

Rapid correction of low vitamin D status in nursing home residents

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Abstract

Summary This prospective study finds that ergocalciferol 50,000 IU three times weekly for four weeks effectively and safely corrects vitamin D inadequacy in nursing home residents.

Introduction Low vitamin D status is common among nursing home residents and contributes to bone loss, falls and fractures. The objective of this study was to evaluate the efficacy and safety of short course, high dose, oral vitamin D₂ (ergocalciferol) treatment.

Methods This prospective study included 63 nursing home residents. The 25 with low vitamin D status (serum 25(OH)D ≤ 25 ng/ml) received oral ergocalciferol 50,000 IU three times weekly for four weeks; the others received no change to their routine care. Serum total 25(OH)D, 25(OH)D₂, 25(OH)D₃, calcium, parathyroid hormone (PTH), bone turnover markers and neuro-cognitive assessments were obtained at baseline and four weeks.

Results Mean total 25(OH)D concentration increased ($p < 0.0001$) from 17.3 to 63.8 ng/ml in the treated group and remained unchanged in the comparison group. Serum 25(OH)D₃ remained stable in the comparison group, but declined ($p < 0.0001$) with D₂ treatment from 15.4 to 9.1 ng/ml. Serum

PTH trended down in the treatment group ($p = 0.06$). No treatment-induced improvement in ambulation, cognition or behavior was observed. No hypercalcemia or other adverse effects were observed with ergocalciferol treatment.

Conclusion Four weeks of oral vitamin D₂ supplementation effectively and safely normalizes serum 25(OH)D in nursing home residents.

Keywords Deficiency · Nursing home · Repletion · Vitamin D · 25(OH)D

Introduction

Vitamin D inadequacy is a multifactorial problem common in the general population due to low dietary intake, avoidance of sun exposure, inadequate supplementation and presence of other comorbidities [1–3]. In nursing home residents, low dietary vitamin D intake [4] reduced skin capacity to produce vitamin D with advancing age [5], and minimal sun exposure make vitamin D deficiency extremely common in this population [6, 7]. In older adults, vitamin D deficiency is associated with muscle weakness, bone loss, falls and fractures [8, 9]. Given the high prevalence of both vitamin D deficiency and osteoporosis among nursing home residents, which contributes to their extremely high fracture risk [10–12], it is logical that rapid correction of vitamin D inadequacy would reduce the morbidity, mortality and expense of osteoporosis [13] associated with falls and fractures in this population.

Optimizing vitamin D status may well have beneficial effects not limited to the musculoskeletal system [14]. For example, vitamin D receptors and the enzymes necessary to produce active vitamin D (1, 25 dihydroxyvitamin D) are present in many tissues [15, 16], implying that local

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vitamin D production (with autocrine/paracrine action) has importance in addition to the classical (endocrine) effects. Consistent with this, recent work documents beneficial effects of vitamin D repletion on immune function [17, 18] and cancer risk [19]. Additionally, active vitamin D produced in neurons could be postulated to have clinically relevant effects on cognitive function and behavior, as supported by recent clinical studies showing positive correlations of memory test scores and mood with serum 25-hydroxyvitamin D [25(OH)D] concentration [20, 21].

Despite the scope of this nutritional problem among nursing home residents [6, 22, 23] and potential personal and societal benefits of vitamin D repletion, provision of adequate amounts of vitamin D in this population is far from universal [24, 25]. This plausibly reflects inadequate study of approaches to guide clinicians when prescribing supplements to optimize vitamin D status for older adults [26]. As such, the purpose of this study was to assess the efficacy and safety of a short course of treatment with oral ergocalciferol (vitamin D₂). We evaluated treatment effectiveness with regard to the obtained serum concentration of 25(OH)D, markers of bone health, cognition and gait speed in nursing home patients.

