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ORIGINAL ARTICLE

Effect of calcifediol and cholecalciferol on muscle function in postmenopausal women: a randomized controlled trial

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Abstract

Summary Brief rationale: Limited evidence exists on calcifediol's effect on lower extremity function in postmenopausal women with osteoporosis or osteopenia. Main result: Calcifediol (20 µg/day) showed no greater benefit than vitamin D3 (3200 IU/day) or placebo. Significance of the paper: Findings do not support high-dose vitamin D3 or calcifediol for improving lower extremity function.

Purpose To test the effect of 20 µg/day of calcifediol compared with 3200 IU/day of vitamin D3 and placebo on lower extremity function in postmenopausal women with osteopenia or osteoporosis.

Methods This is a 3-arm double-blind RCT among postmenopausal women aged 50–70 years with serum 25(OH)D < 30 ng/mL, and a DXA-based diagnosis of osteopenia or osteoporosis. Participants were randomized to receive either daily 20 µg calcifediol, daily 3200 IU vitamin D3, or placebo. The primary endpoint was a composite measure of lower extremity function, assessed at baseline, 3, and 6 months, including four tests: gait speed, knee flexor and extensor strength, and repeated sit-to-stand test. The primary endpoint was the probability of success (improvement or maintenance from baseline) in any of the eight tests, four tests at 3 months and four tests at 6 months.

Results The trial enrolled 152 women (mean age, 61.0 years; mean serum 25(OH)D level, 23.4 ng/mL), and all but one woman completed all follow-up visits. Baseline characteristics, including the four tests of lower extremity function, were balanced across the three groups. The adjusted probability of success in any of the eight tests was 53.6% (95% confidence interval 47%, 60%) with calcifediol, 55.5% (50%, 61%) with vitamin D3, and 61.4% (55%, 67%) with placebo, without significant differences between treatment groups.

Conclusions Our findings do not support supplementation with daily calcifediol or equivalent high-dose daily vitamin D3 for improving or maintaining lower extremity function among younger postmenopausal women (age 50–70) with osteopenia or osteoporosis, who were pre-selected for vitamin D insufficiency or deficiency (25(OH)D < 30 ng/mL; baseline mean 25(OH)D 23.4 ng/mL).

Trial registration Clinicaltrials.gov; NCT02527668; https://clinicaltrials.gov/ct2/show/NCT02527668

Keywords Aging · Middle-aged and older adults · Muscle health · Physical performance · Vitamin D · Vitamin D status

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Introduction

Vitamin D deficiency is a global health concern [1, 2]. In Europe, the prevalence of vitamin D deficiency (serum 25-hydroxyvitamin D (25(OH)D) < 20 ng/mL) is high, ranging from 30 to 60% in Western, Southern, and Eastern countries [2]. Among postmenopausal women, vitamin D deficiency is also common, with about half of women in Thailand and Malaysia, 90% in Japan, and 92% in South Korea with levels of 25(OH)D < 30 ng/mL [3]. In Poland [4], about a quarter of postmenopausal women may have levels of 25(OH)D < 10 ng/mL, and, in Croatia, more than 60% have levels of 25(OH)D < 20 ng/mL [2].

Vitamin D deficiency can lead to several negative health outcomes including impaired mineralization, lower bone mineral density, fractures, falls, and muscle weakness [2, 5–8]. This may be relevant also in postmenopausal women as this population is at high risk for decreased muscle mass and strength due to hormonal changes [9, 10]. Notably, a 2021 metanalysis of 54 RTCs (8747 individuals aged 4 years and older) found that vitamin D3 or D2 supplementation (regardless of administration form, dosage, or duration) with or without calcium co-supplementation may have adverse effects on lower extremity function as measured by timed up-and-go test (TUG) and knee flexor strength [11]. However, limited evidence on the effect of calcifediol supplementation on lower extremity function among postmenopausal women exists to date [12].

Findings from prior RCTs and prospective cohort studies suggest that calcifediol may be linked to improvements in lower extremity function [12–15]. A 2022 meta-analysis of RCTs (269 participants, mean age 67.4 years, 100% women in 5 out of 7 studies, median follow-up 24 weeks) reported a beneficial effect of calcifediol on lower extremity function (including measures of repeated sit-to-stand time, gait speed, the Short Physical Performance Battery (SPPB), TUG, handgrip strength, and knee extensor and flexor strength) compared to baseline [12]. However, as acknowledged by the authors, most trials lacked a priori power analysis and effect comparison between groups. Therefore, limited evidence from RCTs with sufficient power to compare the effect of calcifediol against vitamin D3 or placebo on lower extremity function particularly among postmenopausal women exists to date.

Purpose

The present trial was designed to provide evidence of the effect of calcifediol on lower extremity function compared to vitamin D3 at a comparable dose and placebo in postmenopausal women with osteopenia or osteoporosis. In this randomized controlled trial, we tested whether daily oral supplementation with 20 µg of calcifediol compared with a comparable (1) oral dose of 3200 IU/day of vitamin D3 and compared with (2) placebo maintained or improved lower extremity function over 6 months. The secondary aim of the trial was to test the effect of calcifediol and vitamin D3 on the individual components of lower extremity function and the TUG test compared to placebo.

Methods

Study design

This is a 6-month single-center 3-arm double-blind, randomized, parallel, placebo-controlled trial that compared the effect of 20 µg/day of calcifediol with 3200 IU/day of vitamin D3 and with placebo with regards to lower extremity function.

The trial was conducted at the Centre on Aging and Mobility, Waid City Hospital, Zurich, Switzerland. The trial was approved by the Cantonal Ethics Commission of Zurich (KEK-ZH 2013–0582, PB_2016-01877) and Swissmedic (2015DR2011). The trial was closely monitored by an external company (Clinipace) on behalf of the sponsor. The trial protocol and statistical analysis plan are available in the Supplementary material. The trial's registration number at clinicaltrials.gov is NCT02527668.

Study participants

Participants signed the informed consent and were postmenopausal women between the ages of 50 and 70 years with documented osteopenia (BMD by DXA *T*-score: < −1.0 and > −2.5 at the spine or total hip) or osteoporosis (BMD by DXA T-score: ≤ −2.5 at the spine or total hip) and a FRAX score that did not qualify for pharmacologic treatment for osteoporosis [16, 17]. Participants were required to be community-dwelling and ambulatory without help, have serum 25(OH)D concentration < 30 ng/mL, and limit additional vitamin D3 intake to 800 IU/day and calcium intake to 500 mg/day during the trial.

