Vitamin D compounds for people with chronic kidney disease not requiring dialysis (Review)

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[Intervention Review]

Vitamin D compounds for people with chronic kidney disease not requiring dialysis

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ABSTRACT

Background

Vitamin D compounds are used to suppress elevated serum parathyroid hormone (PTH) in people with chronic kidney disease (CKD).

Objectives

To assess the efficacy of vitamin D therapy on biochemical, bone, cardiovascular, and mortality outcomes in people with CKD and not requiring 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) comparing different forms, schedules, or routes of administration of vitamin D compounds for people with CKD not requiring dialysis were included. Vitamin D compounds were defined as established (calcitriol, alfacalcidol, $24,25(OH)_2$vitamin D_3) or newer (doxercalciferol, maxacalcitol, paricalcitol, falecalcitriol) vitamin D compounds.

Data collection and analysis

Data were extracted by two authors. Statistical analyses were performed using the random effects model. Results were summarized as risk ratio (RR) for dichotomous outcomes or mean differences (MD) for continuous outcomes with 95% confidence intervals (CI).

Main results

Sixteen studies (894 patients) were included. No formulation, route, or schedule of vitamin D compound was found to alter the mortality risk or need for dialysis. Vitamin D compounds significantly lowered serum PTH (4 studies, 153 patients: MD -49.34 pg/mL, 95% CI -85.70 to -12.97 (-5.6 pmol/L, 95% CI -9.77 to -1.48)) and were more likely to reduce serum PTH > 30% from baseline value (264 patients: RR 7.87, 95% CI 4.87 to 12.73). Vitamin D treatment was associated with increased end of treatment serum phosphorus (3 studies, 140 patients: MD 0.37 mg/dL, 95% CI 0.09, 0.66 (0.12 mmol/L, 95% CI 0.03, 0.21)) and serum calcium (5 studies, 184 patients: MD 0.20 mg/dL, 95% CI 0.17 to 0.23 (0.05 mmol/L, 95% CI 0.04 to 0.06)). Few data were available comparing intermittent with daily vitamin D administration, or other schedules of dosing.

Authors' conclusions

There are not sufficient data to determine the effect of vitamin D compounds on mortality and cardiovascular outcomes in people with CKD not requiring dialysis. While vitamin D compounds reduce serum PTH (49.3 pg/mL (5.6 pmol/L)) compared with placebo, the relative clinical benefits of PTH lowering versus treatment-related increases in serum phosphorus and calcium remain to be understood.

PLAIN LANGUAGE SUMMARY

Vitamin D compounds for people with chronic kidney disease not requiring dialysis

People with lower 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 (PTH). These metabolic changes alter bone metabolism to release calcium and accordingly lead to bone abnormalities including altered bone production. In turn, bony changes may result in bone deformation, bone pain, and altered risks of fracture.

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 through their direct action on the vitamin D receptor. Newer agents have since been developed that similarly suppress parathyroid hormone but limit changes 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 16 studies of vitamin D preparations in people with CKD and not requiring dialysis (less severe CKD) involving 894 people. No studies were designed to understand the effect of vitamin D therapy on risks of premature cardiovascular disease or mortality. Vitamin D agents lowered PTH significantly compared with no treatment, however also increased both calcium and phosphorus levels. Newer vitamin D therapies have not been compared with older vitamin compounds in CKD directly; whether they are associated with increased calcium and phosphorus is uncertain. In the future, new studies are required to assess outcomes important to patients, such as life expectancy and premature heart disease. It will also be important to know if vitamin D therapy should be used differently (differing target levels of PTH) in differing stages of CKD.

BACKGROUND

All stages of chronic kidney disease (CKD) (see Table 1- *Stages of chronic kidney Disease (KDOQI)* are associated with significantly increased all-cause and cardiovascular mortality rates (Weiner 2004). Abnormalities of mineral metabolism (serum calcium, phosphorus, and parathyroid hormone (PTH)) are important risk factors for death in CKD. These changes occur early in the development of CKD, and become universal as kidney function declines (Coen 2002). The most frequent pattern of biochemical abnormalities includes increased serum phosphorus and PTH levels, while levels of serum calcium may be low, normal, or elevated. These changes are associated with alterations in bone mineral homeostasis, increased bone fragility (Alem 2000; Piraino 1988), muscle weakness (Lazaro 1980), and vascular and soft tissue calcification (Di Leo 2003; Goldsmith 1997). Observational studies in CKD stage 5 have more recently shown abnormal calcium, phosphorus, are associated with adverse cardiovascular out-

comes, and increased mortality (Ganesh 2001).

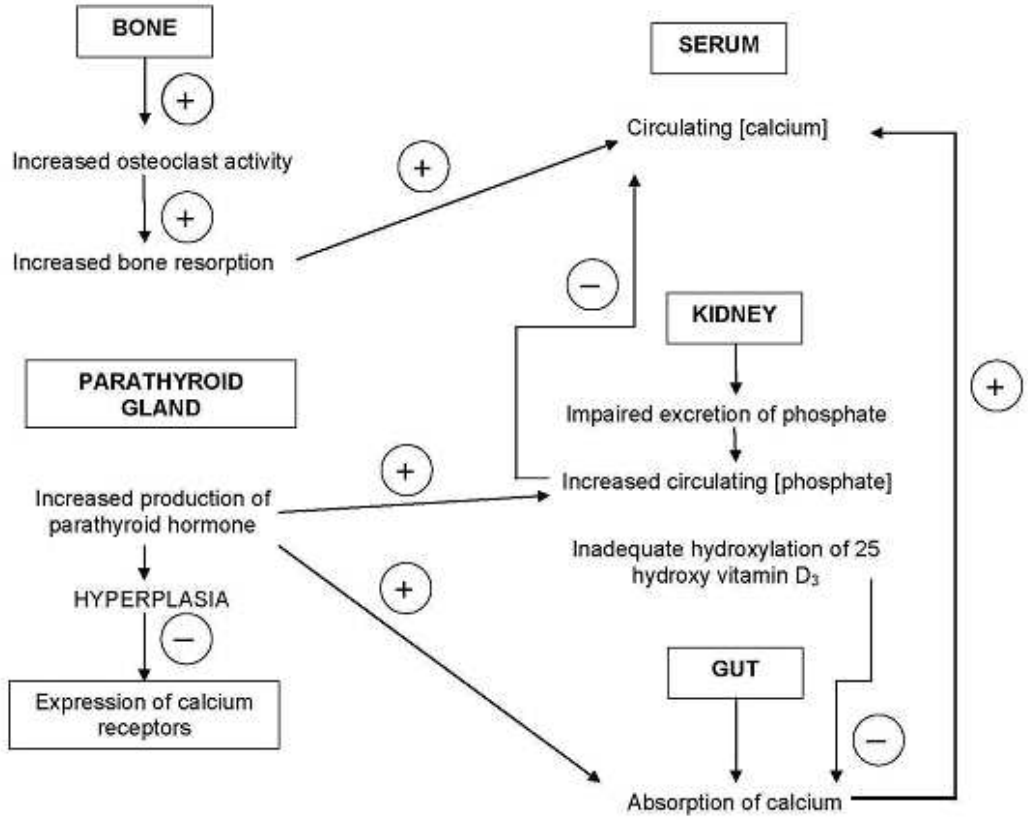
Table 1. Stages of chronic kidney disease (KDOQI)

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

Description of the condition

The bone and soft tissue changes in CKD are the result of interaction between abnormalities of vitamin D metabolism and parathyroid gland activity (see Figure 1 - *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 through 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 (calcitriol, 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 and tissue mineralization provides the rationale for its use in the amelioration of renal bone disease. Vitamin D maintains normal calcium homeostasis via the vitamin D receptor to increase intestinal calcium absorption and to promote modulate mobilization from bone.

Figure 1. Mineral metabolism in chronic kidney disease



Description of the intervention

Interventions, which are widely used to alleviate complications of mineral metabolism for people with CKD, include vitamin D compounds, calcium and non-calcium containing phosphate binders, and calcimimetic agents. Trials for vitamin D therapy initially used alfacalcidol (1α-hydroxyvitamin D_3) or calcitriol, in placebo controlled studies (Baker 1989; Hamdy 1995). Although these compounds reduce PTH levels, they may also increase calcium and phosphorus levels, which are associated with worse cardiovascular and mortality outcomes (Block 1998; Block 2004; Ganesh 2001; Young 2005). Newer vitamin D compounds (maxacalcitol, doxercalciferol, paricalcitol and falecalcitriol) have been developed to provide similar or superior dose-equivalent suppression of PTH, without increasing calcium and/or phosphorus levels to the same extent, with the hope this advantage would translate into improved biochemical and survival outcomes when compared with established vitamin D sterols (calcitriol or alfacalcidol) (Hirata 2003; Slatopolsky 2003; Teng 2003).

Why it is important to do this review

The prescription of vitamin D compounds is widespread in all stages of kidney disease. The influential National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guideline algorithm recommends in stages 3 and 4 CKD (GFR 30-59 mL/min/1.73 m² and 15-29 mL/min/1.73 m²) that oral activated vitamin D treatment (calcitriol, alfacalcidol, or doxercalciferol) are given when serum 25(OH)-vitamin D levels are replete (> 30 ng/mL) and serum PTH levels are above target ranges (KDOQI 2003). Vitamin D therapy increases serum phosphorus levels which may be associated with cardiovascular disease and lower survival in CKD (Kestenbaum 2005). Observational data also suggest elevated serum PTH is associated with accelerated mortality among people with stages 3 and 4 CKD (Kovedsy 2008a). Accordingly, it remains uncertain whether lowering serum PTH with vitamin D therapy is of clinical benefit in CKD.

We evaluated available randomised controlled trials (RCTs) to assess the effects of vitamin D compounds on biochemical, bone

and cardiovascular outcomes for people with CKD not requiring dialysis, together with an analysis of the optimal schedules and routes of administration.

OBJECTIVES

The aim of this review was to assess the benefits and harms of vitamin D compounds for people with CKD and not requiring dialysis (all-cause mortality, fracture, bone pain, stature, muscle weakness, parathyroidectomy, slipped femoral epiphyses, need for renal replacement therapy (RRT)). The secondary aims were to evaluate the effect of these agents on surrogate outcomes of mineral metabolism (serum PTH, calcium, phosphorus, alkaline phosphatase, bone mineral density, bone histomorphometry, vascular calcification). Firstly, the review examined studies of vitamin D compounds (established or newer) with placebo/no treatment or direct comparative studies of newer versus established vitamin D compounds. Secondly, the review explored comparisons of differing routes (oral versus subcutaneous (SC), intravenous (IV)) or schedules (higher versus lower dose, intermittent versus daily) of administration.

