phosphorus product < 70 mg²/dL² • Exclusions: Allergic reaction to calcitriol, paricalcitol injection or other vitamin D compounds; patients who required calcitonin, maintenance or oral or IV glucocorticoids therapy or other drugs that could affect bone metabolism throughout the entire study (other than women on stable oestrogen or progestin therapy) and patients who required the chronic use of phosphate binders containing aluminium; active malignancy; significant liver disease **Newer vitamin D group 1** • Number: 64 • Age: 56.1 (14.2 SD) years • Sex (M/F): 36/28 **Newer vitamin D group 2** • Number: 61 • Age: 55.2 (13.6 SD) years • Sex (M/F): 29/32
Interventions	**Newer vitamin D group 1** • High dose IV paricalcitol: (baseline intact PTH/80) thrice weekly IV and placebo **Newer vitamin D group 2** • Low dose IV paricalcitol: (dry weight x 0.04 µg) thrice weekly IV and placebo Cointerventions: Calcium and aluminium containing phosphate binders
Outcomes	Extractable and relevant to this review • Four consecutive ≥ 30% reductions from baseline PTH levels • Raised calcium x phosphorus product (> 75 mg²/dL²) • Hypercalcaemia (calcium >11.5 mg/dL (2.88 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ Achievement of four consecutive decreases of ≥ 30% from baseline PTH level, experienced a single episode of hypercalcaemia (calcium > 11.5 mg/dL (2.88 mmol/L), or completed a maximum of 12 weeks of study procedures. • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding), events (fractures), end of treatment serum concentrations (calcium, phosphorus, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 125 ○ Analysed: 125 ○ Per cent follow-up: 0%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated

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Martin 2001 (*Continued*)

Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Blinding of participants, investigators, outcomes assessors and data assessors
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

Martinez 1996

Methods	• Setting/Design: NS • Time frame: NS • Follow-up period: 12 weeks • Loss to follow-up: 2/13 (15%)
Participants	• Country: Spain • HD with iPTH > 400 pg/mL • Exclusions: NS **Once weekly group** • Number: 6 • Age: NS • Sex (M/F): NS **Thrice weekly group** • Number: 7 • Age: NS • Sex (M/F): NS
Interventions	**Once weekly group** • IV calcitriol: 6 µg once per week **Thrice weekly group** • IV calcitriol: 2µg thrice weekly for 12 weeks Cointerventions: Dialysate calcium, calcium-containing phosphate binders
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised:13

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Martinez 1996 (*Continued*)

	○ Analysed: NS ○ Per cent follow-up: NS

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Maxwell 1978

Methods	• Setting/Design: Single university dialysis centre • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: NS
Participants	• Country: USA • Stable chronic HD patients; adult men or nonpregnant women; serum calcium level < 9.5 mg/dL (2.34 mmol/L) and fasting serum phosphorus value < 4.5 mg/dL (1.45 mmol/L) • Exclusions: NS **Established vitamin D group 1** • Number: 13 • Age: NS • Sex (M/F): NS **Established vitamin D group 2** • Number: 9 • Age: NS • Sex (M/F): NS
Interventions	**Established vitamin D group 1** • Oral calcitriol: 0.25-1.5 µg/d **Established vitamin D group 2** • Oral vitamin D3: 400 IU/d Cointerventions: Aluminium hydroxide and calcium gluconate

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Maxwell 1978 (*Continued*)

Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding), events (fractures), end of treatment serum concentrations (phosphorus, calcium, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 22 ○ Analysed: NS ○ Percent follow-up: NS

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

Memmos 1981

Methods	• Setting/Design: Single centre dialysis • Time frame: From April 1977 • Follow-up period: 24 months • Loss to follow-up: 7/64 (11%) at one year, 32/64 (50%) at 2 years
Participants	• Country: UK • Received dialysis treatment > one year • Exclusions: Plasma calcium > 12 mg/dL (3 mmol/L) or symptomatic hyperparathyroidism; had already received calcitriol or 1-alpha-hydroxyvitamin D3 or had had a parathyroidectomy **Established vitamin D group** • Number: 27

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Memmos 1981 (*Continued*)

	• Age: 50.1 (10.3 SD) years • Sex (M/F): 18/9 **Placebo group** • Number: 30 • Age: 49.2 (11.2 SD) years • Sex (M/F): 19/11
Interventions	**Established vitamin D group** • Oral calcitriol: 0.5 µg/d **Placebo group** • Placebo Cointerventions: Aluminium hydroxide phosphate binders
Outcomes	Extractable and relevant to this review • All-cause mortality • Development of bone pain • Development of periosteal erosions • Parathyroidectomy • End of treatment plasma PTH concentration • Need for parathyroidectomy • Loss of height
Notes	• **Exclusions post-randomisation but pre-intervention** ○ None stated • **Stop or endpoint/s** ○ Death (2 calcitriol, 1 placebo), transplantation (2 calcitriol), parathyroidectomy (2 placebo) • **Additional data requested and/or received from authors** ○ Methods (randomisation, blinding, allocation concealment), end of treatment serum values (calcium, phosphorus) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 127 ○ Enrolled/randomised: 64 ○ Analysed: 32 at 2 years ○ Per cent follow-up: 50%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	By investigator (with no patient contact) allocated patients into 2 groups
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Yes	Blinding of participants, investigators and outcomes assessors. Blinding of data assessors not stated

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Memmos 1981 (*Continued*)

Intention-to-treat analysis - was it performed?	No	ITT not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Mitsopoulos 2006