Materials and methods

Study criteria and participants

Eligible participants were individuals residing in one of eight nursing homes in northeast or south-central Wisconsin for \geq six months duration. The nursing homes were selected based on the location of patients cared for by the physicians assisting with this study. Potential study participants capable of ambulation and able to answer questions were identified either by their primary care physician or nursing home medical director and approached to consider study participation by nursing home staff; consent was obtained either from the study subject or guardian. For those participants unable to provide consent, study assent was obtained. Participants had to be capable of ambulation independently, or with assistance, and be able to answer questions. The majority of study participants, (50/63, 79%) initiated study participation from October through March. As such, no cutaneous vitamin D production could have occurred for these individuals; moreover, due to the frail nature of these subjects, minimal additional cutaneous exposure would be expected. This study was reviewed and approved by the University of Wisconsin Health Sciences IRB.

Exclusion criteria consisted of a history of renal failure (serum creatinine >2.0 mg/dl) diagnosis of liver failure; known malabsorption (e.g., celiac sprue or radiation enteritis); known disorders of parathyroid function, hypercalcemia, hypocalcemia or other abnormalities of calcium

or phosphate metabolism; known history of vitamin D intoxication and granulomatous diseases (e.g., sarcoidosis or tuberculosis). No calcium or vitamin D intake limitation was specified in the study protocol.

Study design and conduct

The study was designed as a pre-post study in nursing home residents with vitamin D replete subjects constituting a comparison group. At baseline, clinical laboratory parameters were measured and a functional assessment was performed by the investigative staff on all participants at their nursing home of residence. All blood specimens were obtained in a non-fasting state between 0800 and 1100 on the same day as the other assessments. Functional assessments were performed between 0800 and 1300, after the patients had dressed and eaten at least one meal that day.

The ambulation functional assessment consisted of two trials of a timed 4-meter walk test [27] that were administered by research personnel. Participants were allowed to use an assistive device such as a cane or walker for ambulation. Gait belts were used when appropriate to assure participant safety; however, no human assistance was allowed for completion of the 4-meter walk. The faster time of the two trials was used for analysis.

An investigative team physician (RP or NB) performed cognitive testing using the clock drawing test (CDT) and semantic fluency test (SFT) [28]. The CDT, a clinical screening tool for visuo-spatial and constructional disabilities [29] is widely used in the study of dementia; the animal naming SFT has been shown to have better sensitivity and specificity than the Mini-Mental State Examination for identifying dementia [30]. The CDT involved asking the resident to draw the face of a clock, fill in the numbers, and set the hands for "ten past eleven". The test used a free-hand format in that a circle was not provided to the subject; instructions were given sequentially, such that the subject was asked to put in the hands, for example, only after the numbers were placed. A ten point scoring system was used, with ten being given for a perfectly drawn clock with the hands properly placed and of proper proportionate size [31]. The SFT involved asking the participants to name as many animals as possible in 60 seconds. The score was the total number of animals named minus the number of repeats.

The neuropsychiatric inventory (NPI) was used to assess 10 behavioral disturbances (delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy and aberrant motor activity) that may occur in cognitively impaired individuals [32]. A nursing home staff member familiar with each participant completed the NPI questionnaire. Answers given were based on each participant's behavior over the 30 days prior to completion of the questionnaire.

Vitamin D treatment

Eligible participants with low vitamin D status (defined for this study as serum 25(OH)D \leq 25 ng/ml) on their baseline assessment received ergocalciferol (vitamin D₂) 50,000 IU (Pliva; Zagreb, Croatia), three times a week for four weeks in an unblinded fashion. The ergocalciferol, commercially available by prescription in the United States, was dispensed from each nursing home pharmacy in routine clinical manner. The comparison participants (those with serum 25(OH)D values above 25 ng/ml) received no increase of vitamin D supplementation over what they were receiving at baseline and placebo was not administered.

The investigative team revisited all participants following completion of the 12 ergocalciferol doses (5–6 weeks after baseline assessment) at which time blood was obtained between the hours of 0800–1100 and the functional assessments noted above were repeated. The investigative staff was blinded to treatment group assignments. Nursing home staff completed the NPI questionnaire prior to this follow-up visit and at three months after the baseline assessments.