METHODS

Criteria for considering studies for this review

Types of studies

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) using vitamin D compounds to manage CKD mineral and bone disorder (CKD-MBD) were included. The first period of randomised crossover studies were also included.

Types of participants

Participants of all ages with CKD (and not requiring RRT, either dialysis or transplantation) were included. A review of RCTs of vitamin D compounds for people requiring dialysis Palmer 2009 and for kidney transplant recipients Palmer 2005 are published elsewhere in the *Cochrane Database of Systematic Reviews*.

Types of interventions

Studies randomising participants to any form of vitamin D treatment 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
- Established vitamin D compounds versus placebo/no treatment
- Newer vitamin D compounds versus placebo/no treatment
- Newer versus established vitamin D compounds
- Any schedule of treatment (intermittent versus continuous (daily))
- Any routes of treatment (oral versus IV or SC)
- Higher versus lower doses of vitamin D compounds

Any other co-administered treatment such as phosphate binders, calcimimetic compounds, anti-bone resorption agents and dietary manipulation of calcium or phosphate were possible in the included studies, but the randomised intervention was vitamin D compounds.

Types of outcome measures

Primary outcomes

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

Paediatric outcomes also included:

- Genu valgum
- Slipped upper femoral epiphyses
- Stature

Secondary outcomes

- Radiological end points (periosteal erosions, vascular calcification, bone mineral density - measured by dual energy X-ray absorptiometry, reported at the lumbar spine and femoral neck)
- Bone histomorphometry
- Reduction of PTH concentration ≥ 30% or 50% of baseline level
- Development of one or more episodes of
  - hypercalcaemia (≥ 10.4 mg/dL (2.60 mmol/L))
  - hyperphosphataemia (≥ 4.6 mg/dL (1.49 mmol/L))
  - elevated calcium × phosphorus product (> 55 mg^2/dL^2)
- Discontinuation from therapy due to hypercalcaemia
- End of treatment serum PTH, calcium, phosphorus or alkaline phosphatase concentrations
- Adverse events (excluding hypercalcaemia, hyperphosphataemia, elevated calcium × phosphorus product) were reported descriptively.

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, sex, stage of CKD), 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.

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 of these 149 studies 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. Sixty studies were RCTs of vitamin D compounds for people requiring dialysis (CKD - Stage 5D), which are reported in a separate systematic review (Palmer 2009) Thirty publications reporting 16 studies (894 patients) were included in this review. One ongoing study was identified from trial registries (NCT00285467).

Included studies

Two-thirds of studies (10/16) enrolled fewer than 50 patients, and 13 studies were of fewer than 12 months duration. Two studies (141 patients) enrolled children (Ardissino 2000; Chan 1994).
Two studies enrolled patients CKD stage 2 or lower (eGFR of 60-90 mL/min) (Ardissino 2000; Przedlacki 1995), eight enrolled subjects CKD stage 3 or lower (eGFR 30-59 mL/min) (Baker 1989; Birkenhager-Frenkel 1995; Chan 1994; Coburn 2004; Coen 1994; Coyne 2006; Hamdy 1995; Rix 2004) and three included patients with CKD stage 4 or lower (eGFR 15-29 mL/min) (Ardissino 2000; Christiansen 1978; Tougaard 1976). No study enrolled patients with CKD stage 5 not requiring dialysis (eGFR < 15 mL/min). The eGFR for study participants are detailed in Characteristics of included studies. The estimated GFR at enrolment was not stated in three studies (Juttmann 1979; Nordal 1988; Ritz 1995).

Interventions used

- Ten studies were placebo-controlled studies of vitamin D compounds in CKD (Baker 1989; Coburn 2004; Coen 1994; Coyne 2006; Hamdy 1995; Nordal 1988; Przedlacki 1995; Ritz 1995; Rix 2004; Tougaard 1976).
    - Five studies (173 patients) were of calcitriol (Baker 1989; Coen 1994; Nordal 1988; Przedlacki 1995; Ritz 1995)
    - Three studies (236 patients) of alfacalcidol (Hamdy 1995; Rix 2004; Tougaard 1976).
    - One study (55 patients) compared doxercalciferol with placebo (Coburn 2004).
    - One study (220 patients) assessed paricalcitol (Coyne 2006).
- Two studies (75 patients) compared intermittent with daily administration (Ardissino 2000; Panichi 1998).
- Four studies (147 patients) compared an established vitamin D compound with another vitamin D compound.
    - Alfacalcidol and 24,25 dihydroxycholecalciferol versus alfacalcidol alone (Birkenhager-Frenkel 1995)
    - Calcitriol versus dihydrotachysterol (Chan 1994)
    - Calcitriol versus vitamin D_3 (Christiansen 1978
    - Calcitriol versus alfacalcidol Juttmann 1979)

Risk of bias in included studies

Allocation concealment

Allocation concealment was reported and adequate in three studies (Coyne 2006; Hamdy 1995; Nordal 1988) and not reported in the remaining 13 studies.

Blinding

Blinding of participants was reported in six studies (Chan 1994; Coburn 2004; Coyne 2006; Hamdy 1995; Nordal 1988; Tougaard 1976), and of investigators in seven studies (Chan 1994; Coburn 2004; Coyne 2006; Hamdy 1995; Nordal 1988; Ritz 1995; Tougaard 1976). Two studies reported blinding of outcome assessors (Hamdy 1995; Nordal 1988).

Intention to treat analysis

Three studies were considered to have analysed their results on an intention-to treat basis (Coburn 2004; Hamdy 1995; Ritz 1995).

Completeness to follow-up

Three studies reported no patient was lost to follow-up (Ardissino 2000; Coburn 2004; Nordal 1988). Completeness to follow-up was not ascertained in six studies (Birkenhager-Frenkel 1995; Christiansen 1978; Coen 1994; Juttmann 1979; Panichi 1998; Tougaard 1976). Follow-up was between 4% and 22% in the remaining seven studies.

Effects of interventions

Any vitamin D compound versus placebo/no treatment

Patient centred outcomes

Mortality

Four studies (Coburn 2004; Coyne 2006; Hamdy 1995; Przedlacki 1995) reported the number of deaths occurring during treatment. No difference was observed between vitamin D treatment and placebo (Analysis 1.1, 4 studies (477 participants): RR 1.40, 95% CI 0.38 to 5.15). No heterogeneity was evident in this analysis.

Commencement of dialysis

No difference was observed between vitamin D and placebo/no treatment groups for risk of requiring dialysis (Analysis 1.2, 4 studies (301 participants): RR 0.76, 95% CI 0.36 to 1.62) (Coburn 2004; Hamdy 1995; Przedlacki 1995; Ritz 1995). No heterogeneity was observed in this comparison.

Fracture

Baker 1989 reported 1/38 in each group (calcitriol and placebo) experienced a fracture during follow-up (Analysis 1.3).

Parathyroidectomy

Baker 1989 reported that 5/38 required parathyroidectomy during follow-up in the calcitriol group whereas 2/38 required parathyroidectomy in the no treatment group (Analysis 1.4).

Bone pain

Tougaard 1976 reported that bone pain before the study commenced was observed in one participant which resolved following treatment with alfacalcidol.

Other patient centred outcomes

The effect of treatment with vitamin D compounds on muscle weakness was not reported.

Bone histomorphometry outcomes

Vitamin D treatment (alfacalcidol) was associated with significant improvement in bone histomorphometry in Hamdy 1995 (Analysis 1.5, 1 study (100 participants): RR 9.41, 95% CI 2.34 to 37.78). Baker 1989 reported significantly reduced osteoid volume (Analysis 1.6 1 study (13 participants): MD -4.27 mm^3/cm^3, 95% CI -5.69 to -2.85) and osteoid thickness (Analysis 1.7, 1 study (13 participants): MD -3.72 μm, 95% CI -4.76 to -2.68) following treatment with calcitriol. Two studies reported risk of developing of osteitis fibrosa (Analysis 1.8, 2 studies (43 participants): RR 0.54, 95% CI 0.23 to 1.29) (Baker 1989; Nordal 1988) showing a trend toward lower incidence in the vitamin D treated groups. Baker 1989 also reported development of osteomalacia in 3/5 participants receiving calcitriol and 0/9 participants receiving no treatment (Analysis 1.9).

Biochemical outcomes

Parathyroid hormone

Vitamin D treatment lowered serum PTH significantly compared with no treatment (Analysis 1.10, 4 studies (153 participants): MD -49.34 pg/mL, 95% CI -85.70 to -12.97 (MD -5.42 pmol/L, 95% CI -9.76 to -1.48 pmol/L)) (Baker 1989; Coburn 2004; Coen 1994; Przedlacki 1995). There was no heterogeneity in this analysis (I^2 = 0%). Two more recent studies reported PTH as a reduction > 30% from baseline value and showed vitamin D therapy (doxercalciferol or paricalcitol) was associated with an increased achievement of serum PTH lowering (Analysis 1.11, 2 studies (264 participants): RR 7.87, 95% CI 4.87 to 12.73) (Coburn 2004; Coyne 2006).

Data for PTH were not extractable for meta-analysis (as mean (SD or SEM)) in the remaining five studies.

- Hamdy 1995 reported PTH as an average (range). There was a non-significant decrease in PTH after six months of alfacalcidol treatment. Following two years of treatment, no difference was observed between treatment groups.
- Nordal 1988 reported PTH values as median (interquartile range) observing significant lowering of PTH with calcitriol treatment.

- Ritz 1995 reported PTH following a post-hoc categorisation of results according to SCr at baseline (> 3mg/dL and < 3 mg/dL). No difference in end of treatment PTH was observed between treatment groups for the 45 participants who completed treatment per protocol regardless of kidney function.
- Rix 2004 reported PTH as a percent change from baseline in figure format observing an increase in serum PTH in the placebo group compared with a decrease in the alfacalcidol group over 18 months follow-up.
- Tougaard 1976 provided PTH data as individual patient trends in figure format. They reported a "significant" decrease in serum PTH in the alfacalcidol group compared to the change in placebo group.

