Evaluation of responses to vitamin D3 (cholecalciferol) in patients on dialysis: a systematic review and meta-analysis

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ABSTRACT

Vitamin D plays a key role in mineral metabolism and its deficiency is often noted in patients on dialysis for end-stage renal disease (ESRD). We evaluated the efficacy and responses to vitamin D3 (cholecalciferol) in patients undergoing dialysis for ESRD. Randomized controlled trials or prospective studies comparing vitamin D3 supplementation to placebo in patients with ESRD on dialysis were searched from medical databases using the terms, 'Calcitriol/Cholecalciferol, vitamin D, chronic kidney disease, hemodialysis, serum calcium, parathyroid hormones (PTH), phosphorus, 25(OH)D, and 1,25 $(OH)_2D$'. The outcomes analyzed were serum calcium, PTH, phosphorus, 25(OH)D, and 1,25(OH) $_2$D levels. Of the 259 records identified, 9 studies with a total of 368 patients were chosen for the current meta-analysis. The number of patients, age, and gender distribution among the groups were comparable. Results reveal a greater increase in both 25(OH)D (Pooled difference in means=0.434, 95% CI 0.174 to 0.694, p=0.001) and 1,25(OH) $_2$D (Pooled difference in means=0.978, 95% CI 0.615 to 1.34, p<0.001) in the treatment arm, as compared to the placebo. There was no difference in the serum calcium or PTH among the two groups. However, patients in the treatment arm had a significant increase in phosphorus levels (Pooled difference in means=0.434, 95% CI 0.174 to 0.694, p=0.001). Vitamin D supplementation facilitated the maintenance of increased levels of 25(OH) D and 1,25(OH) $_2$D in patients undergoing dialysis for ESRD. This increase in vitamin D was not associated with hypercalcemia or significant changes in PTH levels.

Significance of this study

What is already known about this subject?

- Vitamin D deficiency in patients on hemodialysis is associated with an increased early mortality rate.
- The major form of circulating vitamin D is 25, hydroxyvitamin D, (25(OH)D or calcidiol), and it reflects the vitamin D storage.
- Nutritional deficiency of cholecalciferol or vitamin D3 can lead to secondary hyperparathyroidism.

What are the new findings?

- Vitamin D3 supplementation can increase levels of 25(OH) D and 1,25(OH) 2D in patients undergoing dialysis for end-stage renal disease.
- Vitamin D3 supplementation leads to higher levels of serum phosphate compared to placebo.
- There is no significant change in either serum calcium or parathyroid hormones (PTH) levels with vitamin D3 supplementation.

How might these results change the focus of research or clinical practice?

- In patients with ESRD undergoing dialysis, giving oral cholecalciferol will not disturb serum calcium or PTH, but serum phosphate may need monitoring.

INTRODUCTION

Vitamin D deficiency is not uncommon in the general population, but it is very frequently seen in patients with end-stage renal disease (ESRD), where the prevalence is reported to be over 80%.[1] Low vitamin D levels are correlated with hyperparathyroidism, low calcium and calcitriol serum levels, female gender, obesity and insufficient sunlight exposure.[2] Reports indicate that vitamin D deficiency in patients on incident hemodialysis is associated with an increased early mortality rate,[3] and vitamin D supplementation significantly improves cardiac dysfunction and survival in patients undergoing dialysis.[4]

Cholecalciferol or vitamin D3 is synthesized in the body from 7-dehydrocholesterol, while ergocalciferol or vitamin D2 is obtained primarily though diet and dietary supplements. Both vitamin D3 and D2 are converted to its active forms, 25, hydroxyvitamin D (calcidiol) and 1,25, dihydroxyvitamin D (calcitriol) through hydroxylation. The major form of circulating vitamin D is 25(OH)D, the serum levels of which reflect the status of vitamin D storage.[2 5] The Endocrine Society Clinical Practice Guidelines define vitamin D deficiency

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as serum 25(OH)D concentration of <20 ng/mL.[6] 1,25, dihydroxyvitamin D, (1,25, $(OH)_2D$) is the more potent form of vitamin D, which exerts a number of biological effects in a paracrine or autocrine manner, including calcium/phosphate homeostasis, cellular differentiation and cardioprotection.[5 7 8] The enzyme responsible for the conversion of 25(OH)D to 1,25$(OH)_2D$ was identified in the kidneys and as the kidney function deteriorates, the production of 1,25$(OH)_2D$ decreases.[9] Nutritional deficiency of vitamin D3 can lead to secondary hyperparathyroidism, a hallmark of early and advanced ESRD, the pathogenesis of which are attributed to the deficiency in calcitriol, hypocalcemia and hyperphosphatemia.[10] Seibert *et al*[11] have shown that cholecalciferol supplementation can normalize the levels of 25(OH)D levels without hyperphosphatemia or hypercalcemia.[12] Further, replenishing the vitamin D3 can also lead to decreased iPTH levels and reduced bone resorption.[13]

Oral cholecalciferol supplementation is reported to be an easy and cost-effective therapy to reduce vitamin D deficiency, and provides some control of mineral metabolism in patients undergoing hemodialysis.[4] While meta-analyses of prospective, placebo controlled trials on vitamin D supplementation and reduced mortality risk in the general population are available,[14 15] analyses of the data on the safety and tolerability of vitamin D3 in randomized controlled trials (RCT) in patients undergoing dialysis for ESRD are lacking. Moreover, since the kidney plays a major role in vitamin D activation, the efficacy of nutritional vitamin D3 supplementation has been questioned in patients with ESRD.[16 17] Therefore, we undertook the present study to review the responses to administration of vitamin D3 (cholecalciferol) in patients with ESRD receiving either peritoneal dialysis or hemodialysis.