Methods	• Setting/Design: Single dialysis centre, dose comparison study • Time frame: NS • Follow-up period: 12 weeks • Loss to follow-up: 2/47 (5%) at 12 weeks
Participants	• Country: Greece • Maintenance HD for at least 3 months with secondary hyperparathyroidism (iPTH level, 300 to 900 pg/mL (33-99 pmol/L)); over 18 years; normal serum calcium (8.1-10.4 mg/dL (2.1-2.6 mmol/L)); Ca x P product < 70; off any vitamin metabolite replacement therapy for at least 1 month before enrolment; aluminium levels < 60 µg/L • Exclusions: Administration of calcitonin, bisphosphonates, or corticosteroids; presence of a clinically serious medical condition; previous parathyroidectomy; active malignancy. **Newer vitamin D group 1** • Number: 22 • Age: 61.5 (13.6 SD) years • Sex (M/F): 14/8 **Newer vitamin D group 2** • Number: 21 • Age: 60.8 (11.2 SD) years • Sex (M/F): 14/7
Interventions	**Newer vitamin D group 1** • High dose IV paricalcitol: Initial dose baseline iPTH/80 **Newer vitamin D group 2** • Low dose IV paricalcitol: Initial dose baseline iPTH/120 Cointerventions: Dietary control of phosphorus, sevelamer hydrochloride, and calcium carbonate or aluminium hydroxide
Outcomes	Extractable and relevant to this review • All-cause mortality • Hypercalcaemia (serum calcium > 10.4 mg/dL (2.59 mmol/L)) • Reduction of iPTH > 30% from baseline value
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Death (1 in PTH/80 dose group) and allergic reaction (1 in PTH/80 group) • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding), end of

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Mitsopoulos 2006 (*Continued*)

	treatment serum values (calcium, PTH, phosphorus) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 47 ○ Analysed: 47 ○ Per cent follow-up: 96%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	B - Unclear
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Mochizuki 2007

Methods	• Setting/Design: Seventeen dialysis centres, crossover study design • Time frame: April 2002 to August 2003 • Follow-up period: 3 months • Loss to follow-up: 11/31 (35%)
Participants	• Country: Japan • Maintenance HD; any age; iPTH > 200 pg/mL; not received vitamin D injections for more than 3 months before enrolment. • Exclusions: Refused to participate; severe complications (unspecified) or concomitant conditions such as dementia. **Newer vitamin D group** • Number: 14 • Age: NS • Sex (M/F): 5/9 **Established vitamin D group** • Number: 17 • Age: NS • Sex (M/F): 10/7
Interventions	**Newer vitamin D group** • IV maxacalcitol: Initial dose 10 µg/HD session for iPTH levels > 500 pg/mL, or 5 µg/HD session for iPTH levels < 500 pg/mL

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Mochizuki 2007 (*Continued*)

	Established vitamin D group • IV calcitriol: 1.0 μg/HD session adjusted within 0.5-1.5 μg/HD session
Outcomes	Extractable and relevant to this review • Hypercalcaemia (serum calcium > 11.0 mg/dL (2.75 mmol/L)) • Withdrawal of treatment due to hypercalcaemia (serum calcium > 11.0 mg/dL (2.75 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ 6 • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, randomisation, blinding), end of treatment serum concentrations (calcium, phosphorus, PTH) for the first period of treatment • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 31 ○ Analysed: 20 ○ Per cent follow-up: 65%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Moe 1998

Methods	• Setting/Design: Two dialysis centres • Time frame: January 1993 to January 1995 • Follow-up period: 24 weeks • Loss to follow-up: 3/21 (14%)
Participants	• Country: USA • Age > 18 years; CAPD > 3 months; secondary hyperparathyroidism (intact PTH

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	>200 pg/mL (22 pmol/L)) that was stable or rising since the start of CAPD together with an elevated serum total alkaline phosphatase concentration and/or radiographical evidence of bone resorption • Exclusions: Aluminium associated bone disease (desferrioxamine (DFO) stimulation test); serum calcium > 10 mg/dL or serum phosphorus >7.1 mg/dL, receiving medications known to interfere with vitamin D metabolism or bone turnover such as steroids or anticonvulsants; non-compliant with dialysis prescription **Intermittent group** • Number: 10 • Age: 50.6 (15.9 SD) years • Sex (M/F): 5/5 **Daily group** • Number: 8 • Age: 41.2 (17.8 SD) years • Sex (M/F): 4/4
Interventions	**Intermittent group** • Oral calcitriol: 3 µg twice weekly **Daily group** Oral calcitriol: 0.75 µg/d Cointerventions: Low calcium dialysate, calcium acetate as phosphate binder. Calcium acetate to keep phosphorus < 6.0 mg/dL (1.94 mmol/L). Calcium carbonate if not tolerated.
Outcomes	Extractable and relevant to this review • Fracture • Hypercalcaemia (serum calcium > 11.6 mg/dL (2.9 mmol/L)) • Hyperphosphataemia (serum phosphorus > 7.1 mg/dL (2.3 mmol/L)) • End of treatment serum calcium, phosphorus, and PTH concentrations
Notes	• **Exclusions post-randomisation but pre-intervention** ○ None stated • **Stop or endpoint/s** ○ Transplantation (1 intermittent), unable to take medication (1 daily), non-compliant (1 daily) • **Additional data requested and/or received from authors** ○ Methods (blinding, allocation concealment), events (fracture). • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 21 ○ Analysed: 18 ○ Per cent follow-up: 86%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number generator

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Moe 1998 (*Continued*)

Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants, investigators, outcome assessors or data assessors
Intention-to-treat analysis - was it performed?	No	ITT not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Moe 2001