Laboratory results

Serum 25(OH)D concentration was measured by liquid chromatography mass spectroscopy at a regional clinical laboratory in routine clinical manner. The regional laboratory self-reported inter-assay percent CV for this assay ranges from 8% at high 25(OH)D concentrations to 11% at low 25(OH)D concentrations. Other analytes were measured at the UW Osteoporosis Clinical Research laboratory using commercially available kits as follows: serum parathyroid hormone (PTH; ELISA, Immunodiagnostic Systems, Fountain Hills, AZ), bone specific alkaline phosphatase (BSAP; ELISA, Quidel/Metra, San Diego, CA) and n-telopeptide of type I collagen (NTx; ELISA, Ostex International, Seattle, WA). Intra- and inter-assay % CV's for these analytes are as follows: PTH, 5%/7%; BSAP, 8%/5%; and NTx 5%/8%. To minimize variability, serum from all timepoints for each individual were run on the same assay kit. Serum chemistry determinations were performed in routine clinical manner using a Roche Integra autoanalyzer at a regional clinical laboratory (General Medical Laboratories, Madison, WI).

Statistical analyses

Baseline comparisons were performed using an unpaired T-test. Change in outcome measures over time was evaluated by repeated measures ANOVA. All analyses were performed using Statview software (Cary, NC). These analyses were prospectively defined.

Results

Study enrollment and group assignment

Sixty-seven potential participants were identified by their physicians at eight nursing homes in Wisconsin for study and had baseline assessments performed from September 2004 to July 2006. Sixty-three (47 women and 16 men) met all inclusion criteria and were enrolled. Of these, 61 (95%) completed both the baseline and follow-up assessments. Low vitamin D status was common with 25/63 (40%) having a serum 25(OH)D concentration \leq 25 ng/ml. The mean age of study participants was 87 (range 42–100 years); 47 (73%) were female. No between group (vitamin D treatment vs. comparison) differences in age, serum calcium, creatinine, BSAP, NTx or walk time were observed at baseline (Table 1). Of the entire cohort, 27 (43%) were receiving oral calcium and 29 (46%) oral vitamin D supplements. Interestingly, 85% (23/27) of those receiving calcium and 86% (25/29) of those receiving vitamin D were in the comparison group. Of the 29 individuals receiving vitamin D supplements, 27 were receiving 375–1000 IU daily.

Outcome measures

Serum 25-hydroxyvitamin D

The mean total 25(OH)D increased ($p < 0.0001$) with vitamin D₂ treatment from 17.3 (1.2) ng/ml at baseline to 63.8 (3.4) ng/ml four weeks later (Fig. 1a). Increase in 25(OH)D was unrelated to baseline 25(OH)D, baseline PTH or change in PTH over time (data not shown). No change in total 25(OH)D was observed in the comparison group. At

Table 1 Baseline demographic and laboratory data

Measure	Comparison group baseline n=38; (30 female/8 male)	D ₂ treatment group baseline n=25 (17 female/8 male)
Age; years	87.4 (0.9)	86.2 (2.3)
Creatinine; mg/dl [normal 0.5 – 1.2]	1.1 (0.1)	1.0 (0.1)
Albumin; g/dl [normal 3.4 – 5.2]	3.8 (0.1)	3.9 (0.1)
25(OH)D; ng/ml	34.8 (1.8)	17.3 (1.2)
Calcium; mg/dl [normal 8.5–10.4]	9.4 (0.1)	9.4 (0.1)
ALT; u/l [normal 0 – 41]	9.7 (1.5)	8.0 (1.5)
Alk Phos; u/l [normal 40 – 129]	103.8 (10.6)	83.5 (5.9)

Data as mean (SEM)

