High-dose versus low-dose ergocalciferol for correcting hypovitaminosis D after fragility hip fracture: A randomized controlled trial

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Research article

Keywords: Ergocalciferol, Hypovitaminosis D, 25-hydroxyvitamin D, 25(OH)D, Fragility hip fracture

DOI: https://doi.org/10.21203/rs.3.rs-47838/v1

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Abstract

Background: Hypovitaminosis D can be observed in most fragility hip fracture patients. However, measurement of 25-hydroxyvitamin D [25(OH)D] level is costly and may not be available in some centers. Without the baseline 25(OH)D level, the appropriate dose of vitamin D supplementation is not known. The aim of this study was to evaluate the effectiveness and safety of vitamin D supplementation in fragility hip fracture patients compared between high- and low-dose vitamin D supplementation.

Methods: A total of 140 patients diagnosed with fragility hip fracture were randomly allocated to either the high-dose (60,000 IU/week) or low-dose (20,000 IU/week) vitamin D2 supplementation group for 12 weeks. The number of patients who achieved sufficient vitamin D level [25(OH)D level ≥ 30 ng/mL], the proportion of patients who developed hypercalcemia, and the functional outcome were compared between groups.

Results: Of the 140 patients who were enrolled, 21 patients were lost to follow-up during the study period. The remaining 119 patients (58 and 61 in the high- and low-dose group, respectively) were included in the final analysis. The high-dose group had a higher rate of serum 25(OH)D restoration to sufficient level than the low-dose group (82.8% vs 52.5%, respectively). Approximately 3.4% and 1.6% of patients in the high- and low-dose groups, respectively, had mild hypercalcemia, but none developed moderate, severe, or symptomatic hypercalcemia. There were no differences in functional outcome scores between groups.

Conclusions: In treatment settings where baseline serum 25(OH)D level can't be evaluated, we recommend high-dose vitamin D2 of approximately 60,000 IU/week for 12 weeks, with subsequent switch to a maintenance dose. This regimen effectively restored serum vitamin D to a sufficient level in 82.8% of patients without causing symptomatic hypercalcemia.

Trial registration: The protocol of this study was retrospectively registered in the Thai Clinical Trials Registry database no. TCTR20180302007 on 20 February 2018.

Background

Vitamin D is a fat-soluble vitamin that plays a major role in musculoskeletal health [1]. The main function of vitamin D is to regulate calcium and phosphate balance by enhancing intestinal absorption and renal reabsorption, to maintain bone strength, and to modulate muscle function via receptors that are expressed in muscle cells [2]. Previous studies found hypovitaminosis D to be associated with several musculoskeletal-related problems, especially postural instability, falling among the elderly, and osteoporosis [3]. Prolonged vitamin D deficiency causes secretion of parathyroid hormone, leading to secondary hyperparathyroidism, which is one of the common causes of secondary osteoporosis.

Vitamin D deficiency is a common condition worldwide with a prevalence ranging from 41.6–87.4%, and elderly with hip fractures are among those at greatest risk [4, 5]. Previous literature demonstrated that 78.4% of patients with fragility hip fracture had hypovitaminosis D [6], and a meta-analysis study showed
that patients with a low serum 25-hydroxyvitamin D [25(OH)D] level had significantly increased risk of hip fracture [7]. It is, therefore, crucial to correct low vitamin D status in all patients with osteoporotic hip fracture.

In general, vitamin D supplementation is available in 2 forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) [8]. Although these 2 formulas are different in their side chain structure, both forms are effective in restoring serum vitamin D level [9]. The reason that we used vitamin D2 in this study is because vitamin D2 is the only formula available in Thailand. When treating hypovitaminosis D, measurement of serum 25(OH)D is required to determine the appropriate dose of vitamin D supplementation. However, this laboratory test is not available in many centers. Moreover, the cost to measure serum 25(OH)D level is much higher than the cost of vitamin D supplementation itself. Therefore, some physicians preliminarily administer vitamin D without determination of serum 25(OH)D level before treatment. The effectiveness and safety of this strategy, however, is not known.

The objective of this study was to compare the effectiveness and safety between different doses (high- and low-dose) of vitamin D2 supplementation in fragility hip fracture patients. The clinical relevancy of this study is that if high-dose vitamin D supplementation is safe and more effective to restore sufficient vitamin D status in elderly hip fracture patients, physicians can pretreat all patients with high-dose vitamin D without determination of serum 25(OH)D level.