Methods	• Setting/Design: Three area dialysis units, study of immunomodulatory effects of paricalcitol • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 6%
Participants	• Country: USA • Age > 18 years; HD > 3 months, able to give informed consent; medically stable; serum intact PTH < 200 pg/mL; not on calcitriol or vitamin D therapy for at least 3 months; serum calcium < 10.5 mg/dL (2.63 mmol/L) in 80% of measurements in the last 6 months or last 3 consecutive measures obtained during a 2 week period after reducing the patients dialysis calcium bath calcium concentration or last 3 consecutive measures obtained during a 2-week period after changing a patient from a calcium-containing phosphate binder to sevelamer during the run-in portion of the protocol; serum phosphorus level > 2.5 and < 7.0 mg/dL in 80% of measurements in the last 6 months, or a calcium phosphate product of $\leq$ 70 mg^2/dL^2 in 80% of measures in the last 6 months; serum 1,25(OH2)D3 levels in the normal range and a HCT > 30% • Exclusions: Known active malignancy; liver disease (serum aspartate aminotransferase, alanine transferase, or gamma-glutamyltransferase levels > 2 times the upper limits of normal)L; HIV or other known immune system disorder; history of more than 1 month of therapy with the daily ingestion of 90 mL or 3 tabs of aluminium hydroxide by history or chart review or an elevated aluminium level > 40 µg/L; pregnant or lactating women; or currently administered drugs known to suppress immune function such as corticosteroids **Newer vitamin D group** • Number: 16 • Age: 53.6 (11.4 SD) years • Sex (M/F): 12/4 **Placebo group** • Number: 15 • Age: 53.0 (9.6 SD) years • Sex (M/F): 7/8
Interventions	**Newer vitamin D group** • IV paricalcitol: 1-4 µg thrice weekly

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Moe 2001 (*Continued*)

	Placebo group • Placebo Cointerventions: Sevelamer hydrochloride and adjustment of dialysate calcium
Outcomes	Extractable and relevant to this review • All-cause mortality • End of treatment PTH concentration • End of treatment alkaline phosphatase
Notes	• **Exclusions post-randomisation but pre-intervention** ○ 1 • **Stop or endpoint/s** ○ Inability to tolerate paricalcitol • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, blinding, randomisation methods), events (fracture), end of treatment serum values (calcium, phosphorus) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 32 ○ Analysed: 30 ○ Per cent follow-up: 94%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	No	Funded by a pharmaceutical company

Moriniere 1985

Methods	• Setting/Design: Single centre • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 0%

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Moriniere 1985 (*Continued*)

Participants	• Country: France • Reliable patients on HD; plasma calcium (9.5 mg/dL (2.4 mmol/L)) and phosphorus (5.0 mg/dL (1.6 mmol/L)) well controlled with calcium carbonate alone • Exclusions: NS **Established vitamin D group** • Number: 12 • Age: NS • Sex (M/F): NS **No treatment group** • Number: 15 • Age: NS • Sex (M/F): NS
Interventions	**Established vitamin D group** • Oral 1-alpha-hydroxyvitamin D3: 1 μg/d **No treatment group** • No treatment Cointerventions: Calcium carbonate, aluminium hydroxide
Outcomes	Extractable and relevant to this review • Development of bone pain • Development of vascular calcification • End of treatment serum calcium, phosphorus, PTH, and alkaline phosphatase
Notes	• **Exclusions post-randomisation but pre-intervention** ○ None stated • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, randomisation, blinding), events (fracture) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 27 ○ Analysed: 27 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number generator
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Blinding of participants, outcomes assessors and data assessors, but not investigators

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Moriniere 1985 (*Continued*)

Intention-to-treat analysis - was it performed?	Unclear	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Pecovnik-Balon 1995

Methods	• Setting/Design: Three dialysis centres • Time frame: NS • Follow-up period: 12 months • Loss to follow-up: NS
Participants	• Country: Slovenia • Chronic HD • Exclusions: NS **Established vitamin D group** • Number: 31 • Age: NS • Sex (M/F): 19/13 **No treatment group** • Number: 26 • Age: NS • Sex (M/F): 12/14
Interventions	**Established vitamin D grou**p • Oral calcitriol: 0.25 μg/d **No treatment group** • No treatment Cointerventions: Dietary advice, calcium carbonate or aluminium hydroxide
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ None stated • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, randomisation, blinding, ITT analysis), events (fracture, deaths), end of treatment serum concentrations (calcium, phosphorus, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 93 ○ Enrolled/randomised: 57 ○ Analysed: NS ○ Per cent follow-up: NS

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Pecovnik-Balon 1995 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Popovtzer 1992

Methods	• Setting/Design: Seven Israeli dialysis units • Time frame: NS • Follow-up period: 16 months • Loss to follow-up: 15/56 (27%) (29/56 bone histomorphometry)
Participants	• Country: Israel • Maintenance HD > 3 months • Exclusions: Malignancy; mental illness; current treatments that might affect bone, calcium, or vitamin D metabolism, such as corticosteroid or anticonvulsant administration, or parathyroidectomy **Established vitamin D group 1** • Number: 19 • Age: 45.7 (12.7 SD) years • Sex (M/F): 10/9 **Established vitamin D group 2** • Number: 22 • Age: 49.5 (12.4 SD) years • Sex (M/F): 13/9
Interventions	**Established vitamin D group 1** • Oral 1-alpha-hydroxyvitamin D3: 0.25-1 µg/d **Established vitamin D group 2** • Oral 24,25 dihydroxyvitamin D3: 5 µg twice daily • Oral 1-alpha-hydroxyvitamin D3: 0.25-1 µg/d Cointerventions: Aluminium hydroxide as phosphate binders + oral calcium gluconate supplements
Outcomes	Extractable and relevant to this review • Nil

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Popovtzer 1992 (*Continued*)

Notes	• **Exclusions post-randomisation but pre-intervention**
	  ○ None stated
	• **Stop or endpoint/s**
	  ○ None stated
	• **Additional data requested and/or received from authors**
	  ○ None
	• **Completeness of follow-up**
	  ○ Eligible/considered for inclusion: NS
	  ○ Enrolled/randomised: 56
	  ○ Analysed: 31
	  ○ Per cent follow-up: 55%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants, investigators or outcome assessors not stated. Data assessors were blinded.
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Qiu 2003