ALT = alanine aminotransferase

Alk Phos = alkaline phosphatase

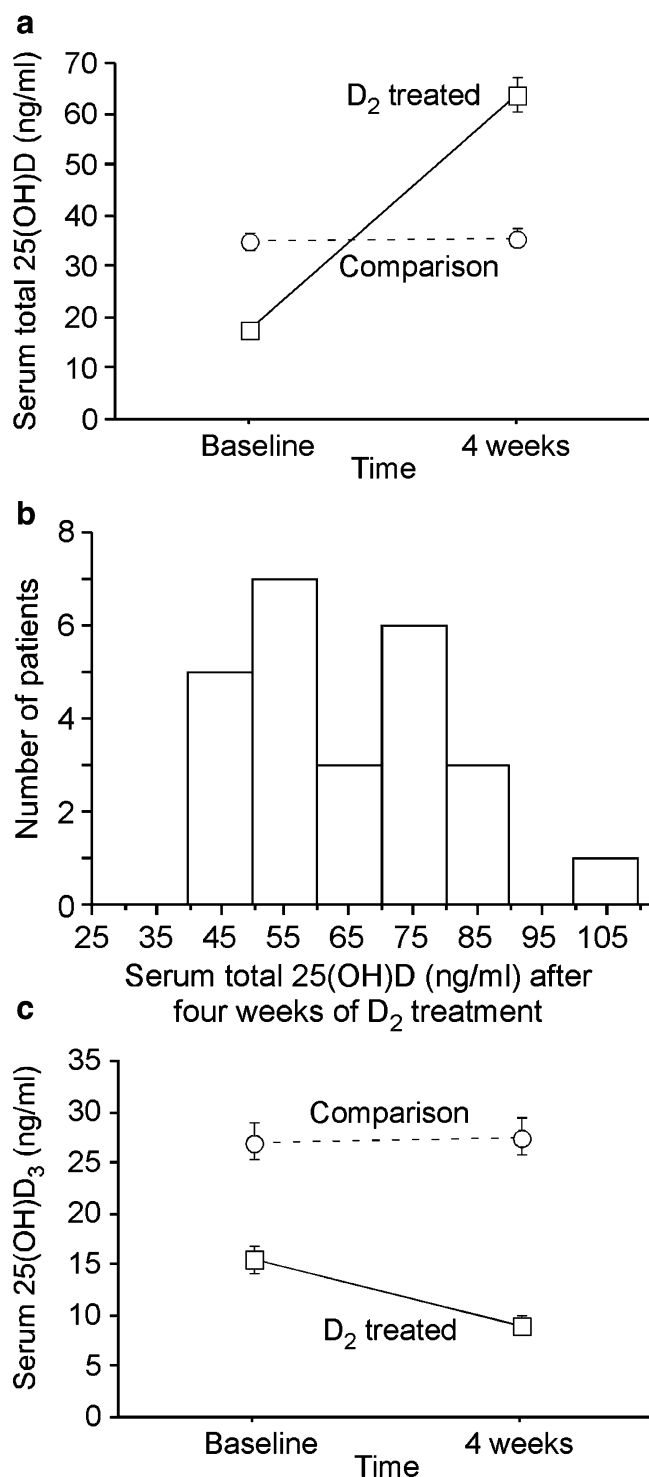


Fig. 1 a–c: Total serum 25(OH)D and 25(OH)D₃. Total 25(OH)D increased ($p < 0.0001$) from 17.3 (1.2) to 63.8 (3.4) ng/ml after one month of D₂ treatment (a). All individuals in the D₂ treatment group achieved a serum 25(OH)D concentration above 30 ng/ml; the highest observed being 102 ng/ml (b). The comparison group total 25(OH)D remained stable being 34.8 (1.8) and 35.5 (1.7) ng/ml at baseline and one month, respectively. In contrast, 25(OH)D₃ declined ($p < 0.0001$) by 41% with D₂ treatment from 15.4 (1.2) to 9.1 (0.8) ng/ml (c). As with total 25(OH)D, 25(OH)D₃ remained stable in the comparison group. Data as mean (SEM)

the four-week follow-up, the serum total 25(OH)D of all 25 patients who received vitamin D₂ was above 30 ng/ml (range 44–102 ng/ml, Fig. 1b). Though vitamin D₂ treatment increased total 25(OH)D, it also led to a significant ($p < 0.0001$) 41% decline in 25(OH)D₃ concentration (Fig. 1c) from 15.4 (1.2) to 9.1 (0.8) ng/ml. As was the case for total 25(OH)D, 25(OH)D₃ remained stable in the comparison group.