Calcium and phosphorus

Vitamin D therapy was associated with increased risk of hypercalcaemia (Analysis 1.12, 7 studies (612 participants): RR 3.04, 95% CI 1.17 to 7.90; I^2 = 0%) (Coburn 2004; Coen 1994; Coyne 2006; Hamdy 1995; Przedlacki 1995; Ritz 1995; Rix 2004) but not hyperphosphataemia (Analysis 1.13, 2 studies (245 participants): RR 1.58, 95% CI 0.47 to 5.30) (Coyne 2006; Przedlacki 1995). A high level of heterogeneity (I^2 = 72%) was observed in this analysis for hyperphosphataemia as Coyne 2006 (230 participants) showed no difference between paricalcitol versus placebo, whereas the older study of calcitriol (Przedlacki 1995, 25 participants) observed more hyperphosphataemia in the active treatment group compared with placebo.

Hamdy 1995 reported that no subject withdrew from a study of alfacalcidol due to hypercalcaemia.

No difference in risk of elevated calcium × phosphorus product was observed (Analysis 1.14, 3 studies (200 participants): RR 1.63, 95% CI 0.57 to 4.66; I^2 = 8%) (Coburn 2004; Coyne 2006; Przedlacki 1995).

Vitamin D treatment was associated with increased end of treatment serum phosphorus (Analysis 1.15, 3 studies (140 participants): MD 0.37 mg/dL, 95% CI 0.09 to 0.66 (MD 0.12 mmol/L, 95% CI 0.03 to 0.21); I^2 = 8%) (Coburn 2004; Coen 1994; Przedlacki 1995) and serum calcium (Analysis 1.16, 5 studies (184 participants): MD 0.20 mg/dL, 95% CI 0.17 to 0.23 (MD 0.05 mmol/L, 95% CI 0.04 to 0.06)) (Baker 1989; Coburn 2004; Coen 1994; Przedlacki 1995; Rix 2004). There was minimal heterogeneity in these analyses.

Alkaline phosphatase

Vitamin D therapy (calcitriol) was associated with significantly lower serum alkaline phosphatase concentrations (Analysis 1.17, 2 studies (38 participants), MD -21.81 U/L, 95% CI -40.39 to -3.22) (Baker 1989; Przedlacki 1995).

Creatinine clearance (CrCl)

No difference was observed between vitamin D treatment and placebo groups for end of treatment CrCl (Analysis 1.18, 4 studies, (111 participants): MD -1.68 mL/min, 95% CI -6.92 to 3.56) (Baker 1989; Coburn 2004; Przedlacki 1995; Rix 2004).

Bone mineral density outcomes

Przedlacki 1995 reported end of treatment bone mineral density finding no difference between treatment groups at the femoral neck (Analysis 1.19, 1 study (25 participants): MD -0.07 g/cm², 95% CI -0.25 to 0.11) or lumbar spine (Analysis 1.20, 1 study (25 participants): MD -0.02 g/cm², 95% CI -0.18 to 0.14).

Adverse events

Baker 1989 reported that no adverse events occurred during treatment, and five studies did not report adverse events (Coen 1994; Nordal 1988; Ritz 1995; Rix 2004; Tougaard 1976).

- Hamdy 1995 reported mild gastrointestinal disturbances (alfacalcidol (6), placebo (1)) and pseudogout (alfacalcidol (2)).
- Przedlacki 1995 described unspecified intolerance to medication (calcitriol (1), placebo (1)).
- Coburn 2004 reported failure to complete 24 week treatment of doxercalciferol or placebo in 9/55 participants. Doxercalciferol treated subjects were withdrawn due to congestive heart failure (1), malabsorption (1), and commencement of dialysis (1). Placebo treated participants were withdrawn because of myocardial infarction (1), sudden death (1), and neuromuscular symptoms (1). Three further placebo treated subjects discontinued treatment due to intolerance (1), move from study area (1), and commencement of haemodialysis (1).
- Coyne 2006 reported nausea (paricalcitol (6), placebo (4)), vomiting (paricalcitol (6), placebo (5)), and rash (paricalcitol (2)). In the paricalcitol group two participants died and 20 participants reported serious adverse events, and in the placebo group one patient died and 18 reported serious adverse events.

Established vitamin D compounds versus placebo/no treatment

Patient centred outcomes

Mortality and commencement of dialysis

No significant difference between established vitamin D compounds and placebo/no treatment was found for any patient centred outcomes, including all-cause mortality (Analysis 2.1, 2 studies (202 participants): RR 1.49, 95% CI 0.14 to 15.69) (Hamdy

1995; Przedlacki 1995) and commencement of dialysis (Analysis 2.2, 3 studies (246 participants): RR 0.74, 95% CI 0.34 to 1.63) (Hamdy 1995; Przedlacki 1995; Ritz 1995). Low to moderate heterogeneity was evident in the result for mortality (I^2 = 38%) due to four deaths (mainly due to cardiovascular disease) in the vitamin D (alfacalcidol) group in Hamdy 1995 compared with none in the vitamin D group (calcitriol) in Przedlacki 1995. The differing risks for mortality with vitamin D compared with placebo in this analysis was likely due to the small size of the studies (176 and 26 individuals, respectively).

Fracture

Baker 1989 reported 1/38 in each group (calcitriol and placebo) experienced a fracture during follow-up (Analysis 2.3).

Parathyroidectomy

Baker 1989 reported that 5/38 required parathyroidectomy during follow-up in the calcitriol group whereas 2/38 required parathyroidectomy in the no treatment group (Analysis 2.4).

Bone pain

Tougaard 1976 reported that bone pain before the trial commenced resolved in one subject receiving alfacalcidol.

Other patient centred outcomes

The effect of treatment with vitamin D compounds on muscle weakness was not reported in the included studies.

Bone histomorphometry outcomes

One small study reported improvement in bone histomorphometry in a significant number of participants in the vitamin D arm, resulting in a wide confidence interval (Analysis 2.5, 1 study (100 participants): RR 9.41, 95% CI 2.34 to 37.78) (Hamdy 1995). Two studies reported risk of developing of osteitis fibrosa (Analysis 2.6, 2 studies (43 participants): RR 0.54, 95% CI 0.23 to 1.29) (Baker 1989; Nordal 1988) showing a trend toward lower incidence in the vitamin D treated groups. Baker 1989 (Analysis 2.7, 16 participants) also reported development of osteomalacia in 3/5 participants receiving calcitriol and 0/9 participants receiving no treatment.

Treatment with established vitamin D compounds reduced osteoid volumes (Analysis 2.8, 1 study (13 participants): MD -4.37 mm^3/cm^3, 95% CI -5.69 to -2.85) and osteoid thickness (Analysis 2.9, 1 study (13 participants): MD -3.72 μm, 95% CI -4.76 to -2.68) in Baker 1989.

Biochemical outcomes

Parathyroid hormone

No significant change in parathyroid hormone levels was demonstrated (Analysis 2.10, 3 studies (98 participants): MD -54.98 pg/mL, 95% CI -124.37 to 14.41 (MD -6.27 pmol/L, 95% CI -14.18 to 1.64)) (Baker 1989; Coen 1994; Przedlacki 1995). A full descriptive analysis of PTH responses to vitamin D therapy is detailed in the Results section for *Vitamin D versus placebo/no treatment.*

Calcium and phosphorus

Use of vitamin D resulted in a significant increase in risk of hypercalcaemia (Analysis 2.11, 5 studies (337 participants): RR 3.36, 95% CI 1.14 to 9.93) (Coen 1994; Hamdy 1995; Przedlacki 1995; Ritz 1995; Rix 2004) and hyperphosphataemia (Analysis 2.12, 1 study (25 participants): RR 3.08, 95% CI 1.10 to 8.57) (Przedlacki 1995).

No patient in either treatment arm of a single study experienced elevated calcium × phosphorus product (Analysis 2.13) or withdrawal of treatment due to hypercalcaemia (Analysis 2.14) (Przedlacki 1995).

Serum phosphorus was no difference between treatment arms (Analysis 2.15, 2 studies (85 participants): MD 0.51 mg/dL, 95% CI -0.19 to 1.20 (MD 0.16 mmol/L, 95% CI -0.06 to 0.39)) (Coen 1994; Przedlacki 1995) whereas serum calcium was significantly increased (Analysis 2.16, 4 studies (129 participants): MD 0.20 mg/dL, 95% CI 0.17 to 0.23 (MD 0.05 mg/dL, 95% CI 0.04 to 0.06) (Baker 1989; Coen 1994; Przedlacki 1995; Rix 2004).

Alkaline phosphatase

Alkaline phosphatase levels were reduced by treatment with an established vitamin D compound in two small studies (Analysis 2.17, 2 studies (38 participants), MD -21.81 U/L, 95% CI -40.30 to -3.22) (Baker 1989 Przedlacki 1995).

Creatinine clearance (CrCl)

CrCl was not altered by treatment with either vitamin D compound or placebo/no treatment (Analysis 2.18, 3 studies (69 participants): MD -1.95 mL/min, 95% CI -9.45 to 5.54) (Baker 1989; Przedlacki 1995; Rix 2004).

Bone mineral density outcomes

No difference was found between established vitamin D compounds and placebo/no treatment in one study for bone mineral density at the femoral neck (Analysis 2.19, 1 study (25 participants): MD -0.07 g/cm^2, 95% CI -0.25 to 0.11) or the lumbar

spine (Analysis 2.20, 1 study (25 participants): MD -0.02 g/cm², 95% CI -0.18 to 0.14) (Przedlacki 1995).

Adverse events

Baker 1989 reported that no adverse events occurred during treatment, and four studies did not report adverse events (Coen 1994; Ritz 1995; Rix 2004; Tougaard 1976).

- Hamdy 1995 reported mild gastrointestinal disturbances (alfacalcidol (6), placebo (1)) and pseudogout (alfacalcidol (2)).
- Przedlacki 1995 described unspecified intolerance to medication (calcitriol (1), placebo (1)).

Newer vitamin D compounds versus placebo/no treatment

One study compared doxercalciferol with placebo (Coburn 2004) and one assessed paricalcitol (Coyne 2006).

Patient centred outcomes

Mortality

Both studies reported mortality events (Analysis 3.1, 2 studies (275 participants): RR 1.09, 95% CI 0.16 to 7.34) (Coburn 2004; Coyne 2006) showing no difference between treatment groups.

Commencement of dialysis

Coburn 2004 reported one patient in each treatment group requiring dialysis during follow-up (Analysis 3.2, 55 participants).

Other patient centred outcomes

No data were available for fracture, bone pain, muscle weakness, parathyroidectomy, or paediatric outcomes (genu valgum, stature, slipped upper femoral epiphyses).