Exclusion criteria were the following: vitamin D intake > 1000 IU on any day in the 4 weeks prior to enrollment, serum calcium levels > 2.60 mmol/L adjusted for albumin if albumin ≤ 35 or ≥ 45 g/L, estimated creatinine clearance < 30 mL/min, severe visual or hearing impairment, malabsorption syndrome (celiac diseases, inflammatory bowel disease), pathologic fracture (excl. fractures due to osteoporosis and stress fractures) in the last year prior enrollment, fracture due to osteoporosis in the last 10 years prior enrollment, chemotherapy or radiation due to cancer

in the last year prior enrollment, treatment which has an effect on calcium metabolism (e.g., PTH, calcitonin, chronic cortisone intake > 5 mg/day for more than 4 weeks in the last year prior enrollment (except for inhalation and sporadic infiltration), current treatment with a bisphosphonate, hormone replacement therapy, and/or selective estrogen receptor modulator.

Intervention and masking

The investigational product was produced by dsm-firmenich AG, and capsules were produced and filled into bottles by Fisher Clinical Services. The same batch of product was used for all study capsules. Study capsules were blinded and labeled with a unique randomization code by the capsule producer. Capsules were analyzed by dsm-firmenich AG and analysis certificates were approved by Swissmedic. Assignment was determined from a computer-generated randomization list produced by Ferrari Data Solutions. Study personnel remained blinded to the treatment assigned to subjects throughout the study.

Rationale for dose selection

At the time of trial preparation, the effectiveness and safety of a daily dose of 20 µg of calcifediol in improving lower extremity function were established in our pilot study among 20 postmenopausal women (mean age 61.5 years, mean serum 25[OH]D level 13.2 ng/mL) [15]. In this pilot trial, women receiving calcifediol had 2.8 times higher odds of maintaining or improving lower extremity function compared to those taking a daily dose of 800 IU of vitamin D3.

The daily dose of 3200 IU (80 µg) of vitamin D3 was chosen as the active comparator to calcifediol based on our pharmacokinetic study, which showed calcifediol to be three times more potent than vitamin D3 [18]. This dose also aligned with the 2010 Institute of Medicine (IOM) recommendation of a safer upper limit of 4000 IU/day (100 µg/day, 1 IU = 0.025 µg) [19]. Furthermore, a safe upper intake of 10,000 IU/day (250 µg/day) of vitamin D3 was supported by a risk assessment study involving 25 RCTs, which found no relationship between oral vitamin D (up to 100,000 IU/day) or serum 25(OH)D levels (up to 257.2 ng/mL or 643 nmol/L) and mean serum calcium levels [20]. Based on these studies, we selected 3200 IU/day of vitamin D3 as the active comparator, which should raise serum 25(OH)D levels similarly to 20 µg/day of calcifediol.

Randomization and procedures

Treatment allocation was stratified by (1) DXA *T*-score at the spine and/or total hip (DXA BMD *T*-score ≤ -2.5 at spine and/or hip was stratified as osteoporosis, all others as osteopenia) and (2) participant agreement to have a muscle biopsy performed, in block sizes 3 and 6, respectively.

Participants were assigned in a 1:1:1 ratio to receive either daily 20 µg calcifediol, 3200 IU (80 µg) vitamin D3, or placebo in a blinded fashion, and were advised to take 1 capsule per day together with a meal. Participants were followed up for 6 months, and clinical visits occurred at baseline, 3, and 6 months. At follow-up visits, participants were assessed for trial outcome measures, adverse events, and compliance with the study medication and had laboratory tests performed. Study intervention ended at month 6, and a phone call at 7 months was conducted to ascertain any adverse events.

We assessed compliance with the treatment medication by pill count at each study visit, at 3 and 6 months. Treatment compliance was defined as taking at least 80% of the study medication and calculated using two different approaches: (1) The conservative approach, which considered failure to bring the pill bottle to the visit as having taken none of the study medication contained in the not returned bottle, and (2) the non-conservative approach, which considered failure to bring the pill bottle to the visit as having taken all the study medication contained in the not returned bottle.

Serum 25(OH)D concentrations were assessed at baseline and at 3 and 6 months follow-up. Serum calcium, serum creatinine, serum albumin, and urine calcium/creatinine ratio in spot urine were assessed in addition to screening and during subsequent visits. Adverse events were monitored by interviews at 3, 6, and 7 months.

DSM laboratories measured serum 25(OH)D by means of a sensitive and selective assay based on liquid chromatography coupled to tandem mass spectrometry detection (HPLC–MS/MS). The samples were centrifuged and stored at − 80 °C at the Centre on Aging and Mobility before and shipped to DSM laboratories for analysis at the end of the trial.

Outcomes

The primary endpoint was a composite measure of lower extremity function, assessed at baseline, 3, and 6 months. This composite measure, predefined in the study protocol, included four tests: gait speed (over a distance of 10 m), knee flexor and extensor strength, and repeated sit-to-stand test. The primary endpoint was defined as the probability of success (improvement or maintenance from baseline) in any of the eight tests, four tests at 3 months and four tests at 6 months. Therefore, the primary endpoint was binary and took on a value of 1 if the participant improved or maintained on a test component, and a value of 0 if declined in one test.

For gait speed, women were asked to walk 10 m at their usual pace. The test was repeated twice, and the faster of the

two measurements was used. Women were allowed to use a cane or other walking aid if needed. Knee flexor and extensor strength were measured in a seated position, with hips and knees at a 90° angle and the feet approximately 30 cm above the floor. The foot was placed in a foot strap, which was connected to a wall-mounted dynamometer through a chain. Arms were folded across the chest. For the knee flexor strength test, participants were asked to bend their knees as much as possible and pull as hard as possible against the resistance of the fixture. Knee extensor strength was measured using the same setting, but with the participant asked to straighten the leg and push against the resistance of the fixture. The test was repeated twice for each leg, with a 30-s break between attempts. Knee flexor and extensor strength were assessed as the mean strength of the right and left knees, determined from the maximum of two repeated strength tests on each knee. The repeated sit-to-stand test was measured as the time to complete five repetitions from an initial seated position and was completed when the participants reached the standing position of the fifth repetition. Women were asked to stand up from a chair five times as quickly as they could without stopping in between. Arms had to stay folded across their chest, and they had to sit with their back against the back of the chair.

