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FOCUSED REVIEW

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Efficacy of weekly *versus* daily cholecalciferol for repleting serum vitamin D (25(OH)D) deficiency: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Background/rationale: Weekly cholecalciferol can replace daily supplementation to reduce pill burden in patients with complex medication regimens and hypovitaminosis D, but evidence supporting this switch is unclear.

Objective: We aimed to determine whether weekly cholecalciferol was superior to daily cholecalciferol to replete patients with hypovitaminosis D.

Methods: We conducted a systematic review of randomized controlled trials involving participants with baseline hypovitaminosis D (<30 ng/ml) comparing weekly *versus* daily cholecalciferol dosing and where serum cholecalciferol was measured within 120 days of starting treatment. We searched MEDLINE, CINAHL and EMBASE from inception to 7 May 2024. A random-effects meta-analysis evaluated the odds ratio for repletion of serum vitamin D levels.

Findings: Eight trials involving 542 patients were included in the analysis. Weekly and daily cholecalciferol were not significantly different in correcting hypovitaminosis D (OR = 1.5, 95% CI = 0.3–6.9, $p = 0.6$, favouring weekly dosing, $I^2 = 85.3\%$). A sensitivity analysis excluding otherwise healthy patients had similar findings (OR = 0.8, 95% CI = 0.3–2.1, $p = 0.6$). Most studies were at risk of bias; the different doses being compared increased the heterogeneity.

Conclusions: Limited direct evidence supports a switch from daily to weekly cholecalciferol dosing; however, weekly supplementation was not demonstrably worse at repleting levels and decreased a patient's daily pill burden.

KEYWORDS
cholecalciferol, deprescribing, dosing strategy, meta-analysis, systematic review

Plain English Summary

Weekly vitamin D can replace daily supplementation to reduce the number of pills for patients with complex medication regimens and vitamin D deficiency, but data supporting this switch is unclear. We aimed to determine whether weekly vitamin D dosing was better than daily dosing to correct vitamin D deficiency through a systematic review and meta-analysis of randomized controlled trials. Eight trials involving 542 patients were included in the analysis. We found that weekly and daily vitamin D were not significantly different in treating vitamin D deficiency, although most studies were at risk of bias because different doses were being compared in each trial.

1 | INTRODUCTION

For countries located at high latitudes, such as Canada, the northern United States and Europe,[1,2] many experts currently recommend cholecalciferol supplementation for all adults during the winter because they are not sufficiently exposed to sunlight to maintain optimal vitamin D levels (above 30 ng/ml).[2] To reduce pill burden, prescribers have increasingly been replacing daily cholecalciferol dosing with weekly cholecalciferol dosing.[3] The process of switching daily dosing to weekly dosing of cholecalciferol is a form of medication regimen simplification, defined as the process of decreasing the pill burdens of various medications to improve medication adherence, decrease medication errors and ultimately lead to better patient outcomes.[4,5]

Medication regimen simplification has never been previously demonstrated for the case of daily vitamin D. Our study aims to evaluate if weekly dosing is as efficient as daily dosing, so a future recommendation to reduce pill burden could be to simplify daily vitamin D to its weekly dosing. While one randomized controlled trial (RCT) in 2016 suggested that weekly dosing of cholecalciferol may be equally effective as daily dosing,[3] we sought to compare the efficacy of two dosing strategies through a meta-analysis. We therefore aimed to perform a systematic review and meta-analysis of RCTs that directly compared the efficacy of both dosing strategies to replete patients with hypovitaminosis D. We hypothesized that weekly vitamin D was not significantly more efficacious than daily vitamin D to replete patients with hypovitaminosis D.

2 | MATERIALS AND METHODS

This systematic review and meta-analysis was registered on International Prospective Register of Systematic Reviews (PROSPERO) (CRD42023486508) on 24 November 2023 and complies with PRISMA guidelines.[6] The protocol was amended on 19 February 2024 to update the methodology for the conduct of the meta-analysis. We initially aimed to conduct a noninferiority meta-analysis; however, after final inclusion of the studies, the study population was too small. We therefore amended the protocol to conduct a traditional meta-analysis.