**Methods**

The study protocol and consent forms were approved by the Institutional Review Board (IRB), and registered in the Thai Clinical Trials Registry (registration no. TCTR20180302007). Patients aged older than 50 years who were diagnosed with pertrochanteric hip fracture (either intertrochanteric or femoral neck fracture) during October 2016 to November 2017 were screened for the study. The exclusion criteria were patients with pathological fracture, hypercalcemia (corrected total serum calcium more than 10.5 mg/dL), renal impairment with estimated glomerular filtration rate (eGFR) less than 30 mL/min/1.73 m², abnormal liver function test with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) level greater than twice the upper limit of the normal range, and previous vitamin D supplementation. Patients who met all of the eligibility criteria were randomized using a computer-generated system with block sizes of four to receive vitamin D (ergocalciferol 20,000 IU capsule, British Dispensary, Bangkok, Thailand) either high- or low-dose for 12 weeks.

Patients in the low-dose vitamin D group received vitamin D2 20,000 IU (1 capsule) per week, while high-dose vitamin D group patients received 60,000 IU (3 capsules) per week. Generally, vitamin D was administered after surgical intervention or when the surgeon chose to treat a hip fracture conservatively. In addition, all patients received calcium carbonate 1,000 mg per day. Baseline serum 25(OH)D and calcium levels were measured prior to supplementation and at 12 weeks after the first dose of vitamin D. After the completion of this study, all patients in both treatment groups were switched to a maintenance
dose of vitamin D2 supplementation (20,000 IU per week). The research assistants who collected data were blinded to each patient's supplementation protocol.

**Outcome measurement**

The primary outcome of this study was the proportion of patients who achieved sufficient vitamin D level at 12 weeks after vitamin D supplementation. The serum 25(OH)D concentration level was classified as hypovitaminosis D, optimal level, and hypervitaminosis D if the serum 25(OH)D level was < 30, 30–50, and > 50 ng/mL, respectively, and vitamin D sufficiency was defined as serum 25(OH)D ≥ 30 ng/mL [10]. Serum 25(OH)D was measured and analyzed by electrochemiluminescence (ECL) binding assay on a cobas e411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). Other outcome measurements were serum parathyroid hormone (PTH) level and the number of patients who developed hypercalcemia. Hypercalcemia was classified as mild, moderate, or severe based on corrected serum calcium, which was calculated based on serum albumin level by adding 0.8 mg/dL of total serum calcium for every 1 mg decrease in serum albumin below 4 mg/dL, as described in the formula: corrected serum calcium (mg/dL) = measured total serum calcium (mg/dL) + [4.0 − serum albumin (g/dL) x 0.8] [11]. Mild hypercalcemia was defined as corrected serum calcium between 10.5 and 12 mg/dL, moderate hypercalcemia defined as corrected serum calcium from 12 to 14 mg/dL, and severe hypercalcemia was clarified when corrected serum calcium > 14 mg/dL [12]. Symptomatic hypercalcemia was diagnosed when corrected serum calcium was ≥ 10.5 mg/dL with one of the following symptoms/signs: neurological dysfunction, myopathy, bradyarrhythmia, or gastrointestinal problems [13]. Functional outcome was evaluated using the Barthel Index and the EuroQol-visual analogue scale (EQ-VAS).

The Barthel Index is a measurement tool that is used to assess activities of daily living (ADLs). It comprises of 10 variables describing ADLs and mobility. A higher score indicates a greater likelihood of being able to live independently at home after discharge from the hospital. This tool has been validated in hip fracture patients [14].

EQ-VAS is a simple self-evaluated scale that rates health status ranging from 0 to 100 points. Patients rated their health status on a visual analogue scale, with a higher score (maximum 100) indicating the best imaginable health state, and a lower score (minimum 0) indicating the worst health status [15]. Similar to the Barthel Index, EQ-VAS was reported to be a reliable tool and has been validated in hip fracture patients [16].

**Statistical analysis and sample size calculation**

Statistical power was considered from the primary outcome, which was the proportion of patients with adequate level of 25(OH)D after supplementation for 12 weeks. A study by Sansanayudh N et al. [17] showed that among patients with metabolic syndrome who were supplemented with vitamin D2 20,000 IU per week for 8 weeks, 33.3% were restored to sufficient vitamin D level, whereas 60% of patients who received vitamin D2 40,000 IU per week for 8 weeks were able to achieve sufficient vitamin D level. Based on the results of that study, power analysis and sample size calculation indicated that a sample
size of 54 patients per group would provide 80% statistical power (a one-sided alpha = 0.05; beta = 0.2). Recruitment was increased by 30% to compensate for a high incidence of loss to follow-up and death in this patient population. Therefore, a total of 140 patients were required for randomization in this study.

Baseline characteristics and all outcome measures are presented as number and percentage for categorial variables, and as mean ± standard deviation (SD) for continuous variables. The normality of data was assessed with Kolmogorov-Smirnov test. Pearson's chi-square test or Fisher's exact test was used for comparison of categorial variables, while Student's *t*-test was used to compare continuous variables. Statistical analysis was performed using SPSS® Statistics version 18.0 (SPSS Inc., Chicago, IL, USA), and statistical significance was defined at a *p*-value of < 0.05.