Secondary outcomes included the individual components of the composite lower extremity battery and TUG at a normal and fast pace. TUG was measured by asking women to stand up from a chair, walk 3 m, walk around a mark on the floor, return to the chair, and sit down again. Women were asked not to use armrests (unless needed) while standing up and sitting down and were not allowed to be assisted by another person. Additionally, women were allowed to stop during the test but could not sit down. Women were given a trial run without timing prior to the actual measurements. Two measures were conducted: (1) women walking at their normal pace and (2) women walking as fast as they could.

Other assessments included cognitive function, assessed using the Montreal Cognitive Assessment (MoCA) [21]; quality of life and self-rated health, measured with the EuroQoL 5 Dimensions 3 Levels instrument [22]. Bone mineral density was measured using Dual-energy X-ray Absorptiometry (DXA; Lunar iDXA, GE Healthcare machines) and analyzed using enCORE software (Version 13.60.033).

Safety endpoints included serum levels of parathyroid hormone (PTH), calcium, creatinine, albumin, urine calcium/creatinine ratio, blood pressure, pulse rate, adverse events (AEs), and serious adverse events (SAEs). Except for AEs and SAEs, safety endpoints were assessed at baseline, 3, and 6 months.

AEs were assessed for causality related to the study intervention and categorized as "not related" when there is no reasonable possibility that the study intervention may have caused or contributed to the occurrence of the adverse event and "related" when there was a reasonable possibility that the intervention may have caused or contributed to the occurrence of the adverse event.

Sample size and statistical analysis

Based on our pilot study [15], we anticipated a 5% dropout rate and estimated that 40% of participants in the placebo group would maintain or improve their lower extremity function. With a sample size of 50 participants per group, the trial had 87% power to detect an odds ratio of at least 2.79 at a significance level of 0.05. Regarding the secondary endpoints, and also based on our pilot study [15], the study had more than 85% power to detect a mean difference between calcifediol and placebo groups of 42 Newtons (SD 38.3) in knee extensors strength and of 1.0 s (SD 1.6) in the repeated sit-to-stand test.

All assessments of treatment effects were based on the intent-to-treat principle. For the primary endpoint, a generalized estimating equations (GEE) model was used to compare the probability of success (improvement or maintenance) in any of the eight tests, four tests at 3 months and four tests at 6 months in the calcifediol group vs the vitamin D3 and placebo groups over 6 months. Changes over time in the secondary outcomes (Δ from baseline) were also compared between treatment groups using GEE.

Models were adjusted for age, BMI, bone status (osteopenia vs osteoporosis; stratification variable), baseline serum 25(OH)D levels, and time. For the secondary outcomes, models were additionally adjusted for the baseline outcome measure. An interaction between time and treatment group was tested. The main effects across all 6 months were derived from models without the interaction term for time, as interactions were not statistically significant (Supplementary file 1).

Additionally, the association between quartiles of achieved 25(OH)D levels and probability of success over 6 months was investigated in a post hoc analysis. The exposure of quartiles of achieved 25(OH)D levels was calculated based on the mean achieved 25(OH)D levels at months 3 and 6. A GEE model was used to assess the association of quartiles of achieved 25(OH)D levels and the probability of success adjusting for the same covariates as in the main analysis except for the treatment effects of calcifediol and vitamin D3 as both may be on the causal pathway. The interaction between the quartile of achieved 25(OH)D levels and the treatment group was tested by adding the interaction term in the model.

Statistical analyses were performed using SAS version 9.4 software (SAS Institute). All endpoints were tested at the 2-sided at 5% significance level, and no adjustments for multiple comparisons were applied.

Results

Recruitment and participant characteristics

Between September 2015 and May 2017, 426 expressed interest in the trial and were assessed for eligibility. A total of 152 women were enrolled and randomized to calcifediol ($n = 49$), vitamin D3 ($n = 52$), and placebo ($n = 51$). The CONSORT diagram of participant flow is presented in Fig. 1. The final follow-up visit was November 20, 2017.

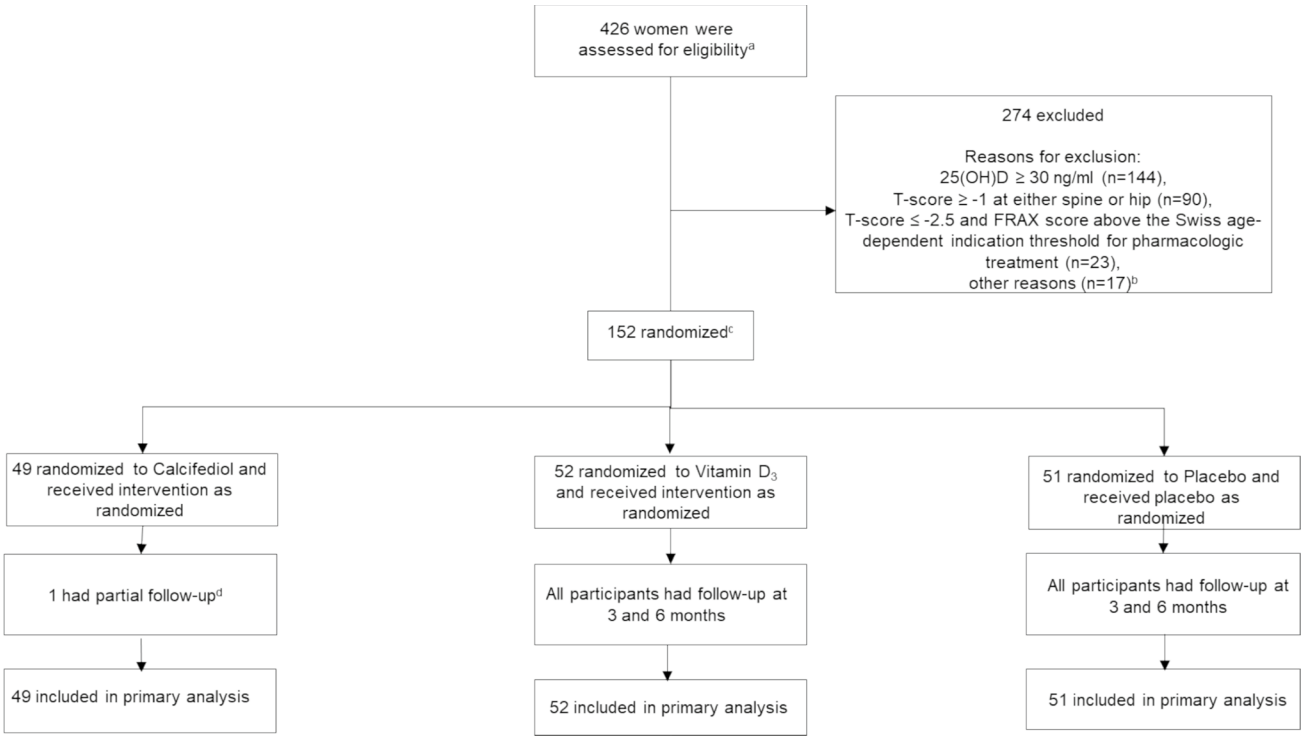
Baseline characteristics were balanced across the three treatment groups. The mean age was 61.0 (SD 4.7) years, mean BMI was 23.9 (SD 3.1) kg/m^2, mean serum 25(OH) D concentration was 23.4 (SD 7.9) ng/mL. Additionally, 34.4% had vitamin D deficiency (< 20 ng/mL, i.e., 50 nmol/L), and 98.0% were white. Overall, women had good cognitive function (mean MoCA score, 27.6 (SD 2.1); maximum of 30), 76.3% had osteopenia and 23.7% had osteoporosis based on DXA (Table 1).