Methods	• Setting/Design: Multicentre study, double-blind placebo controlled • Time frame: NS • Follow-up period: 12 weeks • Loss to follow-up: 4/74 (5%)
Participants	• Country: USA • Adults requiring CAPD or CCPD • Exclusions: NS **Newer vitamin D group** • Number: 36 • Age: NS • Sex (M/F): NS **Placebo group** • Number: 35 • Age: NS • Sex (M/F): NS

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Qiu 2003 (*Continued*)

Interventions	**Newer vitamin D group** • Oral paricalcitol: Initial μg dose iPTH/60 **Placebo group** • Placebo Cointerventions: NS
Outcomes	Extractable and relevant to this review • Two consecutive decreases of iPTH > 30% below baseline
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Two consecutive ≥ 30% decreases in iPTH from baseline • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 74 ○ Analysed: 70 ○ Per cent follow-up: 95%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	No	Funded by Abbott Laboratories

Quarles 1994

Methods	• Setting/Design: Multicentre university study (4 centres) • Time frame: NS • Follow-up period: 9 months • Loss to follow-up: Adverse events 0%

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Quarles 1994 (*Continued*)

Participants	• Country: USA • Age 18-65 years; thrice weekly HD; iPTH 250-2500 pg/mL (28.5-285 pmol/L) • Exclusions: Prior treatment with calcitriol or other vitamin D analogues in doses exceeding 0.5 µg/d; type I diabetes mellitus; prior parathyroidectomy, unsuccessful kidney transplant within one year; iron overload as defined by random serum ferritin > 1000 ng/mL; treatment in the last 6 months with medications such as phenobarbital, diphenylhydantoin or glucocorticoid which may interfere with vitamin D and/or bone homeostasis; inadequate dialysis as evidenced by predialysis BUN > 120 mg/dL; total calcium > 10.5 mg/dL (2.62 mmol/L) and serum phosphorus > 7.0 mg/dL (2.24) or serum aluminium > 100 µg/L **IV group** • Number: 10 • Age: 39.2 (12.6 SD) years • Sex (M/F): 4/6 **Oral group** • Number: 9 • Age: 41 (9.3 SD) years • Sex (M/F): 2/7
Interventions	**IV group** • IV calcitriol: 2-4 µg thrice weekly titrated to serum calcium 10.2-10.5 mg/dL (2.55-2.63 mmol/L) **Oral group** • Oral calcitriol: 2-4µg thrice weekly titrated to serum calcium 10.2-10.5 mg/dL (2.55-2.63 mmol/L) Cointerventions: Dietary calcium and phosphate restriction, calcium carbonate and aluminium containing phosphate binders
Outcomes	Extractable and relevant to this review • Hypercalcaemia (serum calcium >10.5 mg/dL (2.63 mmol/L)) • Hyperphosphataemia (serum phosphorus >7.0 mg/dL (2.3 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ None stated • **Stop or endpoint/s** ○ Transplantation (1 IV group), change to PD (1 oral group) • **Additional data requested and/or received from authors** ○ Methods (ITT analysis), events (fractures), end of treatment serum concentrations (calcium, phosphorus, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 257 ○ Enrolled/randomised: 23/19 ○ Analysed:19 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description

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Quarles 1994 (*Continued*)

Adequate sequence generation?	Yes	Table of random numbers, following pairing according to PTH concentration
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Blinding of participants, investigators and outcomes assessors. Blinding of data assessors not stated.
Intention-to-treat analysis - was it performed?	No	Not performed
Was the study free of potential bias from the funding source?	No	Funded by pharmaceutical company

Salusky 1998

Methods	• Setting/Design: Single dialysis centre • Time frame: NS • Follow-up period: 12 months • Loss to follow-up: 0%
Participants	• Country: USA • Medically stable paediatric patients on CCPD for at least 2 months; age 2-18 years. For those begun on dialysis due to AKI a period of 6 months stabilisation was required before subjects became eligible; bone biopsy evidence of secondary hyperparathyroidism or normal rates of bone formation. • Exclusions: Other skeletal lesions of renal bone disease such as adynamic lesions, osteomalacia or mixed lesions; noncompliance with medication; parathyroidectomy in previous 12 months; received prednisone or other immunosuppressive agents while undergoing regular dialysis. **IP group** • Number: 16 • Age: 12.5 (4.4 SD) years • Sex (M/F): 9/7 **Oral group** • Number: 17 • Age: 13.2 (5.4 SD) years • Sex (M/F): 9/8
Interventions	**IP group** • IP calcitriol: 1 µg/d titrated to serum calcium < 10.5 mg/dL (2.63 mmol/L) and phosphorus < 6.0 mg/dL (1.94 mmol/L) **Oral group** • Oral calcitriol: 1 µg/d titrated to serum calcium < 10.5 mg/dL (2.63 mmol/L) and phosphorus < 6.0 mg/dL (1.94 mmol/L) Cointerventions: Calcium carbonate, dietary modification, dialysate modification, aluminium-containing phosphate binders

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Salusky 1998 (*Continued*)

Outcomes	Extractable and relevant to this review • Hypercalcaemia (serum calcium > 11.0 mg/dL (2.75 mmol/L)) • Hyperphosphataemia (serum phosphorus > 7.0 mg/dL (2.26 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ None stated • **Stop or endpoint/s** ○ Persistent serum calcium > 11.0 mg/dL despite reduction of calcitriol dose, reduction of dialysate calcium content, and switch from calcium containing to aluminium containing phosphate binding agents • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, blinding, randomisation method, ITT analyses), events (death or fractures), end of treatment serum calcium, phosphorus, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 46 ○ Enrolled/randomised: 33 ○ Analysed: 33 ○ Per cent follow-up: 100%

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Biostatistician using 3 randomisation schedules, one for each skeletal lesion, that is, osteitis fibrosa, secondary hyperparathyroidism and normal bone formation.
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants or investigators. Blinding of outcome assessors or data assessors not stated
Intention-to-treat analysis - was it performed?	No	ITT not performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

