

Cochrane Nursing Care Field: Vitamin D compounds for people with chronic kidney disease requiring dialysis

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Review Question:

What is the best available evidence on the safety and efficacy of vitamin D compounds on clinical, biochemical, and bone outcomes in people with chronic kidney disease requiring dialysis?

Relevance for Clinical Practice:

Individuals with chronic kidney disease (CKD) develop changes in circulating blood levels of calcium and phosphorus. The kidney progressively loses the power to eliminate phosphorus from the blood and cannot activate enough vitamin D to maintain normal levels of calcium. The parathyroid gland perceives these changes and compensates to extend calcium by elevating and releasing more parathyroid hormone (PTH). These metabolic changes alter bone metabolism to release calcium which can result in altered bone production which results in bone deformation, bone pain, and increased risks of fracture.

Therapy for these mineral abnormalities in CKD include activated vitamin D replacement to suppress PTH release. While lowering PTH, earlier activated vitamin D preparations (calcitriol and alfacalcidol) elevated circulating calcium and phosphorus by their direct action on the vitamin D receptor. Newer agents have since been developed that similarly suppress PTH, however they may have smaller adverse effects on serum calcium and phosphorus levels. Avoidance of elevated calcium and phosphorus is considered vital as these minerals may lead to calcification in arteries and tissues. Increasing evidence suggests abnormal

calcium and phosphorus levels are associated with increased risks of death and cardiovascular disease. This issue is of importance to the nephrology nurses who are frequently involved in the care of patients with chronic kidney disease.

Characteristics of the Evidence:

The evidence included in this summary is from a Cochrane systematic review containing 60 randomised controlled trials (RCTs) involving 2773 participants. Adults and children with CKD requiring dialysis (CKD stage 5 requiring dialysis) were included. Recipients of kidney transplants and those not receiving dialysis were excluded and are covered in separate Cochrane systematic review. Fifty studies enrolled patients on haemodialysis. Two studies used both dialysis types (haemodialysis and peritoneal dialysis). For one study the dialysis modality could not be ascertained. Seven RCTs enrolled children.

The formulation, route and schedule of vitamin D administration varied and included: Vitamin D compound versus placebo (18 studies); Vitamin D compound versus another vitamin D compound (13 studies); and vitamin D compound versus Calcium (1 study). The differing routes of administration included intravenous versus oral vitamin D (12 studies); intraperitoneal versus oral vitamin D (3 studies); subcutaneous versus oral vitamin D (1 study); intermittent versus daily vitamin D (5 studies); and differing dosing schedules (7 studies).

Key Words

Vitamin D compounds, chronic kidney disease, dialysis, safety, efficacy, clinical outcomes, biochemical outcomes, bone outcomes.

While the majority of the studies were designed to examine the effect of vitamin D treatment on biochemical outcomes — serum PTH, serum calcium, serum phosphorus, and serum alkaline phosphatase concentrations — only a few studies reported important clinical outcomes including all-cause mortality, fracture, bone pain, muscle dysfunction, need for parathyroidectomy, changes in height, and bone mineral density. Paediatric outcomes regarding genu valgum, slipped upper femoral epiphyses were hardly ever reported.

The methodological quality of the included studies varied and was generally poor. The standard quality items assessed were allocation concealment, blinding (participants, investigators, outcome assessors and data analysts), intention-to-treat analysis (ITT) and completeness of follow-up. Included studies were commonly reported incompletely and of poor quality. Key design features in terms of allocation concealment, blinding, ITT, completeness of follow-up were incompletely reported for most studies. Meta-analysis was undertaken where possible (due to heterogeneity) otherwise results were presented narratively.

- Among 18 studies that compared vitamin D compounds with placebo or no treatment no significant difference was observed between

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the groups for the following clinical outcomes (in pooled analysis): all cause mortality (five studies - 233 patients); the occurrence of fracture (four studies - 181 patients); risk of developing bone pain (4 studies - 109 patients); need for parathyroidectomy (2 studies - 133 patients); subperiosteal erosions (three studies - 120 patients); and calcification (2 studies - 103 patients). However none were powered to understand the effect of treatment.