Biochemical outcomes

Parathyroid hormone, phosphorus and calcium

Two studies showed significantly more participants achieved a reduction in the PTH level ≥ 30% from baseline levels (Analysis 3.3, 2 studies (264 participants): RR 7.87, 95% CI 4.87 to 12.73) (Coburn 2004; Coyne 2006). However, results for end of treatment parathyroid hormone (Analysis 3.4, 1 study (55 participants): MD -47.20 pg/mL, 95% CI -89.89 to -5.41 (MD 5.34 pmol/L, 95% CI -10.25 to -0.51)), calcium (Analysis 3.5, 1 study (55 participants): MD 0.34 mg/dL, 95% CI 0.00 to 0.68 (MD 0.13 mmol/L, 95% CI 0.00 to 0.17)), and phosphorus (Analysis 3.6, 1 study (55 participants): MD 0.20 mg/dL, 95% CI -0.19 to 0.59 (MD 0.06 mmol/L, 95% CI -0.06 to 0.19)) were only extractable from Coburn 2004, limiting the strength of any conclusions drawn about the effect of newer vitamin D compounds on biochemical indices in the earlier stages of CKD.

No difference was found between newer vitamin D compounds and placebo/no treatment for hypercalcaemia (Analysis 3.7, 2 studies (275 participants): RR 2.15, 95% CI 0.28 to 16.23) (Coburn 2004; Coyne 2006), hyperphosphataemia (Analysis 3.8, 1 study (220 participants): RR 0.89, 95% CI 0.42 to 1.91) (Coyne 2006), or raised calcium × phosphorus product (Analysis 3.9, 2 studies (275 participants): RR 1.63, 95% CI 0.57 to 4.66) (Coburn 2004; Coyne 2006). All analyses had wide confidence intervals, showing considerable imprecision for the point estimates.

Creatinine clearance (CrCl)

End of treatment CrCl was not different between treatment groups in Coburn 2004 (Analysis 3.10, 1 study (42 participants): MD -3.90 mL/min, 95% CI -12.54 to 4.71).

Adverse events

- Coburn 2004 reported failure to complete 24 week treatment of doxercalciferol or placebo, in 9/55 participants. Doxercalciferol treated subjects were withdrawn due to congestive heart failure (1), malabsorption (1), and commencement of dialysis (1). Placebo treated participants were withdrawn because of myocardial infarction (1), sudden death (1), and neuromuscular symptoms (1). Three further placebo treated subjects discontinued treatment due to intolerance (1), move from study area (1), and commencement of haemodialysis (1).
- Coyne 2006 reported nausea (paricalcitol (6), placebo (4)), vomiting (paricalcitol (6), placebo (5)), and rash (paricalcitol (2)). In the paricalcitol group two participants died and 20 participants reported serious adverse events, and in the placebo group one participant died and 18 reported serious adverse events.

Intermittent versus daily vitamin D compounds

Two studies (75 participants) compared intermittent with daily administration (Ardissino 2000; Panichi 1998).

The effect of different schedules of treatment on hypercalcaemia (> 11.5 mg/dL) was the only extractable outcome. No difference was found between treatment groups (Analysis 4.1, 1 study (59 participants): RR 0.97, 95% CI 0.06 to 14.74) (Ardissino 2000). Ardissino 2000 examined daily versus intermittent oral calcitriol in 59 children. After eight weeks of treatment no difference was observed between groups in the serum PTH concentrations. One

subject in the daily group experienced hyperphosphataemia (> 7.5 mg/dL). Panichi 1998 compared daily oral calcitriol with intermittent calcitriol (thrice weekly) in a crossover study design (16 participants) and observed lowering of serum PTH in the intermittently administered calcitriol group without differences in serum phosphorus or calcium.

Adverse events

With the exception of biochemical changes neither study reported adverse events (Ardissino 2000, Panichi 1998).

Vitamin D versus vitamin D compound

Four studies (147 participants) compared a vitamin D compound with another vitamin D compound: alfacalcidol and 24,25 dihydroxycholecalciferol versus alfacalcidol alone (Birkenhager-Frenkel 1995); calcitriol versus dihydrotachysterol (Chan 1994); calcitriol versus vitamin D_3 (Christiansen 1978); and calcitriol versus alfacalcidol (Juttmann 1979).

- Birkenhager-Frenkel 1995 reported treatment of alfacalcidol and 24,25 dihydroxycholecalciferol versus alfacalcidol alone in 24 participants. No directly comparative end of treatment data were available for either biochemical or bone histomorphometry outcomes.
- Chan 1994 compared calcitriol versus dihydrotachysterol in 82 children finding no difference in growth (linear height Z scores), decrease in GFR, or time to hypercalcaemia between groups.
- Christiansen 1978 compared calcitriol with vitamin D_3 in 17 participants with CKD finding no differences in groups for end of treatment changes in serum PTH or phosphorus. Serum calcium increased significantly in the calcitriol group at end of treatment compared with vitamin D_3 therapy.
- Juttmann 1979 compared alfacalcidol and calcitriol in 10 participants. This study was reported in abstract form only. Direct comparisons between treatment groups were not reported.

Newer versus established vitamin D compounds

No directly comparative studies of newer and established vitamin D compounds were identified.

DISCUSSION

Summary of main results

We identified 16 studies assessing vitamin D therapy in people with CKD and not yet requiring dialysis. Studies published between 1976 and 2004 examined the earlier activated forms of vitamin D available (calcitriol, 24,25 dihydroxyvitamin D_3 and alfacalcidol) whereas two more recent studies (in 2004 and 2006) evaluated doxercalciferol and paricalcitol, newer activated vitamin D compounds developed to suppress PTH levels without increasing serum calcium and phosphorus to the same extent as earlier compounds. None of the included studies were designed to evaluate patient-centred events as primary outcomes.

Mortality and need for RRT events however were described in study reports; mortality was reported in four placebo-controlled studies (Coburn 2004; Coyne 2006; Hamdy 1995; Przedlacki 1995) with no significant difference between treatment groups. Need for RRT was reported in four studies (Coburn 2004; Hamdy 1995; Przedlacki 1995; Ritz 1995) and showed no difference in event rates between treatment groups. Data were insufficient to draw conclusions regarding the efficacy of vitamin D therapy on fracture, bone pain or need for parathyroidectomy.

Vitamin D compounds reduced serum PTH concentrations (overall by 50 pg/mL (5 pmol/L)) more effectively than placebo (Coburn 2004; Coen 1994; Przedlacki 1995) and also lowered PTH by 30% below baseline more frequently than placebo (Coburn 2004; Coyne 2006). Vitamin D compounds, while suppressing PTH, were consistently associated with elevated serum phosphorus (Coburn 2004; Coen 1994; Przedlacki 1995) and serum calcium (Baker 1989; Coburn 2004; Coen 1994; Przedlacki 1995; Rix 2004). Episodes of hypercalcaemia were more frequent with vitamin D therapy. Newer vitamin D compounds were also more frequently associated with reductions in PTH > 30% from baseline, compared with placebo with trends toward elevated serum calcium and phosphorus at the end of treatment in a single study (Coburn 2004).

Four older studies provided data for the effects of vitamin D therapy on bone histomorphometry (Baker 1989; Hamdy 1995; Nordal 1988) and bone mineral density (Przedlacki 1995). Vitamin D compounds improved bone histomorphometry (Hamdy 1995), and reduced osteoid volume and thickness significantly (Baker 1989) but had no effect on bone mineral density (Przedlacki 1995).

No studies in this review directly compared new and established vitamin D compounds. A single study reported hypercalcaemia events comparing intermittent versus daily vitamin therapy showing no difference between treatment groups (Ardissino 2000).

Overall completeness and applicability of evidence

Despite identifying 16 studies of vitamin D therapy in CKD, limitations in the data available for this review preclude full understanding of the clinical efficacy of vitamin D compounds in people with earlier stages of CKD. The current review is notable for

the paucity or absence of RCTs that were powered to interrogate the effects of vitamin D treatment on mortality and cardiovascular outcomes for people with CKD stages 1 to 5, a finding that is highly significant in light of the widespread use of these agents in CKD.

Early studies of vitamin D compounds focused on the effects of vitamin D treatment on bone structure and strength (including bone histomorphometry) (Baker 1989; Birkenhager-Frenkel 1995; Hamdy 1995; Nordal 1988; Przedlacki 1995; Tougaard 1976). This was appropriate in light of the prevailing understanding of calcium and phosphorus changes in CKD at the time, with abnormalities of bone mineralization at the forefront of early clinical study. However, it is now clear that alterations of calcium and phosphorus, and less so PTH, may be associated with increases in mortality and cardiovascular outcomes in CKD. The most recent studies in the current review evaluate efficacy based on the effects of vitamin D therapy on serum PTH suppression, in combination with changes in serum phosphorus and calcium.

The meta-analysis found that while vitamin D compounds lower serum PTH, they also elevate serum calcium and phosphorus in CKD, and increase rates of hypercalcaemia and hyperphosphataemia. It is unclear whether these changes in calcium and phosphorus are clinically relevant although extrapolation from observational data suggest they may be detrimental to the cardiovascular system over the long-term. Using the available RCTs in the current analysis, the implications of these clinical sequelae to vitamin D therapy remain poorly characterised due to the small number of studies conducted in people with CKD (fewer than 900 participants overall) and the absence of cardiovascular events and mortality as predefined study outcomes. Further, the available studies in the present review were not designed to achieve specific the serum PTH values recommended for each stage of CKD (KDOQI 2003) other than targeted reductions in PTH (> 30% from baseline) in two recent studies (Coburn 2004; Coyne 2006). Accordingly, the clinical benefit of using vitamin D compounds to lower PTH to specific target values as recommended by guideline algorithms remains uncertain.

Newer vitamin D compounds offer the potential for PTH suppression while limiting or avoiding concomitant increases in serum calcium and phosphorus. The relative effects of the more recently developed compounds (doxercalciferol and paricalcitol) over more established vitamin D compounds on serum PTH suppression and calcium and phosphorus metabolism were not assessed and remain unknown in the earlier stages of CKD. The present analysis includes two placebo-controlled studies of calcium and phosphorus outcomes with newer vitamin D compounds although the studies reported these differently (end of treatment values or episodes of hypercalcaemia/hyperphosphataemia) such that the data are not available for meta-analysis. Importantly, no head-to-head study is available in individuals with CKD to know whether paricalcitol or doxercalciferol are associated with similar PTH suppression and smaller elevations in serum phosphorus or calcium than more established activated vitamin D sterols (such as calcitriol or alfacalcidol).