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Sanchez Perales 1999

Methods	• Setting/Design: Single centre • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 0%
Participants	• Country: Spain • HD patients with biochemical hyperparathyroidism • Exclusions: NS **Weekly group** • Number: 11 • Age: 52.9 (16 SD) years • Sex (M/F): 5/6 **Thrice weekly group** • Number: 11 • Age 48.4 (20 SD) years • Sex (M/F): 6/5
Interventions	**Weekly group** • IV calcitriol: 3 µg/wk **Thrice weekly group** • IV calcitriol: 1 µg 3 times/wk Cointerventions: Calcium carbonate and aluminium-containing phosphate binders
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 22 ○ Analysed: 22 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated

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Sanchez Perales 1999 (*Continued*)

Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Sprague 2003

Methods	• Setting/Design: Multicentre (27 centres) • Time frame: 1995 to 1996 • Follow-up period: Up to 8 months • Loss to follow-up: 29/266 (11%)
Participants	• Country: USA • Medically stable patients undergoing chronic HD three times/week for at least 6 months who had not previously enrolled in a paricalcitol study • Exclusions: Screening PTH value > 250 pg/mL (28.5 pmol/L) or 300 pg/mL (33 pmol/L) if naive to vitamin D therapy; screening calcium value > 11.5 mg/dL (2.63 mmol/L); screening Ca X P > 70 mg^2/dL^2; history of significant allergy to calcitriol or other vitamin D compounds; necessity for calcitonin; maintenance oral or IV glucocorticoids or other drugs that could have affected calcium or bone metabolism other than females or stable oestrogen or progestin therapy **Newer vitamin D group** • Number: 130 • Age: 56.7 (15.5 SD) years • Sex (M/F): 70/60 **Established vitamin D group** • Number: 133 • Age: 56.6 (14.3 SD) years • Sex (M/F): 80/53
Interventions	**Newer vitamin D group** • IV paricalcitol: 0.04-0.24 µg/kg/thrice weekly **Established vitamin D group** • IV calcitriol: 0.01-0.06 µg/kg/thrice weekly Cointerventions: Phosphate binders using calcium carbonate or calcium acetate
Outcomes	Extractable and relevant to this review • Reduction in PTH concentration > 50%
Notes	• **Exclusions post-randomisation but pre-intervention** ○ None stated • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, randomisation, blinding), events (fractures, deaths, complete follow-up, hypercalcaemia), end of treatment serum concentrations (calcium, phosphorus, PTH)

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Sprague 2003 (*Continued*)

	• **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 266 ○ Analysed: 237 ○ Per cent follow-up: 89%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	No	Funded by Abbott Laboratories

Tarrass 2006

Methods	• Setting/Design: Single university centre • Time frame: NS • Follow-up period: 12 weeks • Loss to follow-up: 0%
Participants	• Country: Morocco • HD patients with basal iPTH over 4 times the normal upper limit. All patients had plasma aluminium levels < 50 µg/L. • Exclusions: NS **Intermittent group** • Number: 18 • Age: 47.16 (15.11 SD) years • Sex (M/F): 5/13 **Continuous group** • Number: 16 • Age: 46.64 (14.6 SD) years • Sex (M/F): 6/10
Interventions	**Intermittent group** • Oral alfacalcidol: 2 µg/dialysis session, thrice weekly **Continuous group** • Oral alfacalcidol: 1 µg 6 days/wk Cointerventions: Calcium carbonate

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Tarrass 2006 (*Continued*)

Outcomes	Extractable and relevant to this review • Hypercalcaemia (serum calcium > 10.5 mg/dL (2.63 mmol/L)) • Hyperphosphataemia (serum phosphorus > 7mg/dL (2.26 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding) end of treatment serum concentrations (calcium, phosphorus, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 34 ○ Analysed: 34 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Tsuruoka 2003

Methods	• Setting/Design: Single centre, crossover design • Time frame: NS • Follow-up period: 12 months • Loss to follow-up: 3/13 (23%)
Participants	• Country: Japan • HD patients • Exclusions: NS **Morning group** • Number: NS • Age: NS • Sex (M/F): NS

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Tsuruoka 2003 (*Continued*)

	Evening group • Number: NS • Age: NS • Sex (M/F): NS
Interventions	**Morning group** • Oral vitamin D3: 3 μg thrice weekly 08:00 **Evening group** • Oral vitamin D3: 3 μg thrice weekly 20:00 Cointerventions: NS
Outcomes	Extractable relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ None stated • **Stop or endpoint/s** ○ None stated • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 13 ○ Analysed: 10 ○ Per cent follow-up: 77%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants, investigators, outcome assessors or data assessors.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

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Turk 2002

Methods	• Setting/Design: Two centres • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 1/28 (3.6%)
Participants	• Country: Turkey • HD patients with secondary hyperparathyroidism • Exclusions: NS **Oral group** • Number: 14 • Age: 42 (15 SD) years • Sex (M/F): 7/7 **IV group** • Number: 14 • Age: 38 (14 SD) years • Sex (M/F): 6/8
Interventions	**Oral group** • Oral calcitriol: 1-3 µg thrice weekly **IV group** • IV calcitriol: 1-3 µg thrice weekly Cointerventions: Calcium acetate and aluminium salts
Outcomes	Extractable and relevant to this review • All-cause mortality • End of treatment serum calcium, phosphorus, iPTH, alkaline phosphatase concentration • End of treatment bone mineral density (femoral neck and lumbar spine)
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ None stated • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 28 ○ Analysed: 27 ○ Per cent follow-up: 96%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Alternating
Allocation concealment?	No	Inadequate
Blinding? All outcomes	Unclear	Not stated

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Turk 2002 (*Continued*)

Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

van der Merwe 1990

Methods	• Setting/Design: Single hospital HD centre • Time frame: NS • Follow-up period: 12 weeks • Loss to follow-up: 3/19 (16%)
Participants	• Country: Scotland • HD patients with biochemical evidence of hyperparathyroidism • Exclusions: NS **Daily group** • Number: 9 • Age: NS • Sex (M/F): NS **Intermittent group** • Number: 10 • Age: NS • Sex (M/F): NS
Interventions	**Daily group** • Oral calcitriol: 0.25-3 µg/d titrated with increasing doses until serum calcium 10.4-10.8 mg/dL (2.1-2.2 mmol/L) **Intermittent group** • Oral calcitriol: 0.5-4 µg thrice weekly with increasing doses until serum calcium 10.4-10.8 mg/dL (2.1-2.2 mmol/L) Cointerventions: NS
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ Intolerance of medication (1 in intermittent group), transplantation (1 patient, unreported treatment assignment), urological surgery (1 patient, unreported treatment assignment) • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding, ITT analysis), events (death, fracture, hypercalcaemia), end of treatment serum concentrations (calcium, phosphorus, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 71

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van der Merwe 1990 (*Continued*)

	○ Enrolled/randomised: 35 ○ Analysed: 35 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants or investigators. Blinding of outcome assessors or data assessors not stated.
Intention-to-treat analysis - was it performed?	Yes	ITT performed
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Varghese 1992

Methods	• Setting/Design: Single centre crossover study • Time frame: NS • Follow-up period: 3 months • Loss to follow-up: 0%
Participants	• Country: UK • Chronic HD patients • Exclusions: NS **Established vitamin D group** • Number: NS • Age: NS • Sex (M/F): NS **Placebo** • Number: NS • Age: NS • Sex (M/F): NS **Overall** • Number: 12 • Age range: 27-69 years • Sex (M/F): 6/6
Interventions	**Established vitamin D group** • Oral 24,25(OH)2D3: 10 µg/d **Placebo group**

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Varghese 1992 (*Continued*)

	• Placebo Cointerventions: Phosphate binding antacids
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding, ITT), events (fracture), end of treatment serum calcium, phosphorus, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 12 ○ Analysed: 12 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Alternating envelopes
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	Unclear	Funding source not stated

Watson 1989

Methods	• Setting/Design: University study • Time frame: NS • Follow-up period: 6 months • Loss to follow-up: 0%
Participants	• Country: Canada • Paediatric patients requiring CAPD; no evidence on clinical or radiological grounds of bone disease (i.e. less than severe erosions on plain film) • Exclusions: NS **Established vitamin D group** • Number: 6

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Watson 1989 (*Continued*)

	• Age: 11.5 (6 SD) years • Sex (M/F): 4/2 **No treatment group** • Number: 6 • Age: 10.1 (6.9 SD) years • Sex (M/F): 4/2
Interventions	**Established vitamin D group** • Oral 1-alpha-hydroxyvitamin D3: 10-20 ng/kg/d **No treatment group** • No treatment Cointerventions: Restriction of dietary phosphorus, cholecalciferol 400 IU/d, calcium carbonate, vitamin B and C, aluminium hydroxide
Outcomes	Extractable and relevant to this review • Fracture at any site • Hypercalcaemia (undefined) • Hyperphosphataemia (undefined) • Withdrawal of treatment due to hypercalcaemia • End of treatment PTH concentration
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ Methods (blinding), events (fractures, hypercalcaemia), end of treatment serum phosphorus and calcium concentrations • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 12 ○ Analysed: 12 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Yes	Adequate (sealed envelopes)
Blinding? All outcomes	Yes	No blinding of participant or investigators. Outcomes assessors and data assessors were blinded.
Intention-to-treat analysis - was it performed?	Yes	ITT performed

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Watson 1989 (*Continued*)

Was the study free of potential bias from the funding source?	No	Funded by Abbott Laboratories

Zisman 2005

Methods	• Setting/Design: Phase IV open-label single-centre study • Time frame: NS • Follow-up period: 1.5 months • Loss to follow-up: NS
Participants	• Country: USA • Medically stable adult patients receiving chronic HD 2-3 times weekly for at least 6 months and who had been treated with a stable dose of paricalcitol for at least 6 months • Exclusions: Serum calcium > 10.5 mg/dL (2.63 mmol/L), phosphorus > 8mg/dL (2.6 mmol/L), Ca x P > 70 mg^2/dL^2 **Low dose group** • Number: 9 • Age: 56 (15.3 SD) years • Sex (M/F): 6/3 **Intermediate dose group** • Number: 8 • Age: 57 (15.6 SD) years • Sex (M/F): 6/2 **High dose group** • Number: 10 • Age: 54 (10.9 SD) years • Sex (M/F): 7/3
Interventions	**Low dose group** • IV doxercalciferol: 35% of previous paricalcitol dose, thrice weekly **Intermediate dose group** • IV doxercalciferol: 50% of previous paricalcitol dose, thrice weekly **High dose group** • IV doxercalciferol: 65% of previous paricalcitol dose, thrice weekly Cointerventions: Phosphate binders, dietary phosphorus restriction
Outcomes	Extractable and relevant to this review • End of treatment serum calcium, PTH, phosphorus concentrations
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ None stated • **Additional data requested and/or received from authors** ○ None • **Completeness of follow-up** ○ Eligible/considered for inclusion: 46

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Zisman 2005 (*Continued*)

	○ Enrolled/randomised: 27 ○ Analysed: NS ○ Per cent follow-up: NS

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	No blinding of participants, investigators, outcome assessors or data assessors.
Intention-to-treat analysis - was it performed?	Unclear	Not stated
Was the study free of potential bias from the funding source?	No	Funded by pharmaceutical company

AKI - acute kidney injury; CAPD - continuous ambulatory peritoneal dialysis; CCPD - continuous cyclic peritoneal dialysis; GFR - glomerular filtration rate; HCT - haematocrit; HD - haemodialysis; IP - intraperitoneal; IV- intravenous; NS - not stated; PD - peritoneal dialysis; SC- subcutaneous