- Compared with placebo, vitamin D compounds lowered serum PTH at the expense of increasing serum phosphorus. The pooled analysis observed:
 - a significant decrease in end of treatment serum PTH (6 studies, 212 patients, Mean difference [MD] -196.05 pg/mL, 95% Confidence Intervals [CI] -298.43 to -93.66) (MD -22.3 pmol/L, 95% CI -34.0 to -10.7)
 - PTH reduction \geq 30% from baseline (7 studies, 361 patients, Relative Risk [RR] 5.90, 95% CI 3.17 to 10.96)
 - a significant increase in the end of treatment serum phosphorus (2 studies, 105 patients, MD 0.70 mg/dL, 95% CI 0.08 to 1.33, MD 0.23 mmol/L, 95% CI 0.03 to 0.43) and one or more episodes of hyperphosphataemia (2 studies, 59 patients, RR 1.57, 95% CI 0.97 to 2.54) and
 - lowering of serum alkaline phosphatase (ALP) (3 studies, 135 patients, MD -27.35 U/L, 95% CI -50.69 to -4.01).
- However, trends toward increased hypercalcaemia and serum calcium did not reach statistical significance (2 studies, 105 patients); and episodes of hypercalcaemia (5 studies, 182 patients, RR 3.80, 95% CI 0.90 to 16.12).
- Reported subgroup analyses data illustrate that
 - although serum PTH was insignificantly lowered with established vitamin D compounds compared with placebo (4 studies, 104 patients), newer vitamin D compounds — paricalcitol, maxacalcitol, doxercalciferol— significantly lowered PTH compared with placebo (2 studies, 212 patients, MD -183.88 pg/mL, 95% CI -217.88 to -149.89) (MD -21.0 pmol/L, 95% CI -24.8 to -17.1) } with narrow confidence interval.
 - however, therapy with newer vitamin D compounds were associated with increased risks of hypercalcaemia (2 studies, 108 patients, RR 11.97, 95% CI 1.48 to 96.58) although confidence intervals were wide indicating imprecision around the point estimate.
 - inadequate data were available for serum phosphorus.
 - Biochemical outcomes data on serum PTH, serum phosphorus and serum calcium reported in 6 studies, 14 studies, 9 studies respectively were not in a format extractable for meta-analysis, therefore, presented narratively. The results varied between the studies and no conclusive evidence generated.
 - The outcome data from Vitamin D compound versus vitamin D compound (13 studies) {except mortality data}; Vitamin D compound versus Calcium (1 study) intraperitoneal versus oral vitamin D (3 studies); subcutaneous versus oral vitamin D (1 study); and differing dosing schedules (7 studies) were not subject to meta-analysis, therefore the results are presented in narrative summary. The evidence; however; is inconclusive.
 - Among 12 studies that compared Intravenous versus oral vitamin D, no difference in mortality was observed between newer versus established vitamin D (2 studies, 94 patients, RR 2.00, 95% CI 0.19 to 21.21). Other clinical outcomes were reported incompletely.
- Intravenous vitamin D may lower PTH compared with oral treatment D (8 studies, 171 patients, MD -76.20 pg/mL, 95% CI -150.92 to -1.48) (MD 8.7 pmol/L, 95% CI -17.2 to -0.17)}, and be associated with lower serum phosphorus (5 studies, 112 patients, MD -0.30 mg/dL, 95% CI -0.58 to -0.03) (MD -0.09 mmol/L, 95% CI -0.19 to -0.01).
- However no difference between the groups for serum calcium levels (6 studies, 146 patients); and alkaline phosphatase (4 studies, 116 patients).
- Serum PTH, serum phosphorus and serum calcium reported in 4 studies, 5 studies, 4 studies respectively were not in a format extractable for meta-analysis, therefore, presented narratively. The results varied between the studies and no conclusive evidence observed.
- Among 5 studies that compared intermittent versus daily vitamin D:
 - No data were available for clinical outcomes.
 - All five studies reported effects of treatment on serum PTH that were not in a format extractable for meta-analysis. Although no difference was observed between groups, the evidence is inconclusive.
 - No difference was observed between the groups with regard to risk of hyperphosphataemia (3 studies, 97 patients, RR 1.74, 95% CI 0.44 to 6.79); hypercalcaemia (4 studies, 118 patients, RR 1.15, 95% CI 0.36 to 3.69).

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- No data were available for serum alkaline phosphates.

Implications for Clinical Practice:

- The evidence for the effect of vitamin D compounds on mortality, stature, fracture or need for parathyroidectomy for patients requiring dialysis is inconclusive. Studies were not designed to evaluate these outcomes..
- The evidence for suppression of serum PTH with newer vitamin D compounds is persuasive but inconclusive.

- Newer vitamin D compounds cannot be recommended as superior to established treatments because of risks of increasing serum phosphorus, and calcium
- No recommendation regarding the route or schedule of administration can be made due to incomplete reporting and limitations of available study data.

Implications for Research:

- Adequately powered placebo-controlled RCT studies evaluating the effect of vitamin D compounds on

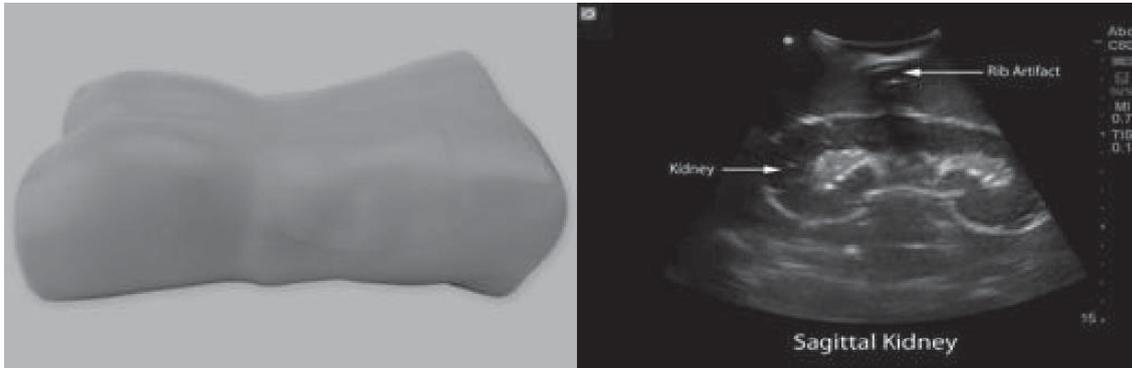
clinical outcomes including survival and cardiovascular disease are still required

- Because of limited information in paediatric recipients studies in children need to be undertaken to develop the robust and valid evidence for paediatric population.

Reference:

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

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