Quality of the evidence

The majority of studies were reported before Consolidated Standards of Reporting Trials (CONSORT) statements were published (www.consort-statement.org) and were incompletely reported or were of poor quality. Allocation concealment was adequate in 3/16 studies. Blinding of investigators occurred in less than half of the 16 studies. Only three studies were considered to have analysed outcomes according to the allocated treatment and completeness-to-follow-up was not known in six studies. The majority of studies were small; two-thirds of studies (10/16 studies) enrolled fewer than 50 participants and 13 studies were of fewer than 12 months duration suggesting insufficient power to discern differences between treatment groups even when clinical differences might exist. Data summary was also difficult due to the variable methods of reporting in the individual studies. Particularly relevant was the heterogeneous manner of reporting PTH concentrations. Some studies did not report an estimate of variance (standard error of mean or standard deviation) and some provided data in descriptive or figure format only. A more recent development is the reporting of PTH as a dichotomous outcome (achievement of PTH suppression $\geq$ 30% from baseline) which reduces comparisons between studies from differing eras. There were no or few evaluable data comparing differing vitamin D compounds.

Agreements and disagreements with other studies or reviews

To the best of our knowledge this is the first systematic review of RCTs of vitamin D treatment in CKD and not 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 requiring dialysis* (Palmer 2009). Similar to the present analysis, insufficient data were evaluable to discern the effects of vitamin D therapy on mortality, cardiovascular disease and other clinical outcomes in people with CKD receiving dialysis.

In experimental studies, the use of vitamin D has been reported to cause both an increase and a reduction in vascular calcification (Cardus 2006; Haffner 2005; Jegger 2006; Lopez 2006), the disparity between results possibly reflecting dose effects and differences between animal models. Differences have also been reported for the proliferation and calcification of vascular smooth muscle cells both between newer vitamin D agents (Wu-Wong 2006) and when newer and older vitamin D compounds have been directly compared (Cardus 2003). By influencing the balance of calcification inducers and inhibitors, vitamin D compounds display potential beneficial effects on vascular calcification (Andress 2006)

although these advantages may be counteracted if therapy causes calcium and phosphorus levels to rise. Taken together, these data indicate significant uncertainties about the benefit of using vitamin D compounds.

Increasing observational data are available for clinical outcomes in CKD in patients with altered mineral metabolism (abnormal serum phosphorus, calcium or PTH) or following activated vitamin D therapy. Comparing the results of our review with available observational studies is difficult because the existing RCTs are underpowered for detection of vitamin D treatment effects on cardiovascular, bone, and mortality end points, and because of the inherent problem of residual confounding in observational studies. Indeed, most of the studies included in this systematic review were not intended or designed to evaluate patient centred outcomes.

While no RCTs to date have examined differing PTH levels (akin to cholesterol targets or haemoglobin thresholds), observational studies have consistently found an association between abnormalities of bone and mineral metabolism, and increased cardiovascular mortality in people requiring dialysis (Block 2004; Ganesh 2001). In relative terms these studies have shown that, for every 300 pg/mL (33 pmol/L) increase in PTH, compared to values between 150-300 pg/mL (16.5 to 33 pmol/L), the risk of death increases by approximately 10-20%. Similarly, for every 0.5 mg/dL (0.16 mmol/L) increase in phosphorus (compared to a referent value of 5.0-5.5 mg/dL (1.6-1.8 mmol/L)), or calcium levels (compared to a referent value of 9-9.5 mg/dL (2.25-2.38 mmol/L)) the risk of death increases by approximately 10-20%. Corresponding observational data evaluating risks of death in people with earlier stages of CKD are fewer; separate studies have shown that in 6730 individuals (2/3 with GFR 30-59 mL/min/1.73 m²) mortality increases linearly with serum phosphorus levels above 3.5 mg/dL (1.1 mmol/L) (Kestenbaum 2005) while in 515 US Veterans, increases in serum PTH above the normal limit (65 pg/mL (6.2 pmol/L)) was associated with increased adjusted mortality compared with PTH $\leq$ 65 pg/mL and that this risk was similar between CKD stages 3 and 4 (Kovedsy 2008a).

Emerging observational data support an association between vitamin D therapy and improved patient centred outcomes in adults with CKD, requiring dialysis (Dobrez 2004; Kalantar-Zadeh 2006; Lee 2007; Shinaberger 2008; Shoji 2004; Teng 2003; Teng 2005; Tentori 2006). In four retrospective studies treatment with any 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 haemodialysis when compared with calcitriol (3 studies, 86,573 patients) (Dobrez 2004; Tentori 2006; Teng 2003). 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. Observational data for outcomes with vitamin D therapy are now becoming available in all stages of CKD. In a recent retrospective study of nearly 1500 individuals with CKD not requiring dialysis and hyperparathyroidism, oral calcitriol was associated with a 26% lower risk of death (Shoben 2008). This was consistent with a second study of 520 male Veterans with CKD stages 3 to 5 and not yet receiving dialysis, showing lower mortality and mortality-dialysis outcomes combined for subjects receiving calcitriol (Kovedsy 2008b).

Current clinical guidelines recommend vitamin D compounds to achieve specific target thresholds for serum PTH (KDOQI 2003), although the serum targets differ with different stages of CKD (Table 1; Table 2). Importantly, published target values for serum PTH are derived from both analysis of observational studies and from expert opinion and accordingly the strength of such evidence is low. While the goal of treatment with vitamin D compounds is to lower serum PTH and therefore improve clinical outcomes, serum PTH currently remains a surrogate marker. It is not yet proven that reducing serum PTH concentrations reduces adverse clinical events in CKD within a randomised, controlled trial setting. Further, the clinical utility of intervening with vitamin D treatment to lower PTH remains unknown in all stages of CKD. The relationships between serum PTH and clinical outcomes (mortality, cardiovascular disease) is undefined necessarily because the link identified between PTH and survival in observational studies may be highly confounded.

Table 2. 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)

Table 2. Current guidelines for the use of vitamin D compounds in chronic kidney disease (*Continued*)

			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 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

Accordingly, caution is needed when extrapolating outcomes from observational studies. Discrepancies between observational studies and RCTs are evident elsewhere in nephrology to emphasize this issue. For example, observational data suggest higher haemoglobin concentrations (Locatelli 2004; Robinson 2005) are associated with significantly improved survival in CKD whereas RCTs of differing haemoglobin targets indicate higher haemoglobin values are associated with increased mortality (Phrommintikul 2007). Such a discrepancy between the findings of observational studies and RCTs indicate that currently recommended targets for serum PTH, phosphorus and calcium in CKD are not validated; formal studies of vitamin D agents or differing PTH targets are required to know whether specific treatment alters clinical outcomes in CKD. The increased awareness of the link between mineral metabolism and clinically relevant outcomes in CKD mandates that clinical investigators respond to this information, when designing studies. The need to understand the effect of vitamin D compounds on mortality and cardiovascular outcomes can be argued more strongly in light of evidence that other interventions in CKD (high haemoglobin targets, intensive dialysis) are either associated with no benefit (Eknoyan 2002) or net harm to patients (Phrommintikul 2007).

In conclusion, based upon current epidemiological standards for assessing the validity of interventions, vitamin D compounds are of unproven efficacy in CKD. Compared with placebo, vitamin D compounds suppress PTH, while increasing serum phosphorus and calcium. No studies in this review directly compared newer and established vitamin D compounds. Biochemical and experimental data suggest vitamin D compounds may have opposing influences on mortality in people with CKD requiring dialysis, but data to support their use in people with earlier stages of CKD are even less conclusive.

AUTHORS' CONCLUSIONS

Implications for practice

- No well-designed adequately powered studies have been performed to address the association of vitamin D treatment with patient-centred endpoints (mortality, cardiovascular mortality, fracture, or need for parathyroidectomy) in CKD.
- Newer vitamin D analogues cannot yet be regarded as superior to existing treatments, although they may be at least equivalent for the suppression of PTH. Their 'less calcaemic' or 'non calcaemic' status compared with older vitamin D compounds cannot be confirmed.

Implications for research

- A placebo-controlled RCT (in addition to routine care and vitamin D_3 repletion) of vitamin D therapy in people with CKD and not requiring dialysis should be considered. It would be appropriate to assess calcitriol or a newer activated vitamin D agent, aiming to lower serum PTH targets to those recommended for each stage of CKD. An alternative approach would be to consider either a placebo-controlled RCT of a fixed dose of activated vitamin D treatment or a direct comparative RCT of an older vitamin D compound (alfacalcidol or calcitriol) with a newer agent (paricalcitol, doxercalciferol). Primary outcomes would be mortality, cardiovascular events and hospitalisation events.
- While surrogate outcomes for future research (such as PTH, bone mineral density, markers of bone turnover) may prove useful, their clinical relevance is not established in CKD. An RCT of differing serum PTH targets (regardless of therapy) according to published guidelines for each stage of CKD, powered to examine clinical end points could be considered.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Ardissino 2000

Methods	• Setting/Design: Multicentre (15 European specialized nephrology centres) • Time frame: NS • Follow-up period: 2 months • Loss to follow-up: 0%
Participants	• Country: Germany • Children with CKD (CrCl < 75 mL/min/1.73 m²) and iPTH > 70 pg/mL (8 pmol/L) • Exclusions: Primary metabolic diseases; gastrointestinal malabsorption; endocrine or liver disease and malignancy; receiving steroid or recombinant human growth hormone treatment; hypo- or hypercalcaemia (< 8.5 mg/dL or > 10.5 mg/dL (< 2.13 mmol/L or >2.63 mmol/L) and hypo- or hyperphosphataemia (< 3.5 mg/dL or > 7.5 mg/dL (<1.13 mmol/L or > 2.42 mmol/L)). **Daily group** • Number: 29 • Age: 8.6 (4.7 SD) years • Sex (M/F): 24/5 • eGFR: 22 (10.1 SD) mL/min/1.73 m² **Intermittent group** • Number: 30 • Age: 8.3 (4.8 SD) years • Sex (M/F): 21/9 • eGFR: 22.8 (13.0 SD) mL/min/1.73 m²
Interventions	**Daily group** • Oral calcitriol: 10 ng/kg/d **Intermittent group** • Oral calcitriol: 35 ng/kg twice weekly Cointervention/s: Phosphate binders
Outcomes	Extractable and relevant to this review • One of more episodes of hypercalcaemia (defined by investigators as serum calcium > 11.5 mg/dL (2.88 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, blinding), events (deaths, fracture), end of treatment serum values (calcium, phosphorus, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 59 ○ Analysed: 59 ○ Per cent follow-up: 100%