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

NCT00257920

Trial name or title	A study to evaluate the effects of two vitamin D analogs, Zemplar injection and Hectorol injection, on intestinal absorption of calcium in patients with Stage 5 CKD
Methods	
Participants	Stage 5 CKD patients on HD three times a week for at least 2 months, iPTH level > 200 pg/mL
Interventions	Zemplar injection versus Hectorol injection
Outcomes	Intestinal calcium absorption
Starting date	May 2006
Contact information	stacey.orzel@abbott.com

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NCT00257920 (*Continued*)

Notes	

NCT00397475

Trial name or title	Evaluation of colecalciferol substitution in dialysis patients
Methods	
Participants	Dialysis patients, vitamin D levels < 60 ng/mL
Interventions	Colecalciferol versus placebo
Outcomes	Bone metabolism and immune system
Starting date	November 2006
Contact information	Eric Seibert, MD dreric seibert@gmx-topmail.de
Notes	

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DATA AND ANALYSES

Comparison 1. Vitamin D compounds versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	5	233	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.34, 5.24]
1.1 Established vitamin D compounds	3	168	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.24, 5.05]
1.2 Newer vitamin D compounds	2	65	Risk Ratio (M-H, Random, 95% CI)	3.00 [0.13, 68.26]
2 Fracture	4	181	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.06, 15.41]
2.1 Established vitamin D compounds	3	103	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.06, 15.41]
2.2 Newer vitamin D compounds	1	78	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Development of bone pain	4	109	Risk Ratio (M-H, Random, 95% CI)	0.29 [0.03, 2.63]
3.1 Established vitamin D compounds	3	74	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.02, 9.25]
3.2 Newer vitamin D compounds	1	35	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.01, 4.65]
4 Parathyroidectomy	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Established vitamin D compounds	2	133	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.05, 12.47]
4.2 Newer vitamin D compounds	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
5 Development of subperiosteal erosions	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Established vitamin D compounds	3	120	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.07, 2.38]
5.2 Newer vitamin D compounds	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6 Resolution of subperiosteal erosions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Established vitamin D compounds	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.2 Newer vitamin D compounds	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
7 Development of vascular calcification	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Established vitamin D compounds	2	103	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.45, 2.67]
7.2 Newer vitamin D compounds	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
8 Progression of vascular calcification	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Established vitamin D compounds	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

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8.2 Newer vitamin D compounds	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
9 Development of osteitis fibrosa	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Established vitamin D compounds	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2 Newer vitamin D compounds	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
10 Development of osteomalacia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Established vitamin D compounds	1		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 Newer vitamin D compounds	0		Odds Ratio (M-H, Fixed, 95% CI)	Not estimable
11 End of treatment parathyroid hormone (pg/mL)	6	212	Mean Difference (IV, Random, 95% CI)	-196.05 [-298.43, -93.66]
11.1 Established vitamin D compounds	4	104	Mean Difference (IV, Random, 95% CI)	-220.54 [-473.63, 32.55]
11.2 Newer vitamin D compounds	2	108	Mean Difference (IV, Random, 95% CI)	-183.88 [-217.88, -149.89]
12 Reduction in parathyroid hormone level by 30%	7	361	Risk Ratio (M-H, Random, 95% CI)	5.90 [3.17, 10.96]
12.1 Established vitamin D compounds	1	47	Risk Ratio (M-H, Random, 95% CI)	2.72 [1.12, 6.61]
12.2 Newer vitamin D compounds	6	314	Risk Ratio (M-H, Random, 95% CI)	7.05 [3.82, 13.04]
13 End of treatment serum phosphorus (mg/dL)	2	105	Mean Difference (IV, Random, 95% CI)	0.70 [0.08, 1.33]
13.1 Established vitamin D compounds	1	27	Mean Difference (IV, Random, 95% CI)	0.60 [-0.40, 1.60]
13.2 Newer vitamin D compounds	1	78	Mean Difference (IV, Random, 95% CI)	0.77 [-0.04, 1.58]
14 One or more episodes of hyperphosphataemia	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
14.1 Established vitamin D compound	2	59	Risk Ratio (M-H, Random, 95% CI)	1.57 [0.97, 2.54]
14.2 Newer vitamin D compound	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
15 End of treatment serum calcium (mg/dL)	2	105	Mean Difference (IV, Random, 95% CI)	0.36 [-0.26, 0.98]
15.1 Established vitamin D compounds	1	27	Mean Difference (IV, Random, 95% CI)	Not estimable
15.2 Newer vitamin D compounds	1	78	Mean Difference (IV, Random, 95% CI)	0.64 [0.22, 1.06]
16 One or more episodes of hypercalcaemia	5	182	Risk Ratio (M-H, Random, 95% CI)	3.80 [0.90, 16.12]
16.1 Established vitamin D compounds	3	74	Risk Ratio (M-H, Random, 95% CI)	1.96 [0.62, 6.22]
16.2 Newer vitamin D compounds	2	108	Risk Ratio (M-H, Random, 95% CI)	11.97 [1.48, 96.58]
17 Withdrawal of treatment due to hypercalcaemia	4	196	Risk Ratio (M-H, Random, 95% CI)	4.17 [1.36, 12.77]

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17.1 Established vitamin D compounds	2	88	Risk Ratio (M-H, Random, 95% CI)	3.66 [0.96, 14.03]
17.2 Newer vitamin D compounds	2	108	Risk Ratio (M-H, Random, 95% CI)	5.61 [0.74, 42.45]
18 One or more episodes of elevated calcium x phosphorus product	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18.1 Established vitamin D compounds	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
18.2 Newer vitamin D compounds	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
19 End of treatment alkaline phosphatase (U/L)	3	135	Mean Difference (IV, Random, 95% CI)	-24.34 [-44.34, -4.33]
19.1 Established vitamin D compounds	1	27	Mean Difference (IV, Random, 95% CI)	-16.0 [-54.83, 22.83]
19.2 Newer vitamin D compounds	2	108	Mean Difference (IV, Random, 95% CI)	-27.35 [-50.69, -4.01]