Serum calcium and PTH

Serum calcium was unaffected by vitamin D₂ treatment; the mean (SD) was 9.4 (0.3) mg/dl at baseline and 9.4 (0.5) at follow-up (Fig. 2a). No between-group differences were observed. Serum calcium did not exceed the normal range in any vitamin D₂ treated participant. However, hypercalcemia

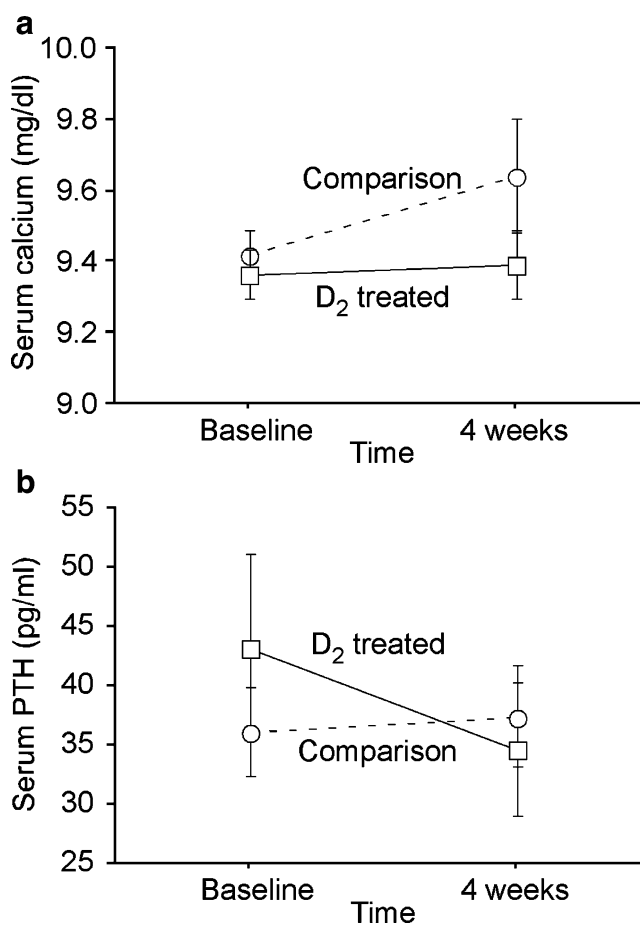


Fig. 2 a, b: Serum calcium and PTH. Mean serum calcium did not change in either the D₂ treated or comparison group (a). Hypercalcemia was not observed in the vitamin D₂ treated group; the highest serum calcium in the vitamin D₂ treated group was 10.2 mg/dl. The mean serum calcium was 9.4 (0.1) mg/dl both at baseline and following one month of vitamin D₂ treatment. A downward trend ($p = 0.06$) in serum PTH was observed from a mean of 43.2 (7.8) to 34.6 (5.7) pg/ml after one month of vitamin D₂ treatment (b). Serum PTH was stable in the comparison group. Data as mean (SEM)

was observed in three individuals in the comparison group at four weeks. The mean serum PTH trended down (mean [SD] 43.2 [38.9] at baseline to 34.6 [28.6] at follow up; $p=0.06$) with vitamin D₂ treatment and remained unchanged in the comparison group (Fig. 2b).

Markers of skeletal turnover

Serum NTx (Fig. 3a) and BSAP (Fig. 3b) did not change with vitamin D₂ treatment. No between group differences were observed with either of these markers.

Functional assessments

Results for the timed walk test, animal fluency, clock drawing and NPI are presented in Table 2. There were no differences between the vitamin D₂ treated and comparison groups for any of these parameters.