At baseline, women had an overall mean of 1.5 (SD 0.2) m/s in the 10-m walk test, 147.5 (SD 34.8) Newtons in the knee flexor strength test, 284.6 (SD 73.6) Newtons in the knee extensor strength, 5.9 (SD 1.0) s in the TUG at fast pace, and median of 6.6 (IQR 5.3–7.9) s in the repeated sit-to-stand test (Table 1).

Retention and adherence

Only one woman (from the calcifediol group) withdrew from the study before the 6-month visit due to personal reasons (Fig. 1).

Overall, the proportion of participants with at least 80% compliance was 89.8% at 3 months and 74.8% at 6 months using the conservative approach and 98.0% at 3 months and 97.4% at 6 months using the non-conservative approach. There were no statistically significant differences in the



[a] A total of 426 women were assessed for eligibility, 274 were excluded, and 152 women were randomized 1:1:1 to receive either calcifediol 20 µg/day, or vitamin D3 3200 IU/day, or placebo. Excepted by one participant in the calcifediol group, all others had follow-up at 3 and 6 months. All 152 were included in the primary analysis.

[b] other reasons for exclusion included medical condition that would make the results of the tests and assessments unreliable and/or would put too much burden on the participant and/or lead to safety concerns, eg, regular alcohol consumption and/or opioid abuse.

[c] Stratified block randomization on a DXA-based diagnosis of osteopenia or osteoporosis, and consent for muscle biopsy (yes/no).

[d] One participant had a follow-up visit at 3 months only. The reason for dropout was withdraw of consent.

Fig. 1 Flow of participants in the trial

Table 1 Baseline characteristics of study population[a]

Characteristic	Overall ($n=152$)[b]	Calcifediol ($n=49$)	Vitamin D3 ($n=52$)	Placebo ($n=51$)	P-value[c]
Age (years), mean (SD)	61.0 (4.7)	61.6 (4.8)	60.3 (4.2)	61.1 (5.2)	0.42
BMI (kg/m^2), mean (SD)	23.9 (3.1)	24.5 (2.8)	23.3 (3.0)	23.8 (3.3)	0.15
Ethnicity (white), *n* (%)	149 (98.0)	48 (98.0)	50 (96.2)	51 (100.0)	0.37
10-Meter walk speed (m/s), mean (SD)[d]	1.5 (0.2)	1.5 (0.2)	1.5 (0.2)	1.5 (0.2)	0.95
Repeated sit-to-stand (sec), median (IQR)[e]	6.6 (5.3–7.9)	6.8 (5.3–8.3)	6.9 (5.6–8.1)	6.4 (5.1–7.8)	0.74
Knee flexor strength (Newtons), mean (SD)[f]	147.5 (34.8)	147.8 (38.8)	148.4 (31.6)	146.1 (34.4)	0.94
Knee extensor strength (Newtons), mean (SD)[f]	284.6 (73.6)	287.0 (85.1)	279.0 (65.7)	288.0 (70.1)	0.79
Timed up-and-go test at a normal pace (sec), median (IQR)[g]	7.4 (6.9–8.1)	7.7 (7.0–8.2)	7.3 (6.9–8.1)	7.4 (6.5–8.1)	0.81
Timed up-and-go test at fast pace (sec), mean (SD)[g]	5.9 (1.0)	6.0 (1.1)	5.9 (0.8)	5.8 (1.1)	0.72
Montreal cognitive assessment, mean (SD)[h]	27.6 (2.1)	27.4 (2.4)	27.3 (2.0)	28.1 (2.0)	0.11
Health-related quality of life score, median (IQR)[i]	1.0 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.0)	0.96
Self-rated health score, median (IQR)[j]	90.0 (81.0–94.0)	90.0 (80.0–95.0)	90.0 (81.0–94.5)	90.0 (81.0–92.0)	0.74
Serum 25-hydroxyvitamin D (ng/mL), mean (SD)[k]	23.4 (7.9)	23.5 (8.2)	22.4 (8.3)	24.3 (7.1)	0.46
Vitamin D deficiency (serum 25(OH)D < 20 ng/mL), *n* (%)[k]	52 (34.4)	18 (37.5)	21 (40.4)	13 (25.5)	0.24
DXA[l]					
BMD total hip (g/cm^2)	0.82 (0.08)	0.84 (0.07)	0.81 (0.07)	0.82 (0.09)	0.21
BMD femur neck (g/cm^2)	0.79 (0.07)	0.81 (0.07)	0.78 (0.06)	0.78 (0.08)	0.09
BMD spine (g/cm^2)	0.99 (0.12)	1.00 (0.12)	0.99 (0.13)	0.98 (0.12)	0.72
Osteoporotic status[l]					0.96
Osteopenia	116 (76.3)	38 (77.6)	39 (75.0)	39 (76.5)	
Osteoporosis	36 (23.7)	11 (22.5)	13 (25.0)	12 (23.5)	