2.1 | Search strategy

The following databases were searched: CINAHL, MEDLINE and Embase via Ovid from inception to 7 May 2024. The artificial intelligence software Elicit[7] and Google Scholar were also used to search for additional articles using the prompt "Noninferiority or superiority of daily or weekly dosing strategies of cholecalciferol, randomized controlled trials" on 7 May 2024. There were no language restrictions, and each database was searched for RCTs in adult populations that compared daily and weekly dosing regimens of cholecalciferol (Appendix S1, Section 1). Reference lists of the final studies included in the analysis were hand searched for additional trials.

2.2 | Study inclusion criteria

Included studies were RCTs comparing weekly to daily doses of cholecalciferol for the treatment of hypovitaminosis D in adult patients. This included comparing cholecalciferol monotherapy or cholecalciferol coadministered with calcium, regardless of patient comorbidities. Studies were required to report on serum vitamin D (25(OH)D) at baseline and at follow-up up to 120 days after the start of treatment. We excluded clinical trial protocols, conference abstracts, grey literature and studies limited to paediatric patients or patients without documented hypovitaminosis D.

2.3 | Study selection

Search results were imported into Covidence[8] and deduplicated by the software. Unique articles were then screened by title and abstract by two independent reviewers (ÉBC and CP). Retained articles for full-text screening were evaluated by two independent reviewers (ÉBC and CP) to assess for fulfilment of inclusion

criteria. When disagreements on the inclusion of an article occurred, they were resolved by consensus or by a third author when necessary.

2.4 | Quality assessment

Quality assessments were performed by two independent reviewers (ÉBC and CP) using version 2 of the Cochrane risk of bias tool for randomized trials (RoB2).[9] A summary figure of the quality assessments was generated using the robvis package in R (Figure S1).[10]

2.5 | Data extraction

Data were extracted by two reviewers (ÉBC and CP) using a standardized form in Covidence.[8] Discrepancies were resolved by consensus or by way of a third author, when necessary. The following data were extracted: authors' names, publication year, blinding strategy, eligibility criteria, study arms, follow-up time, mean baseline age, sex, mean baseline serum 25(OH)D according to each study arm, follow-up 25(OH)D in each study arm and adverse events such as hypercalcemia, falls, fractures or deaths occurring over the course of the study (Table 1).

2.6 | Data analysis

Descriptive statistics were used to describe patient demographics at baseline and other variables. Means and standard deviations (SDs) were used for continuous variables and proportions for categorical variables. Efficacy was the primary outcome, measured by the proportion of patients with a follow-up serum 25(OH)D value above 30 ng/ml, the guideline-recommended minimum.[11] For studies that did not report the proportions directly, we used the reported mean and SD to calculate the proportion of patients with a value above 30 ng/ml from the normal curve, rounded down to the nearest integer (the statistical code can be found in Appendix S1). The administration of weekly cholecalciferol (ranging between 4200 and 60 000 IU) was considered the intervention, and the control was daily cholecalciferol (ranging between 600 and 7000 IU). Using the metafor package in R,[12] we conducted a random-effects meta-analysis using a generalized linear mixed model (GLMM) (Appendix S1). Statistical heterogeneity was described with I^2.

To assess for possible publication bias, we had planned to conduct a visual inspection of a funnel plot, but this was considered uninformative due to the small number of studies. Thus, a Bayesian approach previously described by Shi et al.[13] was used to measure publication bias. A threshold of $p < 0.10$ was selected as an indicator for statistically significant publication bias.

3 | RESULTS

3.1 | Search results

Our search strategy returned a total of 803 results, comprising 706 unique articles. During title and abstract screening, 694 articles were excluded. The remaining 12 articles proceeded to full text review, and, of these, 8 were included in the systematic review and meta-analysis (Figure 1).