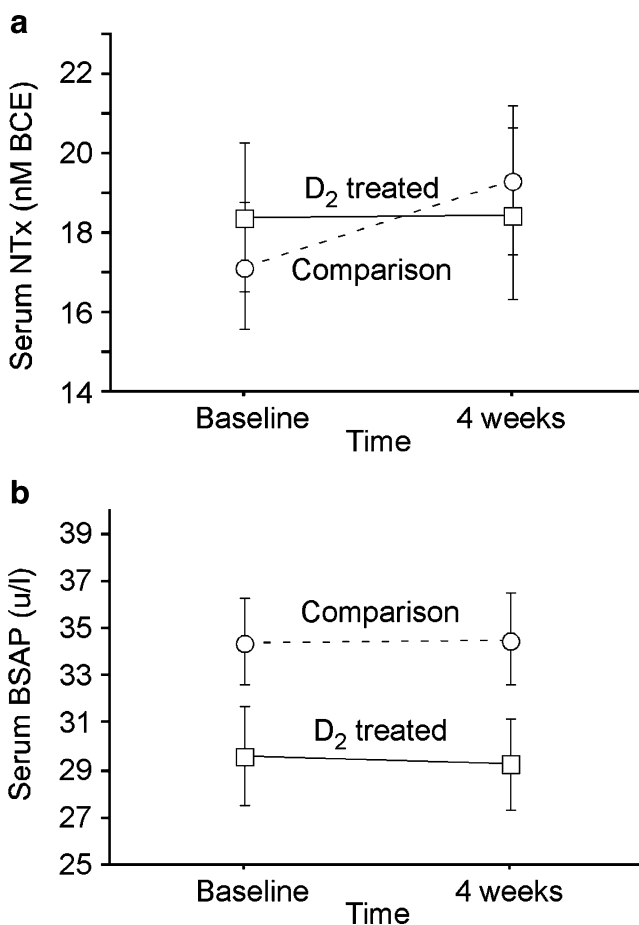


Fig. 3 a, b: Serum NTx and BSAP. Neither serum NTx nor BSAP were altered by vitamin D₂ treatment. In the treated group, serum NTx was 18.4 (1.9) and 18.5 (2.2) nM/BCE at baseline and one month, respectively (a). Serum BSAP was 29.6 (2.1) and 29.2 (1.9) u/l at baseline and one month, respectively (b). Data as mean (SEM)

Table 2 Functional assessments

Measure	Comparison group baseline	Comparison group 4 weeks	D ₂ treatment group baseline	D ₂ treatment group 4 weeks
NPI	7.4 (1.6)	6.4 (1.6)	7.3 (2.0)	5.5 (1.9)
Verbal fluency	8.3 (0.8)	8.1 (0.9)	8.3 (1.2)	8.3 (1.2)
CDT	4.6 (0.6)	5.7 (0.5)	5.1 (0.5)	5.7 (0.5)
Walk; seconds	15.3 (4.0)	15.2 (4.4)	11.7 (1.7)	11.2 (1.5)

Data as mean (SEM)

NPI = neuropsychiatric inventory: Note, lower values indicate better function

CDT = clock drawing test; maximum possible score 10

Walk = 4-meter gait time

Safety

One death occurred and two patients were too ill to undergo follow-up assessments; all three were in the untreated group. Three individuals in the comparison group developed hypercalcemia (10.6, 11.5 and 14.5 mg/dl; normal range 8.4–10.3 mg/dl) at four-week follow-up. Mean serum chemistry values at baseline are reported in Table 1 for the treated and untreated/comparison groups. No adverse events were felt to be related to ergocalciferol.

Discussion

In this unblinded study of nursing home residents, 40% were found to have low vitamin D status and were treated with a total of 600,000 IU of vitamin D₂ (12 doses of 50,000 IU) over a four-week period. Ergocalciferol treatment increased mean serum total 25(OH)D to within the ideal range without causing hypercalcemia. Importantly, all individuals in the vitamin D₂ treated group achieved a serum 25(OH)D concentration above 30 ng/ml, a commonly recommended goal of vitamin D repletion therapy [33]. Though the relationship of vitamin D status, PTH concentration and calcium intake is complex and controversial [34, 35], as might be expected vitamin D repletion was associated with a concomitant downward trend in PTH concentration. Given this complexity, routine measurement of PTH does not seem to be of clinical value in assessment of an individual's vitamin D status.

The incidence of hypovitaminosis D was lower in this cohort of nursing home patients compared to earlier studies [6], possibly reflecting increased physician awareness of this problem. Additionally, recent expert recommendations to increase vitamin D intake [36], education efforts to prevent and treat osteoporosis and more effort to expose residents to sunlight might explain why fewer of these nursing home patients were vitamin D insufficient.