Ardissino 2000 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Central randomisation (using two strata of PTH (71-399 pg/mL and ≥ 400 pg/mL))
Allocation concealment?	Unclear	NS
Blinding? All outcomes	No	No blinding of participants, investigators, outcome assessors or data assessors
ITT - was it performed?	Unclear	Not stated

Baker 1989

Methods	• Setting/Design: Single centre • Time Frame: NS • Follow-up period: 12 months • Loss to follow-up: 3/16 (18.6%)
Participants	• Country: UK • CKD; eGFR 20-59 mL/min with no symptomatic bone disease or biochemical or radiological evidence of bone disease • Exclusions: Pregnancy; hypercalcaemia; kidney stones; poorly controlled hypertension; gastrointestinal or liver disease; urine protein > 3 g/d; psychosis; known tetracycline allergy; treatment with medication known to affect bone or vitamin D metabolites within the previous 6 months. **Established vitamin D group** • Number: 7 • Age: 51-64 years • Sex (M/F): 3/4 • eGFR: NS **Placebo group** • Number: 6 • Age: 31-61 years • Sex (M/F): 4/2 • eGFR: NS
Interventions	**Established vitamin D group** • Oral calcitriol: 0.25-0.5 µg/d **Placebo group** • Placebo Cointervention/s: Calcium and vitamin D
Outcomes	Extractable and relevant to review • End of treatment serum calcium, alkaline phosphatase, and PTH concentrations • End of treatment CrCl

Baker 1989 (*Continued*)

	• End of treatment osteoid thickness and osteoid volume
Notes	• **Exclusions post-randomisation but pre-intervention** ○ None • **Stop or endpoint/s** ○ Hypersensitivity to tetracycline (1 calcitriol), myocardial infarction (1 placebo), unsatisfactory bone biopsy (1 placebo) • **Additional data requested and/or received from authors** ○ Methods (allocation concealment), events (fracture, deaths). • **Completeness of follow-up** ○ Eligible/considered for inclusion: 77/30 ○ Enrolled/randomised: 16 ○ Analysed: 13 ○ Per cent follow-up: 81%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
ITT - was it performed?	No	ITT not performed

Birkenhager-Frenkel 1995

Methods	• Setting/Design: Single University centre • Time Frame: NS • Follow-up period: 3 months • Loss to follow-up: NS
Participants	• Country: The Netherlands • CKD (predialysis) • Exclusions: NS **Established vitamin D group** • Number: 13 • Age: NS • Sex (M/F): NS • eGFR: 18.2 (8-38) mL/min/1.73 m² **Control group** • Number: 12 • Age: NS • Sex (M/F): NS • eGFR: 17.2 (8-39) mL/min/1.73 m²

Birkenhager-Frenkel 1995 (*Continued*)

Interventions	**Established vitamin D group** • Oral 24,25 (OH)2D3: 50 µg twice weekly **Control group** • No treatment Cointervention/s: Calcium, alfacalcidol, aluminium-containing phosphate binders
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, ITT analysis), events (deaths, fractures), end of treatment serum levels (calcium, phosphorus, PTH) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 29 ○ Enrolled/randomised: 25 ○ Analysed: 25 ○ 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
ITT - was it performed?	Unclear	Not stated

Chan 1994

Methods	• Setting/Design: Multicentre • Time Frame: December 1984 to May 1991 • Follow-up period: > 6 months • Loss to follow-up: 13%
Participants	• Country: USA • Children 2-10 years with a GFR between 20-60 mL/min, elevation of PTH > 1 SD above normal range, and bone age ≤ 9 years • Exclusions: Children already treated with dihydrotachysterol, calcitriol, or any other vitamin D **Established vitamin D group 1**

	• Number: 40 • Age: 6 (3 SD) years • Sex (M/F): 29/11 • eGFR: NS **Established vitamin D group 2** • Number: 42 • Age: 5 (3 SD) years • Sex (M/F): 26/16 • eGFR: NS
Interventions	**Established vitamin D group 1** • Oral calcitriol: 20 ng/kg/d **Established vitamin D group 2** • Oral dihydrotachysterol: 15 µg/kg/d Cointervention/s: Calcium carbonate, sodium bicarbonate
Outcomes	Extractable and relevant to this review • Nil
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Non compliance, dialysis or transplantation, moved away • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding), events (hypercalcaemia, fractures, events), end of treatment serum levels (PTH, phosphorus, calcium) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 143 ○ Enrolled/randomised: 94 ○ Analysed: 82 ○ Percent follow-up: 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 and investigators. Blinding of outcome assessors or data assessors not stated
ITT - was it performed?	No	ITT not performed

Christiansen 1978

Methods	• Setting/Design: County hospital • Time Frame: NS • Follow-up period: 6 months • Loss to follow-up: NS
Participants	• Country: Denmark • Stable CKD with two of the following; low bone mineral content, serum calcium lower than normal mean minus 1 SD, and alkaline phosphatase higher than normal mean plus 1 SD • Exclusions: Kidney stone disease; liver or gastrointestinal disorder or corticosteroid treatment **Established vitamin D group 1** • Number: 9 • Age: NS • Sex (M/F): NS • eGFR: 25.1 (9.8 SD) mL/min/1.73 m² **Established vitamin D group 2** • Number: 9 • Age: NS • Sex (M/F): NS • eGFR: 20.2 (11.9 SD) mL/min/1.73 m²
Interventions	**Established vitamin D group 1** • Oral calcitriol: 0.25-1 µg/d **Established vitamin D group 2** • Oral vitamin D: 4000 IU/d Cointervention/s: Calcium
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 (randomisation, allocation concealment, blinding, intention-to-treat analysis) , events (fractures) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 82 ○ Enrolled/randomised:18 ○ Analysed:18 ○ Percent follow-up: 100%

Risk of bias

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

Christiansen 1978 (*Continued*)

Blinding? All outcomes	Unclear	Not stated
ITT - was it performed?	No	ITT not performed

Coburn 2004

Methods	• Setting/Design: Multicentre double-blind placebo-controlled RCT • Time Frame: NS • Follow-up period: 6 months • Loss to follow-up: 0%
Participants	• Country: USA • Plasma Cr > 2.0 mg/dL (0.18 mmol/L); stable kidney function > 4 months • Exclusions: Agents known to influence bone metabolism except phosphate binding agents **Newer vitamin D group** • Number: 15 • Age: 48(range 26-71) years • Sex (M/F): 9/6 • eGFR: NS **Placebo group** • Number: 15 • Age: 47 (range 23-69) years • Sex (M/F): 11/4 • eGFR: NS
Interventions	**Newer vitamin D group** • Doxercalciferol: 1.0 µg increased at monthly intervals by 0.5 µg/d if PTH not reduced by 30% from baseline (serum calcium < 9.6 mg/dL (2.4 mmol/L), serum phosphorus level < 5.0 mg/dL (1.6 mmol/L), 24hour urinary calcium < 200mg, fasting urine Ca:Cr ratio < 0.25 mg/mg. Maximum dose 5 µg/d of doxercalciferol. • Subjects suspended treatment temporarily if they developed low iPTH levels (< 15.0 pg/mL (1.7 pmol/L)) or moderate hypercalcaemia (serum calcium > 10.5 mg/dL (2.62 mmol/L)). **Placebo group** • Placebo Cointervention/s: Calcium-based phosphate binders
Outcomes	Extractable and relevant to this review • One or more episodes of hypercalcaemia (defined by investigators as serum calcium > 10.7 mg/dL (> 2.67 mmol/L)) • Serum raised calcium by phosphorus product (> 65 mg^2/dL^2 (> 5.24 $mmol^2/L^2$)) • Reduction of serum PTH > 30% from baseline value • End of treatment serum calcium, phosphorus, and PTH • End of treatment CrCl
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s**

Coburn 2004 (*Continued*)

	○ NS • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, blinding), events (deaths, fractures) • **Completeness of follow-up** ○ Eligible/considered for inclusion: 55 ○ Enrolled/randomised: 55 ○ Analysed: 55 ○ Per cent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation code by statistician
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated
ITT - was it performed?	Yes	ITT performed

Coen 1994

Methods	• Setting/Design: Single university centre • Time Frame: NS • Follow-up period: 28-29 months • Loss to follow-up: NS
Participants	• Country: Italy • Slowly progressing CKD • Exclusions: Nephrotic syndrome; protein excretion rate > 2 g/d **Established vitamin D group** • Number: 30 • Age: 50.8 (15 SD) years • Sex (M/F): 17/13 • eGFR: 27.5 (11.4 SD) mL/min/1.73 m² **No treatment group** • Number: 30 • Age: 46.3 (16 SD) years • Sex (M/F): 22/8 • eGFR: 28.6 (11.0 SD) mL/min/1.73 m²
Interventions	**Established vitamin D group** • Calcitriol: 0.25 µg/d **No treatment group** • No treatment

Coen 1994 (*Continued*)

	Cointervention/s: Dietary modification protein 0.8 g/kg body weight, phosphate 12 mg/kg, caloric content 30-35 kcal/kg, calcium supplement 500 mg as organic salts
Outcomes	Extractable and relevant to this review • One or more episodes of hypercalcaemia (undefined) • End of treatment serum PTH, phosphorus, calcium concentrations
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding), outcomes (fracture, deaths). • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 60 ○ 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
ITT - was it performed?	Unclear	Not stated