MATERIALS AND METHODS

Literature search and selection criteria

We performed an updated literature search of the Medline, Cochrane, EMBASE, and Google Scholar databases until September 22, 2015 using the following key words: 'Calcitriol/Cholecalciferol, vitamin D, chronic kidney disease (CKD), hemodialysis, serum calcium, PTH or parathyroid hormones, phosphorus, 25(OH)D, and 1,25 $(OH)_2D$'. In addition, the reference lists of relevant studies were manually searched to identify studies meeting the inclusion criteria. A study was considered eligible for inclusion if it was a randomized controlled trial or a prospective study including patients with end-stage CKD on dialysis (either hemodialysis or peritoneal dialysis) for at least 3 months, and reported at least one quantitative primary or secondary outcome. Patients in the treatment group should have received oral cholecalciferol, while the control group may receive either placebo or no treatment.

We excluded letters, comments, editorials, case reports, proceedings, personal communications, and studies with no reported quantitative outcome or that are non-human studies.

Study selection and data extraction

Studies were identified by the search strategy by two independent reviewers. Where there was uncertainty regarding eligibility, a third reviewer was consulted. The following data were extracted from studies that met the inclusion criteria, the name of the first author, year of publication, study design, number of participants in each treatment group, participants' age and gender, types of intervention/treatment received, and outcomes reported. A total of nine studies were included in the current meta-analysis (the details of study selection are represented in figure 1A).

Outcome measures

The outcomes analyzed included levels of serum calcium, PTH, phosphorus, 25(OH)D, and 1,25(OH)2D.

Quality assessment

We utilized the Cochrane Risk of Bias tool[18] to assess the quality of 9 included RCT. Results are shown in figure 1B, C.

Statistical analysis

The primary outcomes were serum calcium, PTH, and phosphorus levels. The secondary outcomes were levels of 25(OH)D and 1,25(OH)2D. Standardized difference in the means was used as the index of effect size. Heterogeneity among the studies was assessed by the Cochran Q and the I-square statistic. The Q statistic was defined as the weighted sum of the squared deviations of the estimates of all studies. $p<0.10$ was considered statistically significant for heterogeneity. For the I-square statistic, which indicated the percentage of the observed between-study variability due to heterogeneity, the suggested ranges are as follows: no heterogeneity ($I^2=0–25\%$), moderate heterogeneity ($I^2=25–50\%$), large heterogeneity ($I^2=50–75\%$) and extreme heterogeneity ($I^2=75–100\%$). The random-effect model (DerSimonian–Laird method) was performed to generate pooled estimates across studies for each outcome. A two-sided p value<0.05 was considered statistically significant. The leave-one-out approach was used to assess sensitivity of meta-analysis. All statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, V.2.0 (Biostat, Englewood, New Jersey, USA).

RESULTS

Literature search

Two hundred and fifty nine studies were identified through the database and reference list searches, and after removing duplicate records, 166 studies were screened for eligibility. Of those, 118 articles were excluded for lack of relevancy. After assessing 48 articles for full text reviewing, we excluded 39 studies for reasons like no outcome of interest (23), one-arm studies (10), comparison design did not meet inclusion criteria (5), and patients not on dialysis (1). Nine studies were chosen for the meta-analysis. The study selection flow chart is shown in figure 1A.

Study characteristics

A total of nine RCT were included in the meta-analysis. The number of patients ranged from 19 to 60, with a mean or median age of 46–75 years. All studies recruited a majority of males, ranging from 37.5% to 76.9% (table 1). Detailed study design and selection criteria are listed in tables 1 and 2. The mean values of all primary and secondary outcomes pretreatment and post-treatment are summarized in table 3. The follow-up duration ranged from