3.2 | Study and population characteristics (Table 1)

The eight RCTs meeting inclusion criteria[3,14–20] comprised 542 patients; 270 were randomized to weekly dosing of cholecalciferol, and 272 were randomized to daily dosing of cholecalciferol (Table 1). Study groups included healthy patients ($n = 280$), patients with type 2 diabetes ($n = 40$), residents of long-term care homes ($n = 109$), women having undergone hip fracture repair surgery ($n = 33$) and patients attending an outpatient internal medicine clinic ($n = 90$). Four studies (50%) reported concomitant administration of daily oral calcium during the course of the trial; strategies were variable, ranging from 200 to 1200 mg daily.

3.3 | Meta-analysis

The random-effects meta-analysis found that weekly cholecalciferol was not statistically significantly different than daily cholecalciferol at repleting hypovitaminosis D among adults (OR = 1.5 numerically favouring weekly dosing, 95% CI = 0.3–6.9, $p = 0.6$) with high heterogeneity ($I^2 = 85.3\%$) (Figure 2). The visual inspection of the funnel plot (Appendix S1, figure X) was uninformative; the Bayesian analysis did not reveal significant publication bias (estimate = 1.09; 95% CI = 0.06–2.5).

3.4 | Safety outcomes

No studies reported fractures, falls, hospitalizations or deaths; one patient randomized to the daily cholecalciferol

TABLE 1 Description of randomized controlled trials included in the meta-analysis.

Study identifier[a]	Intervention	Dose (IU)	Duration of follow-up (days)	Number of participants	Sponsorship source	Calcium taken (y/n, dose in mg)	Age, mean (SD)	Female, *n* (%)	Patients with serum >30 ng/ml at follow-up (%)
Takács 2016	Weekly cholecalciferol	7000	90	23	Pharma Patent KFT	Y, 200 mg PO daily	51.9 (16.1)	18 (78.2)	0 (0)
Takács 2016	Daily cholecalciferol	1000	90	22	Pharma Patent KFT	Y, 200 mg PO daily	51.1 (15.7)	19 (86.4)	0 (0)
Chel 2007	Weekly cholecalciferol	4200	120	54	Solvay Pharmaceuticals, ZonMw	N	84.3 (6.4)	39 (72.2)	14 (29.2)
Chel 2007	Daily cholecalciferol	600	120	55	Solvay Pharmaceuticals, ZonMw	N	84.3 (6.3)	46 (83.6)	17 (37)
Ish-Shalom 2008	Weekly cholecalciferol	10 500	60	16	NA	Y, 8/16, 600-1200 mg daily	81.0 (6.1)	16 (100)	11 (68.8)
Ish-Shalom 2008	Daily cholecalciferol	1500	60	17	NA	Y, 4/17, 600-1200 mg daily	80.9 (8.7)	17 (100)	16 (94.1)
Khawaja 2016	Weekly cholecalciferol	50 000	60	37	None	N	28.7 (5.1)	23 (62.2)	28 (75.7)
Khawaja 2016	Daily cholecalciferol	7000	60	34	None	N	28.6 (3.6)	20 (58.8)	23 (67.6)
Hamedooni-Asl 2020	Weekly cholecalciferol	50 000	56	52	Vice-chancellor for Research and Technology	Y, 400 mg/day	41.31 (14.35)	35 (63.6)	34 (65.4)
Hamedooni-Asl 2020	Daily cholecalciferol	4000	98	55	Vice-chancellor for Research and Technology	Y, 400 mg/day	39.58 (14.04)	39 (60)	46 (83.6)
Habiba 2023	Weekly cholecalciferol	50 000	90	20	None	N	NR	NR	16 (80)
Habiba 2023	Daily cholecalciferol	4000	90	20	None	N	NR	NR	15 (75)
Singh 2019	Weekly cholecalciferol	60 000	70	45	Lupin, Sun	Y, 500 mg PO daily	33.17 (10.53)	26 (57.8)	23 (51.1)
Singh 2019	Daily cholecalciferol	1000	70	45	Lupin, Sun	Y, 500 mg PO daily	39.67 (11.37)	20 (44.4)	0 (0)
Fassio 2020	Weekly cholecalciferol	50 000	56	25	Abiogen	N	36.7 (8.8)	18 (72)	23 (100)
Fassio 2020	Daily cholecalciferol	10 000	56	25	Abiogen	N	30.2 (10)	13 (52)	24 (100)

[a]All studies were involved in the calculation of the proportion of patients with a serum vitamin D greater than 30 ng/ml.