Coyne 2006

Methods	• Setting/Design: Multicentre study (pooled data from three separate RCTs) • Time Frame: April 3, 2002 and March 3, 2004 • Follow-up period: 24 weeks • Loss to follow-up: 18%
Participants	• Country: USA • Males or females ≥18 years diagnosed with CKD for at least 2 months and who had not been active vitamin D therapy for at least 4 weeks. Prior to the pretreatment phase, the patients were required to have a serum intact PTH (iPTH) ≥120 pg/mL (13.7 pmol/L) and an eGFR of 15-60 mL/min/1.73 m² and were not expected to begin dialysis for at least 6 months. Prior to treatment, the patients were required to have an average of two consecutive iPTH values ≥150 pg/mL (16.5 pmol/L), taken at least 1 day apart (all values ≥120 pg/mL), two consecutive corrected serum calcium levels of between 8.0 to 10.0 mg/dL (2.0 to 2.5 mmol/L), and two

	consecutive serum phosphorus levels ≤ 5.2 mg/dL (1.68 mmol/L). • Exclusions: AKI; significant gastrointestinal or liver disease; malignancy; active granulomatous disease; pregnancy; spot urinary/calcium level > 0.2 or history of kidney stones; drugs including calcitonin, bisphosphonates, or glucocorticoids; aluminium-containing phosphate binders were not allowed within 12 weeks prior to study enrolment or > 3 weeks during course of study **Newer vitamin D group** • Number: 107 • Age: 63.6 (13.2 SD) years • Sex (M/F): 73/34 • GFR: 23.1 (8.1 SD) mL/min **Placebo group** • Number: 113 • Age: 61.8 (12.4 SD) years • Sex (M/F): 76/37 • GFR: 23.0 (7.8 SD) mL/min
Interventions	**Newer vitamin D group** • Oral paricalcitol ○ 2-4 µg thrice weekly (combined 2 RCTs, 72 participants) or ○ 1-2 µg daily (1 RCT, 35 participants) **Placebo group** • Placebo Cointervention/s: Phosphate binders
Outcomes	Extractable and relevant to this review • One or more episodes of hypercalcaemia (defined by investigators as at least 2 consecutive corrected serum calcium levels > 10.5 mg/dL (2.62 mmol)) • One or more episodes of hyperphosphataemia (at least 2 consecutive serum phosphorus values > 5.5 mg/dL (1.78 mmol/L)) • One or more episodes of raised calcium by phosphorus product (at least 2 consecutive Ca X P values > 55 mg^2/dL^2 • Reduction of PTH concentrations (2 consecutive decreases from baseline PTH of ≥ 30%)
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Efficacy end point: 2 consecutive decreases from baseline iPTH of ≥ 30%. • **Additional data requested and/or received from authors** ○ End of treatment PTH, serum calcium and phosphorus values. • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 220 ○ Analysed: 178 (81%) ○ Per cent follow-up: 81%

Risk of bias

Item	Authors' judgement	Description

Coyne 2006 (*Continued*)

Adequate sequence generation?	Yes	Computer randomisation with sealed envelopes
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated
ITT - was it performed?	Unclear	Not stated

Hamdy 1995

Methods	• Setting/Design: Multicentre university study • Time Frame: NS • Follow-up period: 2 years • Loss to follow-up: 22%
Participants	• Country: UK • CrCl 15-50 mL/min and no biochemical, clinical, or radiographical evidence of bone disease • Exclusions: Symptomatic bone disease; raised serum calcium concentration (undefined) or total alkaline phosphatase activity; disturbance in liver function (as judged by a 1.5 fold increase or more in liver aminotransferase activity) **Established vitamin D group** • Number: 89 • Age: 53 (15 SD) years • Sex (M/F): 54/35 • eGFR: NS **Placebo group** • Number: 87 • Age: 51 (16 SD) years • Sex (M/F): 53/34 • eGFR: NS
Interventions	**Established vitamin D group** • Oral alphacalcidol: 0.25 µg/d adjusted to between 0.25 µg alternate days to 1 µg daily to maintain serum calcium concentration at upper limit of normal **Placebo group** • Placebo Cointervention/s: Calcium-containing phosphate binders
Outcomes	Extractable and relevant to this review • All-cause mortality • Need for RRT • Improvement in bone histomorphometry • One or more episodes of hypercalcaemia (defined by investigators as serum calcium > 12 mg/dL (3.00 mmol/L)) • Withdrawal of treatment due to hypercalcaemia • Adverse events

Hamdy 1995 (*Continued*)

Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Primarily death, default or need to commence dialysis • **Additional data requested and/or received from authors** ○ Methods (randomisation methods, allocation concealment, blinding for data analysis and outcome assessors), outcomes (fractures), end of treatment serum concentrations (PTH, calcium, phosphorus) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 176 ○ Analysed: 138 ○ Percent follow-up: 78%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Hospital pharmacy
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Blinding of participants, investigators, outcomes assessors and data assessors.
ITT - was it performed?	Yes	ITT performed

Juttmann 1979

Methods	• Setting/Design: Single dialysis centre • Time Frame: NS • Follow-up period: 2 weeks • Loss to follow-up: NS
Participants	• Country: The Netherlands • Predialysis patients with histologically proven bone disease • Exclusions: NS **Established vitamin D group 1** • Number: 5 • Age: NS • Sex (M/F): NS • eGFR: NS **Established vitamin D group 2** • Number: 5 • Age: NS • Sex (M/F): NS • eGFR: NS

Juttmann 1979 (*Continued*)

Interventions	**Established vitamin D group 1** • Oral calcitriol: 0.5 µg/d **Established vitamin D group 2** • Oral alfacalcidol: 0.5 µg/d Cointervention/s: NS
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 (trial quality), outcomes (fracture), end of treatment serum values (calcium, phosphorus, calcium by phosphorus product) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 10 ○ 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	Not stated
ITT - was it performed?	Unclear	Not stated

Nordal 1988

Methods	• Setting/Design: Single centre • Time Frame: NS • Follow-up period: 8 months • Loss to follow-up: 0%
Participants	• Country: Norway • Plasma Cr > 2.0 mg/dL (0.17 mmol/L), stable kidney function > 4 months • Exclusions: Agents known to influence bone metabolism except phosphate binding agents **Established vitamin D group** • Number: 15 • Age: 48(range 26-71) years

	• Sex (M/F): 9/6 • eGFR: NS **Placebo group** • Number: 15 • Age: 47 (range 23-69) years • Sex (M/F): 11/4 • eGFR: NS
Interventions	**Established vitamin D group** • Oral calcitriol: 0.25-0.5 µg/d **Placebo group** • Placebo Cointervention/s: Aluminium-containing phosphate binders
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** ○ Randomisation and allocation concealment, blinding, fracture outcomes • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 30 ○ Analysed: 30 ○ Percent follow-up: 100%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Performed by hospital pharmacy central staff
Allocation concealment?	Yes	Adequate
Blinding? All outcomes	Yes	Blinding of participants, investigators, outcomes assessors and data assessors
ITT - was it performed?	No	ITT not performed

Panichi 1998

Methods	• Setting/Design: Single university centre, crossover design • Time Frame: NS • Follow-up period: 3 months • Loss to follow-up: NS
Participants	• Country: Italy • CKD with iPTH > 150 pg/mL (16.5 pmol/L) • Exclusions: Nephrotic proteinuria; diabetes; immunosuppressant and anticonvulsant therapy **Daily group** • Number: 5 • Age: 44.8 (SD 14.2) years • Sex (M/F): 3/2 • eGFR: 25.4 (11.5 SD) mL/min/1.73 m² **Intermittent group 1** • Number: 5 • Age: 43.2 (12.4 SD) years • Sex (M/F): 4/1 • eGFR: 15.2 (5.7 SD) mL/min/1.73 m² **Intermittent group 2** • Number: 5 • Age: 52.8 (11.5 SD) years • Sex (M/F): 2/3 • eGFR: 23.4 (7.3 SD) mL/min/1.73 m² **Overall** • Number: 16 • Age: 51 (16 SD) years
Interventions	**Daily group** • Oral calcitriol: 0.5 µg/d **Intermittent group 1** • Oral calcitriol: 2 µg thrice weekly **Intermittent group 2** • Oral calcitriol: 2 µg once weekly Cointervention/s: Calcium carbonate and 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 (Randomisation method, blinding, allocation concealment, analysis), outcomes (fracture), end of treatment PTH, calcium, phosphorus concentrations • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 16 ○ Analysed: NS

Panichi 1998 (*Continued*)

	○ 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	Not stated
ITT - was it performed?	Unclear	Not stated

Przedlacki 1995

Methods	• Setting/Design: Single renal outpatient clinic • Time Frame: NS • Follow-up period: 12 months • Loss to follow-up: 1/26
Participants	• Country: Finland • GFR ≤ 51.2 mL/min; age < 70 years • Exclusions: Pregnancy; hypercalcaemia (serum calcium > 10.4 mg/dL (2.6 mmol/L)); kidney stones; intestinal diseases, diabetes; treatment with steroids, vitamin D metabolites, anticoagulants and anticonvulsants **Established vitamin D group** • Number: 13 • Age: 49.3 (10.8 SD) years • Sex (M/F): 2/11 • eGFR: NS **Placebo group** • Number: 12 • Age: 50.3 (10.5 SD) years • Sex (M/F): 8/4 • eGFR: NS
Interventions	**Established vitamin D group** • Oral calcitriol: 0.25 µg/d **Placebo group** • Placebo Cointervention/s: Calcium acetate
Outcomes	Extractable and relevant to this review • All-cause mortality • Need for RRT • One or more episodes of hypercalcaemia (defined by investigators as serum calcium > 10.4 mg/dL (2.6 mmol/L))

Przedlacki 1995 (*Continued*)

	• One of more episodes of hyperphosphataemia (defined by investigators as serum phosphorus > 4.6 mg/dL (1.49 mmol/L)) • One of more episodes elevated calcium by phosphorus product • End of treatment PTH, phosphorus, calcium, alkaline phosphatase concentration • End of treatment CrCl • End of treatment bone mineral density (femoral neck and lumbar spine (g/cm²)
Notes	• **Exclusions post-randomisation but pre-intervention** ○ NS • **Stop or endpoint/s** ○ Death (1 patient placebo group) or commencement of dialysis (2 patients placebo, 1 patient calcitriol group) • **Additional data requested and/or received from authors** ○ Methods (randomisation method, allocation concealment, blinding), outcomes (fracture) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 26 ○ Analysed: 25 ○ Percent follow-up: 96%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Not stated
ITT - was it performed?	No	ITT not performed

Ritz 1995

Methods	• Setting/Design: Five nephrology outpatient clinics • Time Frame: NS • Follow-up period: 12 months • Loss to follow-up: 7/52
Participants	• Country: Germany • 1,84 iPTH levels above the normal range (i.e. 54.5 pg/mL (6.2 pmol/L)) on three separate occasions during the recruitment phase as measured in the recruiting centre; Cr 1.4- 6.5 mg/dL (123-572 µmol/L) • Exclusions: Nephrotic range proteinuria (i.e. > 3.5 mg/24 h); diabetes mellitus; immunosuppressive therapy; vitamin D deficiency (< 10 nmol 25(OH)D3); anticonvulsant therapy and nephrocalcinosis