**Results**

From 181 eligible patients, 41 were excluded for either not wanting to participate (n = 8) or for meeting one of the exclusion criteria, as follows: 16 patients for renal impairment, 14 patients for receiving vitamin D supplementation prior to the study, and 3 patients for abnormal liver function test. From 140 randomized patients, 9 and 10 patients in the low- and high-dose vitamin D groups, respectively, were unable to come for follow-up, and 2 patients in the high-dose group discontinued their medication. Therefore, 119 patients (85%) completed the study with data available for analysis at the end of the 12-week study period (Fig. 1). Demographic and baseline characteristics of patients in both groups are shown in Table 1. The overall mean age of the patients was 78.9 ± 10.3 years, and most patients (72.1%) were female. Just over half (51.4%) of patients were diagnosed with intertrochanteric femoral fracture, and 48.6% had femoral neck fracture. Most patients were treated operatively, while 2 patients in the high-dose group and 1 patient in the low-dose group were treated conservatively. There were no significant differences in demographic and clinical characteristics between groups (Table 1).
Table 1
Patient demographic and clinical characteristics

| Clinical variables                        | Low-dose group (n = 70) | High-dose group (n = 70) | p-value |
|-------------------------------------------|-------------------------|--------------------------|---------|
| Female gender, n (%)                      | 52 (74.3)               | 49 (70.0)                | 0.575   |
| Age (years), mean ± SD                    | 78.5 ± 9.3              | 80.1 ± 10.0              | 0.311   |
| Body mass index (kg/m²), mean ± SD       | 22.7 ± 3.6              | 22.5 ± 4.2               | 0.731   |
| Type of hip fracture, n (%)               | 34 (48.6)               | 38 (54.3)                | 0.112   |
| - Intertrochanteric fracture              | 36 (51.4)               | 32 (45.7)                |         |
| - Femoral neck fracture                   |                         |                         |         |
| Treatment, n (%)                          | 1 (1.4)                 | 2 (2.9)                  | 0.691   |
| - Conservative                            | 3 (4.3)                 | 2 (2.9)                  |         |
| - Multiple screw fixation                 | 8 (11.4)                | 4 (5.7)                  |         |
| - Dynamic hip screw fixation              | 30 (42.9)               | 33 (47.1)                |         |
| - Intramedullary nailing                  | 28 (40.0)               | 29 (41.4)                |         |
| - Arthroplasty                            |                         |                         |         |
| Previous functional status, n (%)         | 48 (68.6)               | 40 (57.1)                | 0.235   |
| - Outdoor                                 | 22 (31.4)               | 30 (42.9)                |         |
| - Indoor                                  |                         |                         |         |
| Pre-operative ambulatory status, n (%)    | 43 (61.4)               | 39 (55.7)                | 0.372   |
| - Independent without gait aid            | 16 (22.9)               | 14 (20.0)                |         |
| - Single cane                             | 3 (4.3)                 | 6 (8.6)                  |         |
| - Tripod cane                             | 0 (0)                   | 0 (0)                    |         |
| - Quad cane                               | 7 (10.0)                | 8 (11.4)                 |         |
| - Pick up walker                          | 0 (0.0)                 | 2 (2.9)                  |         |
| - Unable to walk                           | 1 (1.4)                 | 1 (1.4)                  |         |
| - Wheel chair                             |                         |                         |         |
| - Bed bond                                |                         |                         |         |

Baseline mean serum 25(OH)D levels in the low- and high-dose groups were 20.2 ± 8.2 ng/mL and 18.1 ± 11.1 ng/mL, respectively (p = 0.249). At the completion of the study, the mean serum 25(OH)D level
significantly increased to 31.4 ± 8.8 and 40.5 ± 12.5 ng/mL in the low- and high-dose groups, respectively. There was a significant difference in the post-treatment level of serum 25(OH)D between the 2 groups (p < 0.001) (Fig. 2A). The number of patients who achieved sufficient serum 25(OH)D level was greater in the high-dose group (82.8% and 52.5% for the high- and low-dose vitamin D2 groups, respectively) (Table 2).