Comparison 2. Vitamin D compound versus vitamin D compound

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 New versus established vitamin D compounds	2	103	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.19, 21.21]
2 Fracture	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 New versus established vitamin D compounds	1	73	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Improvement in bone pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Active vitamin D compound versus vitamin D_3	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Improvement in bone histomorphometry	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Active vitamin D compound versus vitamin D_3	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
5 End of treatment parathyroid hormone (pg/mL)	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Active vitamin D compound versus vitamin D_3	0		Mean Difference (IV, Random, 95% CI)	Not estimable
5.2 Calcitriol versus other established vitamin D compounds	1		Mean Difference (IV, Random, 95% CI)	Not estimable
5.3 New versus established vitamin D compounds	1		Mean Difference (IV, Random, 95% CI)	Not estimable
6 End of treatment serum phosphorus (mg/dL)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

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6.1 Active vitamin D compound versus vitamin D_3	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
6.2 Calcitriol versus another established vitamin D	2	91	Mean Difference (IV, Random, 95% CI)	0.52 [-0.40, 1.44]
6.3 New versus established vitamin D compounds	1	73	Mean Difference (IV, Random, 95% CI)	-0.31 [-1.05, 0.43]
7 One or more episodes of hyperphosphataemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Active vitamin D compound versus vitamin D_3	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.2 Calcitriol versus other established vitamin D compounds	0		Risk Ratio (M-H, Random, 95% CI)	Not estimable
7.3 New versus established vitamin D compounds	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
8 End of treatment serum calcium (mg/dL)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Active vitamin D compound versus vitamin D_3	1	31	Mean Difference (IV, Random, 95% CI)	0.85 [0.35, 1.35]
8.2 Calcitriol versus other established vitamin D compounds	2	91	Mean Difference (IV, Random, 95% CI)	1.00 [-0.56, 2.57]
8.3 New versus established vitamin D compounds	1	73	Mean Difference (IV, Random, 95% CI)	0.30 [-0.11, 0.71]
9 End of treatment alkaline phosphatase (U/L)	0		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.1 Active vitamin D versus vitamin D_3	0		Mean Difference (IV, Random, 95% CI)	Not estimable
9.2 Calcitriol versus other established vitamin D compounds	0		Mean Difference (IV, Random, 95% CI)	Not estimable
9.3 New versus established vitamin D compounds	0		Mean Difference (IV, Random, 95% CI)	Not estimable
10 One or more episodes of hypercalcaemia	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Active vitamin D compound versus vitamin D_3	2	53	Risk Ratio (M-H, Random, 95% CI)	9.56 [1.32, 69.04]
10.2 Calcitriol versus other established vitamin D compounds	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
10.3 New versus established vitamin D compounds	3	125	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.26, 2.54]
11 Withdrawal of treatment due to hypercalcaemia	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11.1 Active vitamin D compound versus vitamin D_3	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.2 Calcitriol versus other established vitamin D compounds	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
11.3 New versus established vitamin D compounds	2	52	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.17, 2.22]

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12 Reduction in parathyroid hormone concentration by 50%	1	Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.1 New versus established vitamin D compounds	1	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 3. IV versus oral vitamin D compounds

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Fracture	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 End of treatment absolute BMD femoral neck (g/cm²)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 End of treatment absolute BMD lumbar spine (g/cm²)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 End of treatment parathyroid hormone (pg/mL)	8	171	Mean Difference (IV, Random, 95% CI)	-76.20 [-150.92, -1.48]
6 End of treatment serum phosphorus (mg/dL)	5	112	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.58, -0.03]
7 One or more episodes of hyperphosphataemia	5	102	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.65, 1.48]
8 End of treatment serum calcium (mg/dL)	6	146	Mean Difference (IV, Random, 95% CI)	0.08 [-0.35, 0.52]
9 One of more episodes of hypercalcaemia	6	128	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.80, 1.52]
10 End of treatment alkaline phosphatase (U/L)	4	116	Mean Difference (IV, Random, 95% CI)	3.61 [-50.06, 57.28]

Comparison 4. Intraperitoneal (IP) versus oral vitamin D compounds

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Improvement in bone histomorphometry	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 End of treatment parathyroid hormone (pg/mL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 One or more episodes of hyperphosphataemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 One or more episodes of hypercalcaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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Comparison 5. Intermittent versus daily vitamin D compounds

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fracture	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 End of treatment parathyroid hormone (pg/mL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 One or more episodes of hyperphosphataemia	3	97	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.44, 6.79]
4 End of treatment serum phosphorus (mg/dL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 One of more episodes of hypercalcaemia	4	118	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.36, 3.69]
6 End of treatment serum calcium (mg/dL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 End of treatment alkaline phosphatase (U/L)	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

HISTORY

Protocol first published: Issue 1, 2006

Review first published: Issue 4, 2009

CONTRIBUTIONS OF AUTHORS

- Suetonia C Palmer: Concept and design, data extraction, analysis and interpretation of data, writing the final manuscript, final approval of version to be published
- David O McGregor: Critical revision for intellectual content, approval of final manuscript to be submitted for publication
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DECLARATIONS OF INTEREST

No conflicts of interest are reported by the authors.

SOURCES OF SUPPORT

Internal sources

- Cochrane Renal Group, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review has been split into two reviews. The second review is Palmer 2009 (Vitamin D compounds for people with chronic kidney disease not requiring dialysis).

INDEX TERMS

Medical Subject Headings (MeSH)

*Renal Dialysis; Bone Density Conservation Agents [adverse effects; *therapeutic use]; Calcium [blood]; Kidney Failure, Chronic [blood; *therapy]; Parathyroid Hormone [*blood]; Phosphorus [blood]; Randomized Controlled Trials as Topic; Vitamin D [adverse effects; *analogs & derivatives; therapeutic use]

MeSH check words

Adult; Child; Humans

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