Abbreviations: *BMD* bone mineral density, *BMI* body mass index, *DXA* dual-energy X-ray absorptiometry, *IQR* interquartile range, *PTH* parathyroid hormone, *SD* standard deviation; *sec* seconds

[a]Medians and IQRs are presented for variables with skewness > 1.5

[b]There was one missing measurement for repeated sit-to-stand, knee flexor and extensor strength, self-rated health, serum 25-hydroxyvitamin D, and BMD total hip and femur neck. The missing measurement was in the vitamin D3 group for knee flexor and extensor strength and in the calcifediol group for other measures

[c]*P*-values are from ANOVA, Kruskal–Wallis, and chi-square tests for normally distributed continuous variables, non-normally distributed continuous variables, and categorical variables, respectively

[d] Participants were asked to walk 10 m twice, and the fastest of the two measurements was used. Lower values mean less time to complete the walk and therefore are better

[e]Repeated sit-to-stand test assesses reaction time and was determined as the minimum of two repeated sit-to-stand tests. Lower values mean less time to complete the stands and therefore are better

[f]Knee flexor and extensor strength was assessed as the mean strength of the right and left knees, determined from the maximum of 2 repeated strength tests on each knee. Higher values mean greater strength and therefore are better

[g]Timed up-and-go test was measured as the time needed to stand up from a chair, walk 3 m, return to the chair, and sit down again. Lower values mean less time to complete the task and therefore are better. Two measures were conducted: (1) women walking at their normal pace and (2) women walking at fast as they could

[h]The Montreal Cognitive Assessment [21] was used to assess cognitive decline. Range 0–30 (higher scores are better). Scores lower than 26 indicating mild cognitive impairment

[i]EuroQol 5 Dimensions 3 Levels (EQ-5D-3L) assesses health-related quality of life [22]. Scores range from less than 0 to a maximum of 1 point, where 0 means health state equivalent to death, negative values are equivalent to a health state as worse than death, and 1 is equivalent to perfect health

[j]Self-rated health was assessed by the EQ-5D-3L vertical visual analog scale, which ranges from 0 to 100 points, where higher scores are better

[k]The blood samples of one participant taken at baseline were destroyed by mistake, i.e., the subject does not have blood values at baseline

[l]Bone mineral density was measured using dual-energy X-ray absorptiometry (DXA; Lunar iDXA, GE Healthcare machines) and analyzed using enCORE software (Version 13.60.033). A *T*-score at the spine and/or total hip between < -1.0 and > -2.5 was defined as osteopenia and a *T*-score of ≤ -2.5 as osteoporosis. The lowest value between the *T*-score at the spine and total hip was used for classification

proportion of participants with 80% compliance between the treatment groups at each time point using both approaches (Supplementary file 2).

At baseline, serum 25(OH)D levels were similar between the treatment groups (mean range, 23.4–24.3 ng/mL, Supplementary file 3). The average achieved 25(OH)D levels in the calcifediol group were 80.8 ng/mL at 3 months and 84.3 ng/mL at 6 months. The average achieved 25(OH)D levels in the vitamin D3 group were 51.0 ng/mL at 3 months and 55.2 ng/mL at 6 months. The placebo group also experienced an increase in serum 25(OH)D levels from 24.3 ng/mL at baseline to 28.8 ng/mL at 3 months and 33.3 ng/mL at 6 months (Supplementary file 3). Notably, most participants initiated treatment during the winter and spring seasons, with 67.10% starting between December and March, which could account for the rising levels of 25(OH)D in the placebo group throughout the 6-month trial period.

Primary and secondary endpoints

Overall, there was a slight, but not statistically significant, decrease in the probability of success (improvement or maintenance) from baseline to 3 and 6 months in any of the 8 tests across all groups, except for the vitamin D3 group, which experienced a small, but not statistically significant increase (Fig. 2).

The adjusted probability of success in any of the eight tests was 53.6% (95% confidence interval [47%, 60%]) with calcifediol, 55.5% ([50%, 61%]) with vitamin D3, and 61.4% ([55%, 67%]) with placebo, without significant differences between treatment groups (Table 2).

There was no significant difference between treatment groups on changes from baseline in the secondary endpoints over 6 months (Table 3).

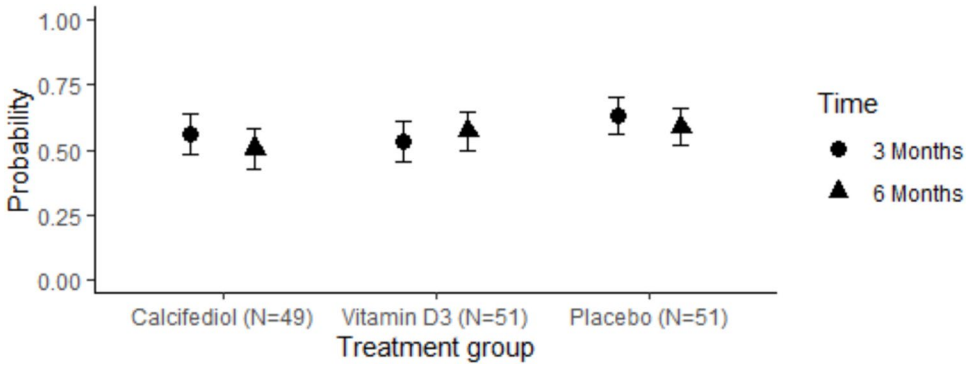


Fig. 2 Unadjusted probability (95% CI)[a] of success in any of the eight tests[b] by treatment group at 3 and 6 months. [a]Estimates are from GEE models adjusted for time, and interaction terms for treatment group and time. The *P*-values for treatment group, time, and treatment group*time interaction were 0.18, 0.44, and 0.31, respectively. [b]The primary endpoint was a composite measure of lower extremity function including four tests: gait speed, knee flexor and extensor strength, and repeated sit-to-stand test. The primary endpoint was the probability of success (improvement or maintenance) in any of the eight tests, four tests at 3 months and four tests at 6 months