FIGURE 1 PRISMA flow diagram.

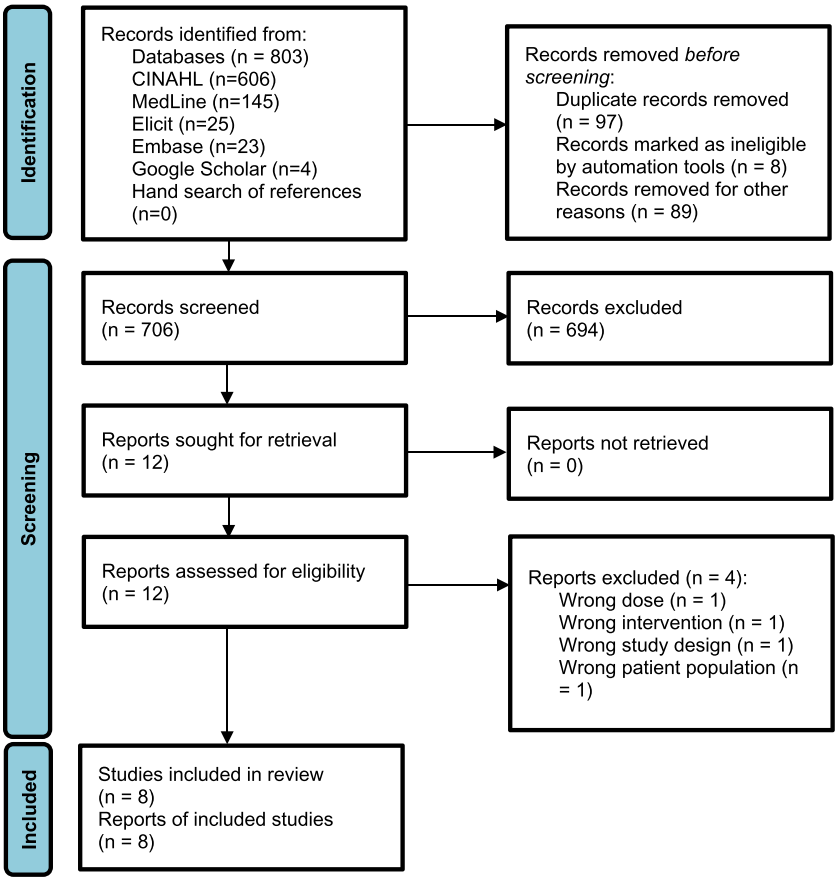
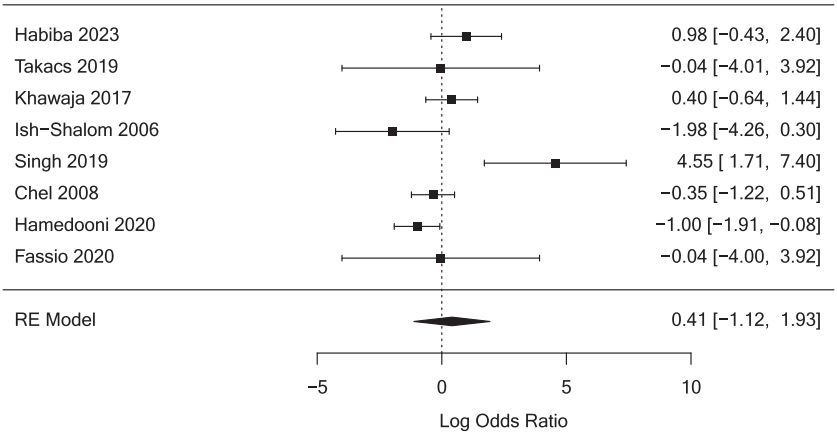


FIGURE 2 Forest plot of the efficacy of daily *versus* weekly cholecalciferol to replete patients with hypovitaminosis D. Exponentiated OR = 1.5 [0.32–6.9], favouring weekly dosing.



dosing group in Ish-Shalom 2008[15] had an episode of hypercalcemia; otherwise, no other adverse drug event was reported.