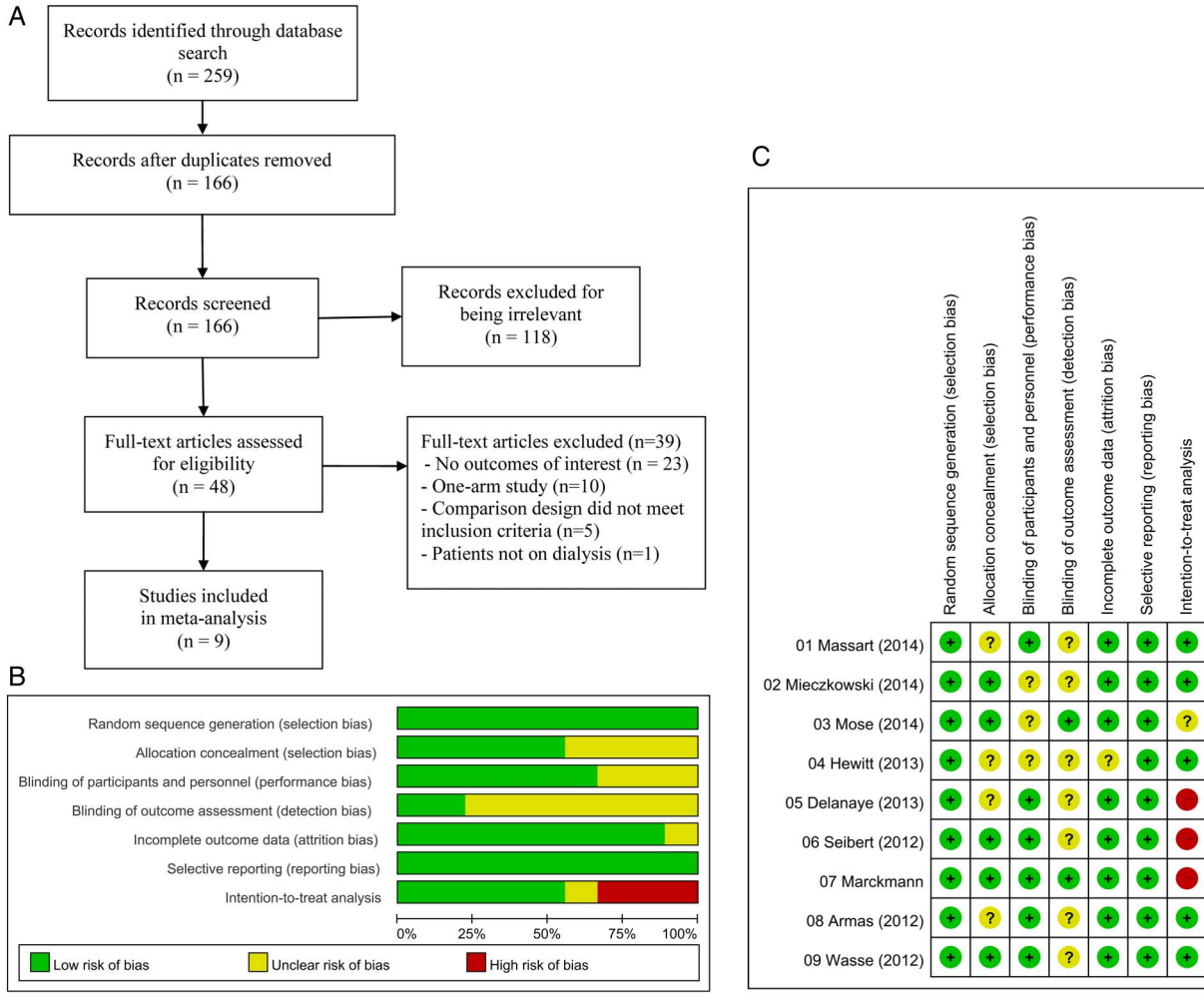


Figure 1 (A) Flow chart for study selection, and quality assessment of overall (B) and individual studies (C) included in the meta-analysis, using the Cochrane Risk of Bias Tool.

6 weeks to 1 year. Patients in the treatment group had significantly higher levels of 25(OH)D and 1,25(OH)2D after treatment with cholecalciferol.

Measures of primary outcomes

The six studies included in the evaluation of the treatment effect on serum calcium showed no heterogeneity among them (Q=2.1, p=0.830, I^2=0%). There was no difference between the treatment and placebo groups (Pooled standardized difference in means=0.025, 95% CI=−0.233 to 0.282, p=0.851; figure 2A). For the PTH level, there was moderate heterogeneity across the six included studies (Q=7.6, p=0.179, I^2=34.3%). The pooled results showed that the increase in the PTH level in the treatment group did not reach statistical significance, as compared to the placebo (Pooled standardized difference in means=0.021, 95% CI=−0.301 to 0.343, p=0.898; figure 2B). Patients treated with cholecalciferol had a significantly greater increase in the phosphorus level than those in the placebo group (Pooled standardized difference in means=0.299, 95% CI=0.009 to 0.589, p=0.044). No heterogeneity was found among the studies for phosphorus levels (Q=6.2, p=0.291, I^2=18.9%; figure 2C).

Measures of secondary outcomes

Heterogeneity was observed among the eight studies for 25(OH)D levels (Q=29.6, p<0.001, I^2=76.4%), and among the seven studies for 1,25(OH)2D levels (Q=12.0, p=0.063, I^2=49.8%). A significantly higher increase in 25(OH)D (Pooled standardized difference in means=2.903, 95% CI=2.265 to 3.542, p<0.001) and 1,25(OH)2D levels were observed, as compared to the placebo group (Pooled standardized difference in means=0.978, 95% CI=0.615 to 1.340, p<0.001; figure 3A, B).

Sensitivity analysis

The leave-one-out sensitivity analyses for primary outcomes are shown in figure 3. Although the direction of association became negative for serum calcium when Marckmann *et al*[21] was removed, the point estimate was close to 0 and no significant results were found (figure 4A). For the PTH level, the pooled standardized differences in means with Mose *et al*, Seibert *et al*, and Marckmann *et al* removed one at a time were quite opposite to the overall pooled results with all six RCTs included, but the point estimates were close to 0 and the p values remained statistically insignificant (figure 4B). In addition, Seibert *et al*