Table 2 Adjusted probability of success[a] in any of the 8 tests by treatment group over 6 months

	Calcifediol ($n=49$)[b]	Vitamin D3 ($n=52$)[b]	Placebo ($n=51$)[b]	*P*-value overall	Calcifediol vs placebo *P*-value	Calcifediol vs vitamin D3 *P*-value	Vitamin D3 vs placebo *P*-value
Probability of success in any of the **eight tests** (95% CI) over 6 months[c]	0.54 (0.47, 0.60)	0.56 (0.50, 0.62)	0.61 (0.55, 0.67)	0.18	0.08	0.65	0.15

Abbreviation: *CI* confidence interval

[a]The primary endpoint was a composite measure of lower extremity function including four tests: gait speed, knee flexor and extensor strength, and repeated sit-to-stand test. The primary endpoint was the probability of success (improvement or maintenance) in any of the eight tests, four tests at 3 months and four tests at 6 months

[b]Number of participants at baseline

[c]Estimates are from GEE models adjusted for baseline age, body mass index, osteoporotic status, 25(OH)D levels, time, and interaction term for treatment group and time. The *P*-value for treatment group*time interaction was 0.31; therefore, the interaction term was omitted from the main model

Table 3 Treatment effect on the secondary endpoints

	Calcifediol ($n=49$)	D_3 ($n=52$)	Placebo ($n=51$)	Calcifediol vs placebo difference (95% CI) *P*-value	Calcifediol vs vitamin D3 difference (95% CI) *P*-value	Vitamin D3 vs placebo difference (95% CI) *p*-value
Knee flexor strength, Newton						
Unadjusted at baseline, mean (SD)	147.81 (38.78)	148.44 (31.62)	146.13 (34.44)			
Adjusted change from baseline, mean (95% CI)[a]						
Month 3	4.15 (−1.72, 10.03)	3.10 (−3.24, 9.44)	7.65 (1.70, 13.60)	−3.49 (−11.86, 4.87), $P=0.41$	1.06 (−7.63, 9.74), $P=0.81$	−4.55 (−13.35, 4.25), $P=0.31$
Month 6	3.25 (−4.08, 10.59)	3.27 (−3.36, 9.91)	11.99 (5.55, 18.42)	−8.74 (−18.46, 0.99), $P=0.08$	−0.02 (−9.96, 9.92), $P=1.00$	−8.71 (−18.08, 0.65), $P=0.07$
Average over 6 months	3.73 (−2.43, 9.89)	3.18 (−2.73, 9.10)	9.82 (4.10, 15.54)	−6.09 (−14.48, 2.29), $P=0.15$	0.54 (−8.05, 9.13), $P=0.90$	−6.64 (−14.99, 1.72), $P=0.12$
Knee extensor strength, Newton[b]						
Unadjusted at baseline, mean (SD)	287.03 (85.09)	278.96 (65.72)	288.04 (70.10)			
Adjusted change from baseline, mean (95% CI)[a]						
Month 3	−8.07 (−20.73, 4.58)	−17.80 (−30.36, −5.24)	−6.24 (−17.22, 4.74)	−1.83 (−18.62, 14.95), $P=0.83$	9.73 (−8.25, 27.70), $P=0.29$	−11.56 (−28.33, 5.21), $P=0.18$
Month 6	−12.54 (−24.60, −0.48)	4.02 (−11.58, 19.62)	−2.20 (−12.56, 8.15)	−10.34 (−26.37, 5.69), $P=0.21$	−16.57 (−36.58, 3.45), $P=0.10$	6.22 (−12.51, 24.96), $P=0.51$
Average over 6 months	−10.22 (−20.82, 0.39)	−6.90 (−19.53, 5.74)	−4.22 (−12.79, 4.35)	−6.00 (−19.73, 7.73), $P=0.39$	−3.32 (−20.07, 13.42), $P=0.70$	−2.68 (−18.00, 12.65), $P=0.73$
Gait speed, m/s						
Unadjusted at baseline, mean (SD)	1.507 (0.178)	1.510 (0.152)	1.517 (0.168)			
Adjusted change from baseline, mean (95% CI)[a]						
Month 3	0.028 (−0.011, 0.066)	−0.012 (−0.045, 0.021)	0.024 (−0.024, 0.072)	0.003 (−0.058, 0.065), $P=0.92$	0.040 (−0.011, 0.091), $P=0.13$	−0.037 (−0.095, 0.021), $P=0.22$
Month 6	0.031 (−0.009, 0.071)	0.018 (−0.015, 0.051)	0.023 (−0.012, 0.059)	0.007 (−0.046, 0.061), $P=0.79$	0.013 (−0.039, 0.065), $P=0.63$	−0.005 (−0.054, 0.043), $P=0.83$
Average over 6 months	0.029 (−0.006, 0.064)	0.003 (−0.025, 0.031)	0.024 (−0.009, 0.057)	0.005 (−0.043, 0.054), $P=0.83$	0.026 (−0.019, 0.072), $P=0.26$	−0.021 (−0.064, 0.022), $P=0.34$
Repeated sit-to-stand, s						
Unadjusted at baseline, mean (SD)	7.16 (2.37)	6.89 (1.75)	6.79 (2.24)			
Adjusted change from baseline, mean (95% CI)[a]						
Month 3	−0.39 (−0.82, 0.04)	−0.22 (−0.60, 0.16)	−0.39 (−0.72, −0.07)	0.00 (−0.54, 0.55), $P=0.99$	−0.17 (−0.74, 0.41), $P=0.57$	0.17 (−0.33, 0.67), $P=0.50$
Month 6	0.18 (−0.38, 0.73)	−0.32 (−0.68, 0.05)	−0.35 (−0.68, −0.02)	0.53 (−0.11, 1.16), $P=0.11$	0.49 (−0.17, 1.15), $P=0.14$	0.03 (−0.46, 0.52), $P=0.89$
Average over 6 months	−0.11 (−0.48, 0.26)	−0.27 (−0.58, 0.04)	−0.37 (−0.61, −0.13)	0.26 (−0.18, 0.71), $P=0.25$	0.16 (−0.32, 0.64), $P=0.51$	0.10 (−0.29, 0.49), $P=0.61$
Up-and-go time normal pace, s						
Unadjusted at baseline, mean (SD)	7.84 (1.74)	7.47 (0.89)	7.52 (1.20)			
Adjusted change from baseline, mean (95% CI)[a]						
Month 3	−0.21 (−0.47, 0.05)	0.21 (−0.19, 0.61)	−0.01 (−0.32, 0.30)	−0.20 (−0.61, 0.21), $P=0.33$	−0.42 (−0.90, 0.06), $P=0.08$	0.22 (−0.29, 0.72), $P=0.40$
Month 6	−0.11 (−0.45, 0.23)	−0.08 (−0.29, 0.13)	−0.03 (−0.25, 0.19)	−0.08 (−0.49, 0.33), $P=0.70$	−0.03 (−0.43, 0.36), $P=0.88$	−0.05 (−0.35, 0.25), $P=0.75$