3.5 | Risk of bias

Of the eight retained studies, four (50%) had some concerns,[3,14,16,20] and four (50%) were considered at high risk of bias.[15,17–19] No studies provided a prespecified analysis plan or mentioned protocol deviations. In total, six studies (three with some concerns overall[14,16,20] and three at high risk of bias overall[15,17,18]) did not detail any processes for allocation concealment; five studies (one with some concerns overall[14] and four at high risk of bias overall[15,17–19]) did not provide an explanation for the loss to follow up, and one (at high risk of bias overall[18]) did not provide basic patient demographics such as age, sex or body mass index.

3.6 | Post hoc analyses

A post hoc subgroup analysis was conducted excluding studies at high risk of bias.[3,14,16,21] There was again no statistically significant difference between weekly and daily dosing of cholecalciferol; however, the point estimate was more neutral, and the 95% confidence interval was narrower (OR = 0.95; 95% CI = 0.5–1.9; $p = 0.9$).

A post hoc sensitivity analysis was conducted only including studies of patients with chronic illnesses.[14,15,18] There was also no demonstrable difference between daily and weekly cholecalciferol dosing with a narrower confidence interval (OR = 0.8; 95% CI = 0.3–2.1; $p = 0.62$).

The use of vitamin D during the study was analysed post hoc. Five studies did not permit concomitant prescription of supplemental vitamin D[14,16,17,19,20]; two studies did not clearly specify if concomitant vitamin D was allowed[3,18]; and one study allowed concomitant administration of vitamin D supplementation.[15] In this latter study by Shalom et al.,[15] 3/16 (18.8%) patients assigned to the weekly vitamin D took 200 IU/day, in addition to the 10 500 IU weekly that they were assigned to. In the daily administration arm, 4/17 (23.5%) patients took supplemental vitamin D (two patients took 200 IU daily, one took 400 IU daily, and one took 800 IU daily), in addition to the 1500 IU of vitamin D daily that they were assigned to.

4 | DISCUSSION

Weekly cholecalciferol was not demonstrably worse than daily cholecalciferol to replete patients with hypovitaminosis D. To our knowledge, this is the first systematic review and meta-analysis to directly compare weekly *versus* daily cholecalciferol dosing for the repletion of hypovitaminosis D. The trials identified were small, limited by risk of bias, and heterogeneous. Still, results suggested that once weekly dosing was not worse than daily dosing and was numerically favoured. Based on these results, weekly dosing is likely a reasonable strategy. Simplifying medication regimens when possible is important for patients with medical complexity,[4,5] as they are more likely to require multiple medications to manage,[22] leading to complex medication regimens (e.g., older adults living in long-term care,[5] patients on haemodialysis[23] and older people with HIV[24]). Patients with complex medication regimens have an increased risk of self-administered medication errors, unplanned hospitalizations, and all-cause mortality.[25] Intuitively, remembering seven daily pills is harder than one weekly pill, which was confirmed by one systematic review and meta-analysis that found that the weekly dosing of any prescribed medication when possible for patients with osteoporosis was associated with 1.9 times (95% CI, 1.81–2.00) higher odds of adherence to treatment compared to daily dosing.[26] Furthermore, opting for weekly cholecalciferol dosing can reduce the cost of this supplement compared to daily dosing.[27,28] According to GoodRx, the lowest price for 30 capsules of 10 000 IU of cholecalciferol (a 30-week supply if taken weekly) would cost $7.28 USD, coming out to $0.24/week.[28] However, a 30-week supply of daily 2000 IU of cholecalciferol would cost $9.42 USD, or $0.31/week.[27]