Table 1 Summary of basic characteristics of selected studies for meta-analysis

Study name	Vitamin D analogs	Number of patients	Administration of Vitamin D analogs and placebos	Patients' status	Measurement of PTH	Measurement of 1,25(OH)2D or 25(OH)D	Mean age (year)	Male (%)
Massart *et al*[19]	Cholecalciferol Placebo	26 29	Cholecalciferol, 25,000 IU, per week orally vs placebo for 13 weeks, then 26 weeks of individualized cholecalciferol prescription based on NKF-KDOQI guidelines.	Adults on maintenance HD for 9–80 months with 25(OH)D levels 30 ng/mL.	Chemiluminescence immune-assays (Liaison, DiaSorin)	Chemiluminescence immunoassays (Liaison,DiaSorin)	62 66	69.0 55.0
Mieczkowski *et al*[8]	Cholecalciferol Control	8 11	Cholecalciferol was given 2000 IU orally, 3 times a week, during the hemodialysis. The Control group did not receive vitamin D.	Adult patients with serum 25(OH)D20 gnome, HD treatment duration of at least 3 months.	highly sensitive ECLIA (Electrochemiluminescence Immunoassay)	Manual assay system cat. no. AC-62F1 (Immunodiagnostic Systems, Frankfurt, Germany)	63* 46*	37.5 63.6
Mose *et al*[20]	Cholecalciferol Placebo	25 25	Subjects received 3000 IU(75 μg) cholecalciferol daily or placebo for 6 months	Adults with dialysis for more than 3 months, with no hypercalcemia or malignancy.	NR†	Chemiluminescence immunoassays (Liaison,DiaSorin, Saluggia, Italy)	68 67	680 60.0
Hewitt *et al*[12]	Cholecalciferol Placebo	30 30	Patients with were randomized to receive 50,000 IU oral cholecalciferol or placebo, once weekly for 8 weeks and then monthly for 4 months.	Patients with 25(OH)D 24 ng/mL, were on thrice-weekly HD for 3 months, without hypercalcemia.	Immulite 2000 system	RIA (DiaSorin Inc)	60* 67*	53.0 43.0
Delanaye *et al*[17]	Cholecalciferol Placebo	16 14	Patients were randomized to receive placebo or cholecalciferol (25,000 IU) therapy every 2 weeks.	On HD for at least 12 months, serum 25 (OH)D 30 ng/mL, P 65 mg/L, and Ca 2.57 mmol/L. without hypercalcemia	Liaison DiaSorin,	Liaison DiaSorin	75 73	75.0 64.0
Seibert *et al*[11]	Cholecalciferol Placebo	15 18	Patients were randomized to receive capsules, both red and looking alike, contained either mannitol/aerosil (placebo) or cholecalciferol 20,000 IU plus mannitol/aerosil (verum). Dosages depend on vitamin D levels.	Adults who had 25(OH)D depletion or insufficiency (serum 25(OH)D 80 nmol/l), >3 months on dialysis, without hypercalcemia or hyperphosphatemia within 4 weeks.	1–84-intact, ECLIA	$1,25(OH)_2D$ (Radio-Immuno-Assay, BioSource Europe), 25(OH) D (Chemiluminescence Immunoassay, DiaSorin)	66.9 67.4	60.0 50.0
Marckmann *et al*[21]	Cholecaciferol Placebo	13 14	The treated group received one capsule containing 40,000 IU of vitaminD3 weekly for 8 weeks. The placebo group received lactose capsules that looked identical.	Adults on HD for median 32 months (range 4–158 months) with plasma 25-OHD50 nmol/L without hypercalcemia or hyperphosphatemia.	NR	NR	N/A† N/A†	73.0 76.9
Armas *et al*[22]	Cholecalciferol Placebo	20 22	Immediately after each dialysis session, subjects received oral cholecalciferol or placebo once per week for 15 weeks. Placebo was lactose encapsulated in an opaque capsule.	Adults on HD for more than 3 months. Vitamin D status was not a criterion for selection.	RIA using DiaSorin N-tact PTH SP IRMA kit	RIA kit (Nichols Institute, San Clemente, California, USA)	57.6* 54.3*	70.0 73.0
Wasse *et al*[23]	Cholecalciferol Placebo	25 27	Vitamin D3 and placebo were identical in shape and color. The cholecalciferol group received 200,000 IU (4 pills of 50,000 IU vitamin D3) once weekly for 3 weeks.	Adults on HD (means of 259 days for study group and 839 days for placebo group) with majority (94%) having 25 (OH)D 30 ng/mL, and without hypercalcemia within 4 weeks.	NA†	$1,25(OH)_2D$ (solid-phase extraction and RIA by ARUP Laboratory), 25 (OH) D (Chemiluminescence Immunoassay, DiaSorin)	49 52	60.0 63.0

*Presented by median.
†NR, information not reported.
Ca, calcium; ECLIA, electrochemiluminescence immunoassay; HD, hemodialysis; iPTH, intact parathyroid hormones; IU, international unit; NA, not applicable; NKF-KDOQI, National Kidney Foundation–Kidney Disease Outcomes Quality Initiative); P, phosphorus; RCT, random controlled trials; RIA, radioimmunoassay.

Table 2 Details of subject selection criteria of included studies

Study name	Subject selection criteria	Active vitamin D use	Phosphate binder use	Cinacalcet (or other calcimimetic agent) use
Massart *et al*[19]	No hypersensitivity to study medications, pregnancy or lactation period, women without effective contraception, and plasma calcium level 10.2 mg/dL, prior para-thyroidectomy, no granulomatous disorder, no active malignancy, and/or estimated life expectancy of at least 1 year.	No paricalcitol, alfacalcidol, cholecalciferol and/or calcitriol dosage adjustment 1 month prior to enrollment.	Yes	Yes
Mieczkowski *et al*[8]	Total serum calcium concentrations of 2.55 mmol/L, serum phosphate of 2.08 mmol/L, not taking any vitamin D supplement, calcitriol, its analogs, or calcimimetic within the past 6 months, and no serious overall condition or cachexia.	No use within 6 months prior to enrollment.	NR	No use within 6 months prior to enrollment
Mose *et al*[20]	No malignant disease, no hypercalcemia (albumin corrected serum calcium >2.60 mmol/L), no intolerance toward cholecalciferol tablets.	Supplementation of more than 10 μg of ergo or cholecalciferol daily was paused 3 months prior to baseline measurement.	Yes, fewer than half of the subjects had the dose changed during the study	23/25 did not change dose, 1 increased and 1 decreased doses during the study
Hewitt *et al*[12]	No parathyroid surgery or treatment with cinacalcet in the preceding 3 months, no hypercalcemia defined as albumin corrected serum calcium 10.4 mg/dL (2.60 mmol/L), no bisphosphonate treatment at any time, and no planned surgery except for dialysis access.	Used but no dose adjustment for 4 weeks prior to study	Used but dosage unchanged for 4 weeks prior to study	No
Delanaye *et al*[17]	Subjects without hepatic failure, sarcoidosis, digestive malabsorption or hypercalcaemia, with intact PTH levels >800 pg/mL or PTH >400 pg/mL with a duplicate value over the last 3 months were excluded	No ergo or cholecalciferol used within the past year.	Yes, and no dosage change during the study was reported	No use within l year
Seibert *et al*[11]	Without pregnancy or lactation, known malignancy, liver disease, defined as 2-fold upper limit of ASAT, or ALAT levels, PTH 50 pg/mL, no current infections, chronic viral infection, not taking immunosuppressive medication, and no hematologic disorders other than renal anemia, no anaphylactic reaction against the study medication, no renal calculus, no pseudohypopara-thyroidism, no sarcoidosis, and no intake of cardiac glycosides	No pre-existing cholecalciferol supplementation. For other pre-existing vitamin D: no dose adjustment in all except one pt increased slightly in 11th week	Adjusted based on K/DOQI 2003 recommendations	Pre-existing use in 1/15 in study and 3/18 in placebo group; whether dose changed during study is not reported
Marckmann *et al*[21]	No hypercalcemia or severe hyperphosphatemia (P-phosphate >2.2 mmol/L at two consecutive measurements >1 week apart), no sarcoidosis, malignant disease, psychotic disorder, alcohol or drug abuse, pregnancy, breastfeeding, or allergy toward soy protein, and no estrogen use or not on safe contraception for fertile women.	Supplementary of a total of >10,000 IU ergo or cholecalciferol within the past 3 months was excluded	Yes, and almost all patients (except one who stopped using sevelamer) had no dosage changed during study	Not reported for HD patients, but yes for the overall group with dosage unchanged during study.
Armas *et al*[22]	Exclude those who were not ambulatory, were unable to complete the questionnaire with a research nurse, or had unusual difficulty with venous access. PD patients.	NR	NR	NR
Wasse (2012)[23]	Those who had a corrected serum calcium >10.5 mg/dL within 4 weeks of study screening were excluded.	Excluded if taking >2000 IU vitamin D2 (ergocalciferol) or D3 (cholecalciferol) per day	NR	NR