There were no safety issues with the rapid repletion of vitamin D levels in these frail and mostly elderly individuals, in that the one death and two ill patients were all in the untreated group. Similarly, the major potential safety concern associated with rapid vitamin D treatment, hypercalcemia, did not occur in vitamin D₂ treated patients.

Suboptimal adherence with daily vitamin D supplementation, even in controlled clinical trials, is common [37, 38]. This confounds vitamin D clinical trial results in that vitamin D supplementation may have only a minimal impact on serum 25(OH)D concentration [39]. Despite the poor adherence with daily supplementation, only limited data exist evaluating intermittent dosing approaches. Intermittent intramuscular vitamin D injections have been studied; these approaches do increase serum 25(OH)D [40] and may reduce fracture risk [41]. Similarly, intermittent high-dose (100,000 IU every three months) oral vitamin D₃ dosing reduced osteoporotic fracture risk [42]. Unfortunately, both parenteral vitamin D and high-dose oral D₃ are unavailable by prescription in the United States; making vitamin D₂ treatment the only prescription option. The mean serum 25(OH)D increase observed in this study (~47 ng/ml) following 600,000 IU of ergocalciferol, is reasonably congruent with the increment reported following 50,000 IU administered once-weekly for eight weeks (~18 ng/ml) [43]. Other approaches (e.g., daily administration of lower doses) to achieve vitamin D repletion could be effective. However, in this population, rapid correction of vitamin D inadequacy seems desirable. Moreover, lower dose approaches would add one or more pills daily contributing to the widespread polypharmacy present in this population.

The decrease in 25(OH)D₃ concentration (from 15.4 to 9.1 ng/ml) in the treatment group is consistent with prior reports [44, 45] in which vitamin D₂ administration leads to a reduction of 25(OH)D₃. The mechanism(s) and potential importance of this remain unclear. It is possible that this decline simply reflects competition for available 25-hydroxylase activity, however, in-vivo regulation of vitamin D 25 hydroxylation in humans is not entirely understood [46]. Of more importance is the impact of a vitamin D₂-induced reduction in circulating 25(OH)D₃ on clinical outcomes. To our knowledge, there is no current evidence that 25(OH)D₂ has different biological effects than 25(OH)D₃. Clearly, the mechanism(s) by which vitamin D₂ administration reduces 25(OH)D₃ and the clinical importance of this, if any, requires elucidation.

Small sample size and short treatment duration are limitations of this study that may explain the lack of vitamin D₂ treatment effects on gait, cognition and behavior. The lack of benefit for ambulation was unexpected, given the evidence for improved gait and stability with vitamin D treatment [47] and reduced incidence of falls and

fractures [8, 9, 48]. Potentially, the well-recognized heterogeneity of nursing home residents may have contributed to the inability to observe a beneficial effect. Though the multiple co-morbidities and frail status of these nursing home residents, and thus the heterogeneity of the study population, may be considered a weakness, alternatively, this may be considered a study strength in that these participants are likely reflective of “real world” nursing home residents. Consistent with a real world approach, we did not exclude individuals receiving bone active agents; this may have compromised the ability to detect changes in markers of skeletal turnover.

The lack of cognitive and neuropsychiatric improvement following treatment is in contrast to recent reports documenting an association and does not support a role for vitamin D in normal cognition and mood [20]. Again, it is possible that the small sample size, short treatment duration and test reproducibility precluded identification of positive effects; further studies in this realm are clearly warranted. One could also consider use of D₂ (ergocalciferol) rather than D₃ (cholecalciferol) to be a study weakness, in that some studies find D₃ to be more potent and persistent than D₂ at maintenance of serum 25(OH)D concentration [44, 49]. However, as noted above, use of ergocalciferol reflects clinical reality in the United States. Moreover, a recent work suggests that D₂ may be equally effective as D₃ in maintaining 25(OH)D levels [50]

In conclusion, this study demonstrates that a simple regimen of vitamin D repletion with a standard preparation, ergocalciferol, can rapidly and safely correct low vitamin D status in nursing home residents. Further work is needed to determine a treatment regimen that safely and effectively maintains the level of 25(OH)D, before a long-term treatment study of sufficient size can be done to better assess possible functional and cognitive benefits of vitamin D therapy in nursing home residents.

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