	Established vitamin D group • Number: 24 • Age: NS • Sex (M/F): NS • eGFR: NS **Placebo group** • Number: 21 • Age: NS • Sex (M/F): NS • eGFR: NS
Interventions	**Established vitamin D group** • Oral calcitriol: 0.25 µg/d **Placebo group** • Placebo Cointervention/s: Calcium carbonate titrated to phosphate level
Outcomes	Extractable and relevant to this review • Need for RRT • One or more episodes of hypercalcaemia (defined by investigators as serum calcium > 10.8 mg/dL (2.7 mmol/L))
Notes	• **Exclusions post-randomisation but pre-intervention** ○ 14 • **Stop or endpoint/s** ○ Three or more episodes of hypercalcaemia (serum calcium > 10.8 mg/dL (2.7 mmol/L)) or hyperphosphataemia (serum phosphorus > 6.8 mg/dL (2.2 mmol/L)). Other end points included non compliance, death or commencement of RRT. • **Additional data requested and/or received from authors** ○ Methods (allocation concealment, randomisation method, blinding) outcomes (fractures), end of treatment serum levels (PTH, calcium, phosphorus, calcium by phosphorus product) • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 66 ○ Analysed: 52 ○ Percent follow-up: 79%

Risk of bias

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

Ritz 1995 (*Continued*)

ITT - was it performed?	Yes	ITT performed

Rix 2004

Methods	• Setting/Design: NS • Time Frame: NS • Follow-up period: 18 months • Loss to follow-up: 5/36
Participants	• Country: Denmark • CrCl 10-60 mL/min and plasma levels of ionised calcium and phosphate below 5.4 (1.35 mmol/L) and 6.2 mg/dL (2.0 mmol/L) respectively • Exclusions: Dialysis requiring, kidney transplanted patients; patients taking medication known to influence bone metabolism (i.e. vitamin D analogues, immunosuppressive agents, antiepileptics or hormone replacement therapy) **Established vitamin D group** • Number: 18 • Age: 52.5 years • Sex (M/F): 13/5 • eGFR: 49 (20 SD) mL/min/1.73 m² **Placebo group** • Number: 18 • Age: 52.5 • Sex (M/F): 6 female, 12 male • eGFR: 36 (13 SD) mL/min/1.73 m²
Interventions	**Established vitamin D group** • Oral 1-alpha-hydroxyvitamin D3: 0.25-0.75 µg/d **Placebo group** • Placebo Cointervention/s: Calcium-containing phosphate binders
Outcomes	Extractable and relevant to this review • One or more episodes of hypercalcaemia (defined by investigators as ionised calcium > 5.68 mg/dL (1.42 mmol/L)) • End of treatment serum calcium concentration • End of treatment CrCl (mL/min/1.73 m²)
Notes	• **Exclusions post-randomisation but pre-intervention** ○ Nil • **Stop or endpoint/s** ○ Death or requirement for RRT • **Additional data requested and/or received from authors** ○ Methods (randomisation method, trial quality data), outcomes (mortality and fracture) , end-of-treatment serum biochemistries • **Completeness of follow-up** ○ Eligible/considered for inclusion: NS ○ Enrolled/randomised: 36

Rix 2004 (*Continued*)

	○ Analysed: 31 ○ Percent follow-up: 86%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Coded randomisation
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Unclear	Blinding of participants and investigators. Blinding of outcome assessors or data assessors not stated
ITT - was it performed?	No	ITT not performed

Tougaard 1976

Methods	• Setting/Design: Single out patient centre • Time Frame: NS • Follow-up period: 3 months • Loss to follow-up: NS
Participants	• Country: Denmark • CKD; CrCl 5-25 mL/min; stable; not on dialysis; presence of bone disease disregarded • Exclusions: NS **Established vitamin D group** • Number: 12 • Age: NS • Sex (M/F): NS • eGFR: NS **Placebo group** • Number: 12 • Age: NS • Sex (M/F): NS • eGFR: NS
Interventions	**Established vitamin D group** • Oral 1-alphahydroxyvitamin D3: 1 µg/d **Placebo group** • Placebo Cointervention/s: Calcium lactogluconate
Outcomes	Extractable and relevant to this review • Nil

Tougaard 1976 (*Continued*)

Notes	• **Exclusions post-randomisation but pre-intervention** ○ None • **Stop or endpoint/s** ○ NS • **Additional data requested and/or received from authors** ○ Methods (randomisation, allocation concealment, blinding, ITT analysis), outcomes (mortality, fracture), end of treatment biochemical variables. • **Completeness of follow-up** ○ Eligible/considered for inclusion: 70 ○ Enrolled/randomised: 19 ○ Analysed: 16 ○ Percent follow-up: 84%

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	No	Blinding of participants and investigators but not outcome assessors or data assessors
ITT - was it performed?	Unclear	Not stated

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

AKI - acute kidney injury; CKD - chronic kidney disease; Cr - creatinine; CrCl - creatinine clearance; eGFR - estimated glomerular filtration rate; ITT - intention-to-treat; NS - not stated; RRT - renal replacement therapy

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

NCT00285467

Trial name or title	Comparison of cholecalciferol versus doxercalciferol in the treatment of secondary hyperparathyroidism in CKD stage three and four
Methods	
Participants	Subjects with CKD not on dialysis who have vitamin D deficiency (iPTH > 100 pg/mL (11 pmol/L) for stage 3 CKD or iPTH > 150 pg/mL for stage 4 CKD (16.5 pmol/L)
Interventions	Doxercalciferol versus cholecalciferol
Outcomes	Suppression of elevated PTH levels
Starting date	January 2006
Contact information	Sharon Moe, MD smoe@iupui.edu
Notes	

DATA AND ANALYSES

Comparison 1. Vitamin D versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	4	477	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.38, 5.15]
2 Commencement of dialysis	4	301	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.36, 1.62]
3 Fracture	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Parathyroidectomy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Improvement in bone histomorphometry	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 End of treatment osteoid volume (mm^3/cm^3)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 End of treatment osteoid thickness (µm)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8 Development of osteitis fibrosa	2	43	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.23, 1.29]
9 Development of osteomalacia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 End of treatment parathyroid hormone (pg/mL)	4	153	Mean Difference (IV, Random, 95% CI)	-49.34 [-85.70, -12.97]
11 Reduction of serum PTH > 30% from baseline value	2	264	Risk Ratio (M-H, Random, 95% CI)	7.87 [4.87, 12.73]
12 One or more episodes of hypercalcaemia	7	612	Risk Ratio (M-H, Random, 95% CI)	3.04 [1.17, 7.90]
13 One or more episodes of hyperphosphataemia	2	245	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.47, 5.30]
14 One or more episodes of elevated calcium x phosphorus product	3	300	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.57, 4.66]
15 End of treatment serum phosphorus (mg/dL)	3	140	Mean Difference (IV, Random, 95% CI)	0.37 [0.09, 0.66]
16 End of treatment serum calcium (mg/dL)	5	184	Mean Difference (IV, Random, 95% CI)	0.20 [0.17, 0.23]
17 End of treatment alkaline phosphatase (U/L)	2	38	Mean Difference (IV, Random, 95% CI)	-21.81 [-40.39, -3.22]
18 End of treatment CrCl (mL/min)	4	111	Mean Difference (IV, Random, 95% CI)	-1.68 [-6.92, 3.56]
19 End of treatment absolute BMD femoral neck (g/cm^2)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
20 End of treatment absolute BMD lumbar spine (g/cm^2)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
21 Worsening vascular calcification	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22 Development of vascular calcification	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23 Withdrawal of treatment due to hypercalcaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 2. Established vitamin D versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	202	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.14, 15.69]
2 Commencement of dialysis	3	246	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.34, 1.63]
3 Fracture	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Parathyroidectomy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Improvement in bone histomorphometry	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Development of osteitis fibrosa	2	43	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.23, 1.29]
7 Development of osteomalacia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 End of treatment osteoid volume (mm^3/cm^3)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 End of treatment osteoid thickness (µm)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10 End of treatment parathyroid hormone (pg/mL)	3	98	Mean Difference (IV, Random, 95% CI)	-54.98 [-124.37, 14.41]
11 One or more episodes of hypercalcaemia	5	337	Risk Ratio (M-H, Random, 95% CI)	3.36 [1.14, 9.93]
12 One or more episodes of hyperphosphataemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 One or more episodes of elevated calcium x phosphorus product	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14 Withdrawal of treatment due to hypercalcaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15 End of treatment serum phosphorus (mg/dL)	2	85	Mean Difference (IV, Random, 95% CI)	0.51 [-0.19, 1.20]
16 End of treatment serum calcium (mg/dL)	4	129	Mean Difference (IV, Random, 95% CI)	0.20 [0.17, 0.23]
17 End of treatment alkaline phosphatase (U/L)	2	38	Mean Difference (IV, Random, 95% CI)	-21.81 [-40.39, -3.22]
18 End of treatment CrCl (mL/min)	3	69	Mean Difference (IV, Random, 95% CI)	-1.95 [-9.45, 5.54]
19 End of treatment absolute BMD femoral neck (g/cm^2)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
20 End of treatment absolute BMD lumbar spine (g/cm^2)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
21 Worsening vascular calcification	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22 Development of vascular calcification	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 3. Newer vitamin D versus placebo/no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	2	275	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.16, 7.34]
2 Commencement of dialysis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Reduction of serum PTH > 30% from baseline value	2	264	Risk Ratio (M-H, Random, 95% CI)	7.87 [4.87, 12.73]
4 End of treatment parathyroid hormone (pg/mL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 End of treatment serum calcium (mg/dL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 End of treatment serum phosphorus (mg/dL)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 One or more episodes of hypercalcaemia	2	275	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.28, 16.23]
8 One or more episodes of hyperphosphataemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 One or more episodes of elevated calcium x phosphorus product	2	275	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.57, 4.66]
10 End of treatment CrCl (mL/min)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 4. Intermittent vitamin D versus daily vitamin D

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 One or more episodes of hypercalcaemia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

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
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- Petra Macaskill: Revision of review for intellectual content, final approval of manuscript to be submitted for publication
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- Giovanni FM Strippoli: Concept and design, data extraction, analysis and interpretation of data, writing the final manuscript, final approval of version to be published.

DECLARATIONS OF INTEREST

None declared.

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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 requiring dialysis).

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Humans