HD, hemodialysis; NKF-KDOQI, National Kidney Foundation–Kidney Disease Outcomes Quality Initiative); NR, not reported; PD, peritoneal dialysis; PTH, parathyroid hormone.

Table 3 Summary of primary and secondary outcomes for selected studies for meta-analysis

Study name*	Vitamin D analogs	Number of patients	Last visit	Serum calcium (mg/dL)			PTH (pg/mL)			Phosphorus level (mg/dL)			25(OH)D level (ng/mL)			1,25(OH)2D level (pg/mL)		
				Pre	Post	Change	Pre	Post	Change	Pre	Post	Change	Pre	Post	Change	Pre	Post	Change
Massart *et al*[19]	Cholecalciferol	26	13 weeks										17.1 (6.4)	35.2 (12.1)		12.3 (6.0)	21.2 (8.3)	
	Placebo	29											18.4 (7.9)	16.4 (7.8)		13.7 (6.8)	12.0 (3.8)	
Mieczkowski *et al*[8]	Cholecalciferol	8	6 months										12.3 (3.7)	46.6 (9.5)		8.7 (4.7)	14.0 (3.4)	
	Control	11											13.9 (2.9)	21.0 (8.4)		5.0 (1.9)	10.1 (3.5)	
Mose *et al*[20]	Cholecalciferol	25	6 months	4.84 (0.44)	4.80 (0.36)		127.4 (168.4)	164.15 (185.4)		4.9 (1.2)	5.4 (1.5)		11.22 (8.41)	33.65 (18.03)				
	Placebo	25		4.80 (0.32)	4.80 (0.28)		169.8 (174.1)	121.7 (176.9)		5.1 (1.1)	4.9 (1.2)		11.22 (14.72)	12.02 (8.41)				
Hewitt *et al*[12]	Cholecalciferol	30	6 months										18.0 (5.0)	35.0 (9.0)		18.0 (5.0)	18.0 (8.0)	
	Placebo	30											16.0 (5.0)	16.0 (7.0)		18.0 (10.0)	12.0 (5.0)	
Delanaye *et al*[17]	Cholecalciferol	16	1 year			0.08 (0.84)			−75.3 (204.8)			0.0 (1.3)						
	Control	14				−0.04 (0.56)			58.3 (158.3)			−0.3 (1.0)						
Seibert *et al*[11]	Cholecalciferol	15	12 weeks	9.6 (0.8)	9.6 (0.4)		192.3 (97.8)	177.1 (117.0)		5.1 (1.1)	4.5 (1.1)		11.8 (4.5)	35.2 (8.9)		12.8 (4.1)	19.8 (9.2)	
	Placebo	18		9.2 (0.4)	9.2 (0.8)		200.4 (110.0)	169.4 (121.7)		4.7 (1.1)	4.6 (1.0)		13.5 (6.7)	9.9 (3.2)		14.2 (9.2)	16.1 (9.0)	
Marckmann *et al*[21]	Cholecalciferol	13	8 weeks			0.16 (0.96)			27.5 (199.1)			0.02 (1.07)			46.8 (21.2)			3.7 (6.6)
	Placebo	14				−0.2 (0.44)			−19.1 (64.1)			−0.68 (1.27)			−5.1 (4.5)			−0.4 (2.9)
Armas *et al*[22]	Cholecalciferol	20	15 weeks			0.1 (0.7)			−25.7 (103.3)			0.1 (2.0)			23.6 (8.0)			6.1 (6.9)
	Placebo	22				0.2 (0.6)			−8.3 (90.2)			−0.6 (1.3)			0.5 (3.5)			−0.2 (2.5)
Wasse *et al*[23]	Cholecalciferol	25	6 weeks	8.8 (0.8)	9.0 (0.8)		722.2 (696.4)	674.4 (913.3)		5.0 (1.4)	5.5 (1.6)		14.3 (5.7)	52.4 (18)		14.7 (6.3)	29.3 (17.1)	
	Placebo	27		9.0 (0.6)	9.2 (0.8)		623.9 (925.5)	600.7 (927.1)		4.8 (1.2)	5.9 (1.8)		19.0 (6.5)	18.4 (7.4)		20.9 (9.9)	17.7 (8.5)	

*All data were transformed to the same unit of measurement and presented by mean and SD.
PTH, parathyroid hormone.

had mild to moderate influences on the pooled results for phosphorus level, as it yielded a larger point estimate and statistically significant results when removed (figure 4C).

Publication bias

Publication bias analysis was not performed as more than 10 studies were needed to detect a funnel plot asymmetry.[24]

DISCUSSION

Deficiency of vitamin D has been associated with an increased risk of cardiovascular mortality and decreased survival in patients with CKD.[23 25 26] Therapeutic vitamin D supplementation is often associated with vitamin D toxicity, characterized by hypercalcemia, hyperphosphatemia, and over suppression of PTH, which might in turn increase the risk of cardiovascular diseases.[23 27 28] We evaluated the efficacy and tolerability of vitamin D3 in patients with ESRD undergoing dialysis.