Table 3 (continued)

	Calcifediol ($n=49$)	D_3 ($n=52$)	Placebo ($n=51$)	Calcifediol vs placebo difference (95% CI) *P*-value	Calcifediol vs vitamin D3 difference (95% CI) *P*-value	Vitamin D3 vs placebo difference (95% CI) *p*-value
Average over 6 months	−0.16 (−0.40, 0.08)	0.07 (−0.16, 0.29)	−0.02 (−0.23, 0.19)	−0.14 (−0.47, 0.18), $P=0.39$	−0.23 (−0.56, 0.10), $P=0.18$	0.08 (−0.22, 0.39), $P=0.59$
Up-and-go time fast pace, s						
Unadjusted at baseline, mean (SD)	5.99 (1.13)	5.93 (0.84)	5.83 (1.07)			
Adjusted change from baseline, mean (95% CI)[a]						
Month 3	−0.03 (−0.22, 0.16)	0.17 (0.02, 0.33)	0.15 (−0.09, 0.39)	−0.18 (−0.49, 0.13), $P=0.27$	−0.20 (−0.44, 0.04), $P=0.10$	0.02 (−0.27, 0.32), $P=0.87$
Month 6	0.10 (−0.11, 0.32)	0.01 (−0.15, 0.16)	−0.03 (−0.22, 0.16)	0.14 (−0.15, 0.42), $P=0.35$	0.10 (−0.17, 0.36), $P=0.47$	0.04 (−0.21, 0.28), $P=0.76$
Average over 6 months	0.04 (−0.14, 0.21)	0.09 (−0.04, 0.22)	0.06 (−0.14, 0.25)	−0.02 (−0.28, 0.24), $P=0.87$	−0.05 (−0.27, 0.16), $P=0.62$	0.03 (−0.21, 0.27), $P=0.80$

[a]Estimates are from generalized linear models adjusted for baseline age, BMI, osteoporotic status, time, baseline 25(OH)D levels, and baseline level of the outcome

[b]There was a significant treatment*time interaction at $P=0.02$ only for the outcome of knee extensor strength

Safety endpoints

A total of 212 AEs occurred, of which 7 were serious (Supplementary file 4). There was no statistically significant difference in the number of AEs between the calcifediol group and placebo (80 vs 77, $P=0.47$). However, there was a greater number of AEs in the calcifediol group compared to the vitamin D3 group (80 vs 55, $P=0.02$). There was no AE resulting in death, withdrawal, or hypercalcemia during the study period. Among the 7 serious adverse events, none was categorized as possibly related to the study intervention.

There were no statistically significant differences among the treatment groups in serum levels of PTH, creatinine, or albumin, or for urine calcium-creatinine ratio, blood pressure, or pulse at baseline, 3, and 6 months (Supplementary file 5–10). For serum levels of calcium, women in the calcifediol group had, on average, higher mean levels than those in the vitamin D3 and placebo groups (Supplementary file 11).

Post hocanalysis

The overall mean achieved 25(OH)D level across 3 and 6 months was 55 ng/mL. In the calcifediol, vitamin D3, and placebo groups, the mean achieved 25(OH)D levels across 3 and 6 months were 82.5 ng/mL, 53.1 ng/mL, and 30.9 ng/mL, respectively (Supplementary file 12).

There was no significant difference in the probability of success by quartile of achieved 25(OH)D levels (Supplementary file 13). Additionally, there was no significant interaction between the treatment group and quartile of achieved 25(OH)D level (*P*-value for the interaction was 0.25).

Discussion

In this 6-month trial of 152 postmenopausal women with osteopenia or osteoporosis, supplementation with 20 µg/day of calcifediol exhibited no greater benefit compared to supplementation with 3200 IU/day of vitamin D3 or placebo for improvement or maintenance of lower extremity function. Additionally, we could not find evidence of a beneficial effect of calcifediol on the secondary outcomes of knee flexor and extensor strength, gait speed, repeated sit-to-stand time, and TUG tests compared to vitamin D3 and placebo over 6 months.

Notably, only six small RCTs (sample size range, 20–107; duration range, 4–7 months) have investigated the effect of calcifediol on lower extremity function [12, 23], and only one tested the effect of calcifediol against placebo to date [24]. In line with our findings, the latter did not find a significant benefit of daily supplementation with 10 µg of calcifediol vs daily supplementation with 800 IU of vitamin D3 on muscle strength among 78 at least prefrail community-dwelling older adults over 6 months (mean age 74 years, 45% women, mean baseline 25[OH]D level 15.08 ng/mL) [24].

In contrast, however, a 6-month open-label randomized trial including 107 postmenopausal women with serum 25(OH)D levels between 8 to 24 ng/mL found significantly greater improvement of lower extremity function (assessed by the TUG and repeated sit-to-stand tests; no effect sizes reported) in participants treated with weekly calcifediol 175 µg, compared to those treated with different vitamin D3 dosages (a single dose of 300,000 IU, bimonthly 100,000 IU, or weekly 7000 IU) [13]. Similarly, in our previous 4-month

RCT among 20 postmenopausal women, daily supplementation with 20 µg of calcifediol led to a 2.8-fold increased odds of maintained or improved lower extremity function compared with daily supplementation with 800 IU of vitamin D3 [15]. Despite these earlier trials, the evidence of calcifediol effects on lower extremity function is still scarce, and no standard dosage of calcifediol has been defined to date [12].