Our study was subject to several notable limitations, many of which are inherent to the included studies. First, there was considerable heterogeneity in the estimates. A few factors can account for some of the observed heterogeneity, namely, the small sample sizes and the heterogeneous patient populations and dosing ranges of vitamin D. The recommended dosing for vitamin D varies considerably, as it depends on their baseline deficiency level, the patient's absorptive capacity, their capacity to convert vitamin D to 25(OH)D in the liver, and less impactfully but still relevantly, genetic determinants.[29] Daily dosing can range between 600 and 800 IU daily, but even 10 000–50 000 IU daily can be recommended if patients have malabsorption; clinicians can also choose to prescribe weekly vitamin D, where dosing is recommended to be between 25 000–50 000 IU.[29] In our meta-analysis, we found that doses in the daily administration group varied between 600–7000 IU, and the doses in the weekly administration group varied between 4200–50 000 IU. Second, the confidence interval of the primary outcome was very wide, suggesting that weekly vitamin D was between half and six times as effective as daily administration. However, our subgroup analysis among the studies that were not at a high risk of bias showed a more neutral point estimate and a narrower confidence interval. Third, studies did not consistently report the proportion of patients repleted; as such, our estimates of this outcome in studies that did not report this may have been based on estimates derived by integration. Fourth, the studies largely included healthier patients, which may not be representative of the patient population (i.e., older adults, patients with osteoporosis, women, prior fragility fractures) that stand to gain the most from cholecalciferol supplementation, assuming there is a direct benefit of cholecalciferol supplementation. This was partly mitigated in the subgroup analyses among patients with chronic illnesses, where point estimates were more neutral and confidence intervals narrower. Fifth, adverse event reporting was inconsistent, which precluded a meta-analysis of safety outcomes. Despite these weaknesses, this systematic review and meta-analysis is, to our

knowledge, the only to directly address daily *versus* weekly cholecalciferol dosing efficacy.

Other strengths were our comprehensive search strategy, which included diverse patient populations, including some studies measuring cholecalciferol repletion among patients with chronic illnesses. By not restricting studies to healthy adults with hypovitaminosis D, we demonstrated that weekly cholecalciferol may also be a reasonable approach for populations with chronic illnesses. Furthermore, the use of a hybrid approach in the methodology strengthened this meta-analysis because we leveraged strengths from the GLMM model for the meta-regression[12] and the Bayesian model[13] to assess publication bias. The GLMM model accounted for the double zero events occurring in Takacs 2016.[3]

A larger RCT directly comparing the efficacy of daily *versus* weekly cholecalciferol could be conducted based on the effect size estimates from this meta-analysis to address the limitations found in the included studies. The proportion of patients repleted in the daily cholecalciferol arm was 52.5% and 56.4% in the weekly cholecalciferol arm. Therefore, a future equivalence RCT could set the percentage of success in both the control and intervention groups at 52.5% and an equivalence limit of 51%, so that at least the majority of patients would achieve repletion from hypovitaminosis D. Based on the algorithm for sample size calculations for an equivalence trial, the sample size required per group would be 25, for a total sample size of 50.[30]

5 | CONCLUSION

Based on RCT data in this systematic review and meta-analysis, the efficacy of weekly cholecalciferol supplementation to replete hypovitaminosis D was not significantly different from daily cholecalciferol dosing. Although sample sizes were small and there was heterogeneity, weekly repletion decreases a patient's pill burden and, at least in theory, may improve adherence. Future research should confirm these findings and evaluate the most effective doses and formulations. In the meantime, weekly dosing of vitamin D to replete hypovitaminosis D is likely a reasonable approach for patients with polypharmacy.

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This study was prospectively registered in PROSPERO as a systematic review and meta-analysis.

CONFLICT OF INTEREST STATEMENT

None of the other authors have any relevant conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data will be made available for 6 months following publication of the manuscript, and requests for access can be made to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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