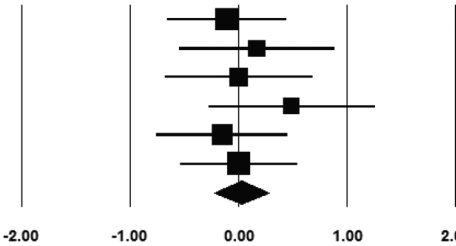
The current meta-analysis of 9 studies favors vitamin D3 supplementation. The treatment group showed a greater increase in 25(OH)D and 1,25(OH) $_2$D, as compared to the placebo group ($p<0.001$; figure 3A, B), without causing an increase in the serum calcium ($p=0.851$; figure 2A) or parathyroid hormone levels ($p=0.896$; figure 2B). In addition, patients treated with cholecalciferol had a significantly greater increase in phosphorus level than those in the placebo group ($p=0.001$; figure 2C). The sensitivity analysis indicates that the direction and magnitude of effect size did not change considerably for serum calcium and phosphorus levels. However, Delanaye *et al*[17] and Armas *et al*[22] might have influenced the overall results for PTH. The higher phosphate levels observed in our analysis could probably be due to elevated serum phosphate baseline levels, in addition to dietary factors. Nevertheless, the overall results show increases in 25(OH)D 1,25(OH)$_2$D levels in patients with ESRD without any significant adverse events such as, hypercalcemia or changes in parathyroid hormone levels. Furthermore, serum phosphate levels should be carefully monitored in these patients.

A low vitamin D level is associated with increased mortality, secondary to hyperparathyroidism and cardiovascular diseases. In a cross-sectional analysis of 825 patients on consecutive hemodialysis, 78% had vitamin D deficiency, while 18% were considered severely deficient.[3] Their results also demonstrated that calcium, phosphorus, and PTH levels correlated poorly with 25D and 1, 25D concentrations. Deficiency of calcitriol caused by impaired renal function is a main factor in the pathogenesis and pathophysiology of secondary hyperparathyroidism.[29] There was also a report indicating that oral depot cholecalciferol could induce a significant decrease in the serum iPTH level, without changing the Ca, P, ratio of CaX P or urinary calcium creatinine rate in patients with stage 3 or 4 CKD.[30] Conversely, cholecalciferol had been shown to increase the serum 25(OH) D and 1,25 (OH)2 D levels, while the serum calcium, phosphorus and iPTH levels were found to be decreased.[4] It has also been found to reduce soluble Klotho levels, a marker of iPTH, while increasing the levels of 1,25 (OH) D levels.[13] The current meta-analysis validates the results of the aforementioned studies. Further, vitamin D3 supplementation is found to be safe and

A **Serum calcium**

Study name	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value
Mose (2014)	-0.112	0.283	-0.667	0.443	-0.395	0.693
Delanaye (2013)	0.166	0.367	-0.553	0.884	0.452	0.651
Seibert (2012)	0.000	0.350	-0.685	0.685	0.000	1.000
Marckmann (2012)	0.489	0.391	-0.278	1.255	1.250	0.211
Armas (2012)	-0.154	0.309	-0.760	0.452	-0.498	0.619
Wasse (2012)	0.000	0.278	-0.544	0.544	0.000	1.000
Pooled	0.025	0.131	-0.233	0.282	0.187	0.851

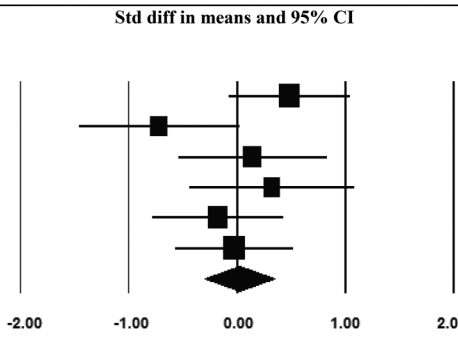
Heterogeneity test: Q = 2.1, P = 0.830, I^2 = 0%



B **PTH**

Study name	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value
Mose (2014)	0.481	0.287	-0.082	1.043	1.675	0.094
Delanaye (2013)	-0.723	0.378	-1.464	0.017	-1.915	0.055
Seibert (2012)	0.140	0.350	-0.546	0.826	0.400	0.689
Marckmann (2012)	0.320	0.388	-0.439	1.080	0.826	0.409
Armas (2012)	-0.180	0.310	-0.787	0.427	-0.582	0.561
Wasse (2012)	-0.028	0.278	-0.572	0.516	-0.101	0.920
Pooled	0.021	0.164	-0.301	0.343	0.128	0.898

Heterogeneity test: Q = 7.6, P = 0.179, I^2 = 34.3%



C **Phosphorus level**

Study name	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value
Mose (2014)	0.552	0.288	-0.013	1.116	1.914	0.056
Delanaye (2013)	0.256	0.367	-0.464	0.977	0.698	0.485
Seibert (2012)	-0.465	0.354	-1.160	0.229	-1.313	0.189
Marckmann (2012)	0.594	0.394	-0.177	1.365	1.510	0.131
Armas (2012)	0.419	0.312	-0.193	1.031	1.342	0.179
Wasse (2012)	0.338	0.280	-0.210	0.886	1.208	0.227
Pooled	0.299	0.148	0.009	0.589	2.018	0.044

Heterogeneity test: Q = 6.2, P = 0.291, I^2 = 18.9%

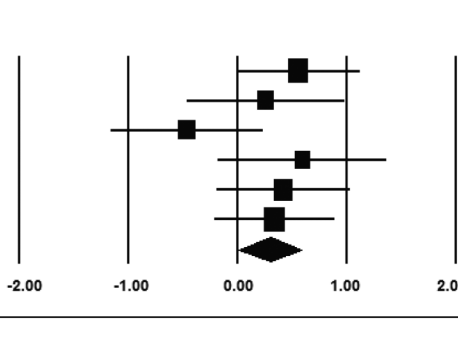


Figure 2 Forest plots of treatment (cholecalciferol vs placebo/control) effects on (A) serum calcium, (B) PTH, and (C) phosphorus levels. PTH, parathyroid hormone.

efficacious at the doses used in individual studies included in this review.