Our hypothesis that calcifediol may have a greater beneficial effect on lower extremity function over vitamin D3 is supported by its higher efficiency to increase and sustain serum 25(OH)D levels [15, 18, 25]. Although our dosage strategy aimed to achieve comparable 25(OH)D levels across the calcifediol and vitamin D3 groups, we observed a greater increase in serum 25(OH)D levels in the calcifediol group compared to the vitamin D3 group over the study period, despite the high dose of 3200 IU/day of vitamin D3. Calcifediol's greater potency in raising and sustaining serum 25(OH)D levels can be explained by its pharmacokinetic profiles. Compared to vitamin D3, calcifediol is better absorbed in the intestine and has a better solubility profile which leads to a greater bioavailability [25]. In fact, vitamin D3 bioavailability is only 36–45% of calcifediol bioavailability [18]. Moreover, vitamin D3 conversion to 25(OH)D mainly depends on the liver enzyme CYP2R1, an enzyme that may be influenced by other medications, liver diseases, as well as genetic polymorphisms [25, 26].

An increase in serum 25(OH)D levels is expected to improve lower extremity function based on in vitro and in vivo studies including both animal and human subjects [2, 8, 27]. Vitamin D receptors are expressed in muscle tissue, with expression upregulated by muscle damage [27]. In vitro studies demonstrate the positive impact of vitamin D on myoblast differentiation, proliferation, myotube formation, maintenance, and size [27]. Further, vitamin D is involved in intracellular calcium movement, oxidative stress, atrophy signaling, and protein turnover in muscle [27]. Interestingly, findings from animal models suggest that muscle may also operate as a dynamic storage for vitamin D, which may regulate serum 25(OH)D levels when sun exposure is low [27]. Moreover, muscle weakness, hypotonia, and falls are clinical consequences commonly observed in individuals with prolonged severe vitamin D deficiency [2, 8].

However, we did not observe differences in the probability of success by quartile of achieved 25(OH)D levels, which aligns with the findings from a 2021 meta-analysis of 54 RCTs (8747 individuals) [11]. In that meta-analysis, no beneficial effect of vitamin D2 or D3 supplementation on lower extremity function, as measured by SPPB, walking distance, knee extensor strength, and repeated sit-to-stand time, was found [11]. In fact, a potential harmful effect of vitamin D supplementation was observed for knee flexor strength (mean difference − 3.3 [95% CI − 6.63, − 0.03] Newtons, 636 participants) and TUG (mean difference 0.15 [95% CI 0.03, 0.26] s, 5223 participants) [11]. However, these findings should be interpreted with caution, as RCTs included participants regardless of age, vitamin D3 or D2 administration form, dosage, or duration.

Young postmenopausal women with osteopenia and a FRAX score below pharmacologic treatment indication have limited treatment options for the prevention of osteoporosis or treatment of osteopenia [28, 29]. Current evidence-based recommendations focus on the population at very high risk for fractures [28, 29], and recommendations for individuals at lower risk for fractures are limited to lifestyle advice [29]. Furthermore, the safety of first-line treatment of osteoporosis, bisphosphonates, has been questioned [30] as long-term use of these medications is associated with an increased risk of rare complications including atypical femur fractures [31, 32], delayed fracture union [33, 34], and osteonecrosis of jaw [35, 36].

Decreased lower extremity function is a global concern as it can negatively impact individuals' intrinsic capacity [37], functional abilities [38], independent aging [39], and quality of life [40]. Furthermore, poor lower extremity function is associated with an increased risk of fractures [41], healthcare costs [42], and mortality [43]. Therefore, therapeutic options to prevent and treat impaired muscle function are timely. In this regard, supplementation with calcifediol may be relevant in individuals in need of a faster increase in 25(OH)D levels, with liver disease, malabsorptive gastrointestinal conditions, or in use of drugs that compete for metabolism by the liver enzyme CYP2R1.

To the best of our knowledge, this is the first trial designed to test the effect of calcifediol vs a high dose of vitamin D3 and placebo on lower extremity function among postmenopausal women [12]. In fact, prior trials were powered to test the effect of calcifediol vs vitamin D3 on the serum 25(OH)D increase, or reported the benefit of calcifediol on muscle function change from baseline values [12–15, 44, 45]. Moreover, our findings suggest that 20 µg/day of calcifediol and 3200 IU/day of vitamin D3 are safe and effective with regard to hypercalcemia and mortality, and the increase in 25(OH)D levels. Other strengths of our study include a high retention rate with only one withdrawal, no deaths, and high adherence to the study interventions measured by pill count and serum 25(OH)D levels.

This study has limitations. Only 34.4% of women had baseline 25(OH)D levels < 20 ng/mL, and participants were allowed to take up to 800 IU/day of vitamin D3 during the trial. Additionally, there was an increase in the mean serum 25(OH)D levels in the placebo group during the trial, from 24.3 ng/mL at baseline to 33.3 ng/mL at 6 months. These factors may have limited our ability to detect the effect of calcifediol and/or vitamin D3 on the study outcomes. Lastly, since women were generally healthy and vitamin D sufficient (> 60% had serum 25(OH)D ≥ 20 ng/mL), our findings may not be

generalizable to frail, older populations with vitamin D deficiency (serum 25(OH)D < 20 ng/mL) who could benefit from the study interventions.

Conclusion

Our findings do not support supplementation with daily calcifediol or high-dose daily vitamin D3 for the improvement or maintenance of lower extremity function among younger postmenopausal women (age 50–70) with osteopenia or osteoporosis, who were pre-selected for vitamin D insufficiency or deficiency (25(OH)D < 30 ng/mL; baseline mean 25(OH)D 23.4 ng/mL).

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Data Availability Data described in the manuscript, code book, and analytic code will not be made available to allow primary researchers to fully exploit the dataset. The data will be made available to external researchers in a second step according to a controlled access system.

Declarations

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Conflict of interest Heike A. Bischoff-Ferrari reports grants from the European Commission (grant agreement no. 278588), the University of Zurich, NESTEC, Pfizer Consumer Healthcare, Streuli Pharma, plus non-financial support from dsm-firmenich AG, and Roche Diagnostics. Furthermore, Heike A. Bischoff-Ferrari reports speaker fees from Wild, Pfizer, Vifor, Mylan, Roche Diagnostics, and independent and investigator-initiated grants from Pfizer and from Vifor, outside the submitted work.
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