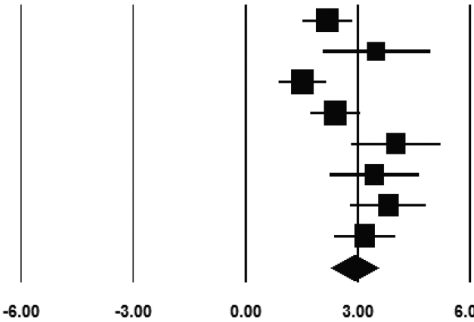
Likewise, reports elsewhere also reveal that supplementation with cholecalciferol is safe and well tolerated.[31] However, only 57% of patients have achieved recommended calcidiol levels, further suggesting dose-finding studies. Jean *et al* suggested that 10–30 μg/day of vitamin D supplementation is sufficient enough to correct most vitamin D deficiencies in patients on hemodialysis, without any evident toxicity.[2] In fact, oral administration has several advantages, including significant cost-effectiveness, and optimal compliance over intravenous administration.[32] All of the included studies utilized oral administration of vitamin D3; however, the doses varied widely among the studies (6000–200,000 IU/week). Wasse *et al*[23] have used a very high dose of 200,000 IU/week of cholecalciferol for 3 weeks and indicated that 90.5% of the subjects achieved serum 25(OH) D concentrations of≥30 ng/mL, whereas a pharmacokinetic analysis revealed that 10,333 IU/week of cholecalciferol produced a steady state of 24 ng/mL of 25 (OH) D with no apparent toxicities.[22] The Kidney Diseases Outcomes Quality Initiative (KDOQI) guidelines recommend 50,000 IU/month to 50,000 IU/week of vitamin D_2 which effectively increase 25(OH) D levels.[19] Estimates of the vitamin D supplement required by patients on dialysis to give 25-OH-D levels >30 ng/mL are between 1800 and 5000 IU/day,[33] which is within the range used in the studies included in the current review.

There are several studies showing different effects of ergocalciferol or cholecalciferol on the PTH level.[34–36]

A 25(OH)D level

Study name	Statistics for each study					
	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value
Massart (2014)	2.188	0.341	1.519	2.857	6.411	0.000
Mieczkowski (201	3.498	0.733	2.061	4.936	4.770	0.000
Mose (2014)	1.515	0.321	0.886	2.144	4.721	0.000
Hewitt (2013)	2.404	0.339	1.740	3.068	7.095	0.000
Seibert (2012)	4.011	0.605	2.826	5.197	6.630	0.000
Marckmann (2012)	3.450	0.607	2.260	4.641	5.681	0.000
Armas (2012)	3.816	0.518	2.800	4.832	7.360	0.000
Wasse (2012)	3.189	0.418	2.369	4.008	7.627	0.000
Pooled	2.903	0.326	2.265	3.542	8.909	0.000

Heterogeneity test: Q = 29.6, P < 0.001, I^2 = 76.4%



B 1,25(OH)2D level

Study name	Statistics for each study					
	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value
Massart (2014)	1.591	0.310	0.984	2.198	5.136	0.000
Mieczkowski (201	0.087	0.465	-0.824	0.998	0.187	0.852
Hewitt (2013)	0.762	0.267	0.238	1.286	2.850	0.004
Seibert (2012)	0.592	0.357	-0.108	1.292	1.658	0.097
Marckmann (2012)	0.815	0.401	0.030	1.601	2.034	0.042
Armas (2012)	1.239	0.337	0.578	1.900	3.675	0.000
Wasse (2012)	1.445	0.347	0.765	2.125	4.165	0.000
Pooled	0.978	0.185	0.615	1.340	5.282	0.000

Heterogeneity test: Q = 12.0, P = 0.063, I^2 = 49.8%

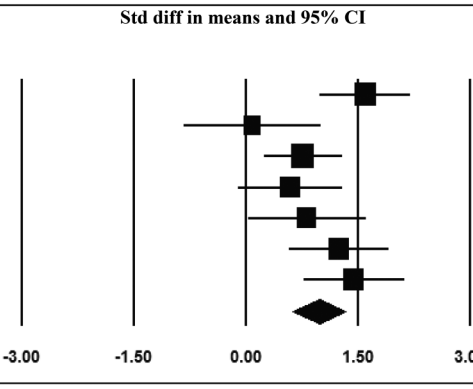


Figure 3 Forest plots for treatment (cholecalciferol vs placebo/control) effect on (A) 25(OH)D, and (B) 1,25 (OH) 2D levels.

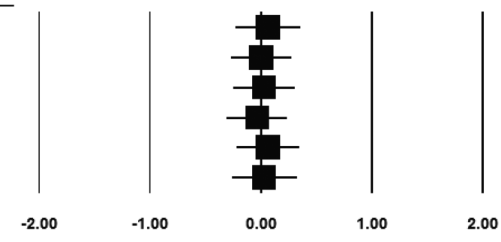
Vitamin D2 (ergocalciferol) has been shown to be safe and sufficient to obtain and maintain optimal serum 25(OH)D concentrations and prevent vitamin D insufficiency in patients with CKD on dialysis.[36] Similarly, vitamin D3 or cholecalciferol supplementation showed higher 25(OH)D, 1,25-dihydroxyvitamin D, and albumin levels, while reducing serum calcium and PTH levels in patients on hemodialysis.[37] Existing evidence does not support the superiority of one or the other form of vitamin D in maintaining adequate levels of 25 (OH) D levels in patients on dialysis. Thus, natural or active vitamin D therapy plays a key role in reducing the secondary hyperparathyroidism associated with ESRD in patients undergoing long-term dialysis. However, it should be noted that besides raising 25-OH-D and 1,25-OH2-D levels and PTH suppression, cholecalciferol supplementation may have non-calciotriopic effects, as vitamin D receptors are expressed in a wide variety of other tissues, including the colon, breast and prostate.[38] Evidences indicate that the extra renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D may have other significant biological roles as well.[35]

Efficacy of nutritional cholecalciferol in ESRD is often debated, as opposed to the active vitamin D analogs, and a limited number of meta-analysis exists in patients undergoing dialysis. Our current analysis is one of the few updated reviews in this field. Moreover, the strength of this review is that all the included studies were RCT, thus avoiding biases inherent with observational studies. The previously published meta-analyses mostly included prospective, observational studies in patients with CKD, regardless of their dialysis status.[16 39] Nevertheless, our results are in agreement with other systematic reviews, where vitamin D supplementation has been found to improve clinical and biochemical end points.

There are several limitations to the current review, including the limited number of studies available for inclusion in the meta-analysis along with the small number of subjects enrolled in each study. Two studies[20 22] did not use vitamin D status as a patient selection criterion. Most studies also excluded patients with hypercalcemia and hyperphosphatemia, but one study, Armas *et al*,[22] did not impose such restrictions. While 8 of the 9 included studies used a placebo as a control intervention, Mieczkowski *et al*[8] did not provide any treatment to the control group. All studies, except for that of Mieczkowski *et al*, used either radioimmunoassay or chemiluminescence to measure the levels of 1,25(OH)2D or 25(OH)D, while Mieczkowski *et al*[8] have used a manual assay system. In addition, there was heterogeneity in the pre-existing active vitamin D use, or the use of phosphate binders and calcimimetics (like cinacalcet), which may be potential confounding factors. Moreover, a majority of the studies either did not adjust the dosage of pre-existing active vitamin D during the study, or totally excluded the patients who used

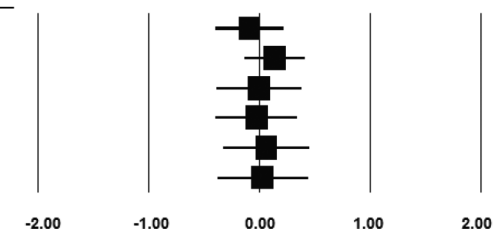
A Serum calcium

Study name	Statistics with study removed						Std diff in means and 95% CI with study removed
	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value	
Mose (2014)	0.062	0.148	-0.228	0.352	0.418	0.676	
Delanaye (2013)	0.004	0.141	-0.272	0.279	0.027	0.978	
Seibert (2012)	0.029	0.142	-0.249	0.306	0.202	0.840	
Marckmann (2012)	-0.034	0.139	-0.307	0.239	-0.247	0.805	
Armas (2012)	0.064	0.145	-0.220	0.348	0.440	0.660	
Wasse (2012)	0.032	0.149	-0.260	0.324	0.213	0.832	



B PTH

Study name	Statistics with study removed						Std diff in means and 95% CI with study removed
	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value	
Mose (2014)	-0.090	0.158	-0.400	0.220	-0.568	0.570	
Delanaye (2013)	0.136	0.141	-0.140	0.413	0.968	0.333	
Seibert (2012)	-0.005	0.198	-0.392	0.383	-0.024	0.980	
Marckmann (2012)	-0.028	0.187	-0.395	0.339	-0.149	0.881	
Armas (2012)	0.061	0.196	-0.324	0.446	0.311	0.755	
Wasse (2012)	0.028	0.208	-0.381	0.436	0.133	0.894	



C Phosphorus level

Study name	Statistics with study removed						Std diff in means and 95% CI with study removed
	Std diff in means	Standard error	Lower limit	Upper limit	Z-Value	p-Value	
Mose (2014)	0.234	0.172	-0.103	0.571	1.359	0.174	
Delanaye (2013)	0.302	0.178	-0.047	0.650	1.696	0.090	
Seibert (2012)	0.429	0.143	0.149	0.709	3.001	0.003	
Marckmann (2012)	0.254	0.167	-0.073	0.581	1.524	0.128	
Armas (2012)	0.268	0.181	-0.087	0.624	1.480	0.139	
Wasse (2012)	0.284	0.188	-0.085	0.652	1.507	0.132	

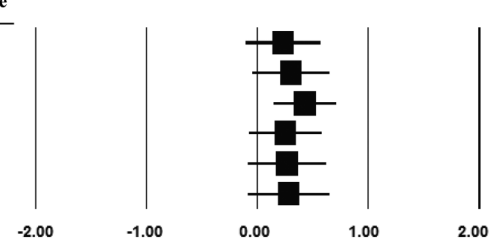


Figure 4 Sensitivity analysis for the treatment effect on (A) serum calcium, (B) PTH, and (C) phosphorus levels. PTH, parathyroid hormone.

them 3 months prior to the study. However, the limitations set on the use of phosphate binders were rather loose among the included studies. Furthermore, the dosages of cholecalciferol and dosing schedules also varied among studies. It is also possible that some studies might have had patients with secondary hyperparathyroidism due to vitamin D deficiency. Regardless, our results reveal increased 25(OH)D and $1,25(OH)_2D$ levels after vitamin D3 supplementation, and further underscores the therapeutic role of vitamin D in maintaining mineral metabolism, preventing secondary hyperparathyroidism and thereby minimizing the cardiovascular risk in patients with ESRD.

In summary, the current analysis indicates that in patients undergoing dialysis for CKD, supplementation of D3 (cholecalciferol) increases serum levels of phosphorus, 25 (OH)D, and $1,25(OH)_2D$, but did not increase serum levels of calcium and PTH, showing their efficacy in correcting vitamin D deficiency with minimal effects on serum calcium and PTH.

Contributors ZL, SZ and CX are guarantors of integrity for the entire study. ZL and CX were involved in the study concepts and study design. CX and YL were involved in the definition of intellectual content, statistical analysis and data acquisition. ZL, CX and YL were involved in the literature research. ZL, CX and YL were involved in the manuscript preparation. ZL and CX were involved in the manuscript editing. ZL and SZ were involved in the manuscript review.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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