Table 2
Percentage of patients with hypovitaminosis D, optimal vitamin D level, and hypervitaminosis D at baseline and at the 12-week follow-up compared between the low-dose and high-dose groups

| 25(OH)D level       | Low-dose group (n = 61) | High-dose group (n = 58) |
|---------------------|-------------------------|--------------------------|
|                     | Baseline | 12-week follow-up | Baseline | 12-week follow-up |
| Hypovitaminosis D   | 52 (85.2%) | 29 (47.5%) | 49 (84.5%) | 10 (17.2%) |
| (< 30 ng/mL)        |          |              |          |                  |
| Optimal vitamin D   | 9 (14.8%) | 30 (49.2%) | 9 (15.5%) | 37 (63.8%) |
| (30–50 ng/mL)       |          |              |          |                  |
| Hypervitaminosis D  | 0        | 2 (3.3%)    | 0        | 11 (19%)        |
| (> 50 ng/mL)        |          |              |          |                  |

The baseline mean serum PTH levels were 41.3 ± 18.4 pg/mL and 50.8 ± 25.3 pg/mL in the low- and high-dose groups, respectively. At the 12-week follow-up, the average PTH level remained within the normal range in both groups (approximately 51.8 ± 36.0 pg/mL in the low-dose group, and 56.6 ± 55.5 pg/mL in the high-dose group). There were no significant differences in serum PTH level between groups, or when compared between before and after vitamin D supplementation. Mean corrected serum calcium level increased significantly from baseline to 12 weeks in both groups (8.8 ± 0.4 mg/dL to 9.3 ± 0.5 mg/dL in the low-dose group, p < 0.001; and, 8.8 ± 0.6 mg/dL to 9.2 ± 0.6 mg/dL in the high-dose group, p < 0.001) (Fig. 2B). Two patients in the high-dose group and 1 patient in the low-dose group developed mild hypercalcemia (10.5 to 11.1 mg/dL), which was transient and asymptomatic.

Regarding functional outcome scores, both Barthel Index and EQ-VAS were significantly improved from baseline to 12-weeks post-treatment in both groups. However, there was no significant difference when comparing between the 2 groups (Fig. 3A, B).

Discussion

Treatment of hypovitaminosis D is essential for osteoporosis patients, especially those with history of fragility fractures. A study by LeBoff MS et al. [18] showed that vitamin D deficiency was associated with low muscle strength, especially in the lower extremities, which affected patient stability and increased risk of falls. Treatment of hypovitaminosis D alone could reduce the fall rate by 14% [19]. Moreover, a meta-
analysis study by Yao P, *et al.* [20] demonstrated that an increased serum 25(OH)D level of 10 ng/mL was related to 20% lower risk of hip fracture. Given that elderly patients with fragility hip fracture had a high incidence of hypovitaminosis D (ranging from 78.4 to 92%) [6, 21], it is, therefore, important to treat this condition in order to prevent future complication.

The effectiveness of different doses of vitamin D supplementation has been evaluated by previous studies, and benefit of high-dose vitamin D supplementation was shown. For instance, Mak JC *et al.* [22] retrospectively reviewed 124 patients with fragility hip fracture who had vitamin D deficiency and found that high-dose vitamin D3 supplementation (approximately 4,000 IU per day for 14 days) improved serum 25(OH)D level to a sufficient status in 88.9% of patients; however, only 62.5% of patients who received vitamin D3 1,000 IU per day achieved sufficient vitamin D level. A randomized controlled trial that compared different doses of vitamin D3 also found that a high-dose vitamin D3 of 2,000 IU per day for 12 months was able to restore serum 25(OH)D level to a sufficient level by in 93% of subjects, while only 70% of those who received a low-dose of vitamin D3 (800 IU per day) reached a sufficient vitamin D status [23]. Although, the efficacy of vitamin D2 and vitamin D3 in maintaining serum 25(OH)D was comparable [9], there is limited data available specific to the effectiveness of vitamin D2 supplementation in different doses, especially in fragility hip fracture patients. Woranitat W *et al.* [24] reported a significant difference in the percentages of postmenopausal women with hypovitaminosis D who achieved sufficient vitamin D level after 12 weeks of supplementation. More than three-quarters (86.4%) of patients who received vitamin D2 supplementation of 40,000 IU per week could reach sufficient vitamin D level, whereas 44.0% and 27.3% of patients who took vitamin D2 of 20,000 IU per week and per 2 weeks, respectively, could achieve sufficient vitamin D level. Another study by Sansanayudh N *et al.* [17] also reported superior results of high-dose vitamin D2 supplementation of 40,000 IU per week for 8 weeks in metabolic syndrome patients with vitamin D deficiency. Similar to those previous reports, our results showed that more patients in the high-dose vitamin D group achieved sufficient vitamin D status (82.8% and 52.5% in the high- and low-dose vitamin D groups, respectively).

Regarding the potential risks of high-dose vitamin D supplementation, alteration in serum calcium can lead to hypercalcemia. Previous study reported that patients with a serum 25(OH)D level exceeding 150 ng/mL were at risk for developing vitamin D intoxication or severe hypercalcemia [25]. Importantly, none of the patients in our study had serum 25(OH)D above 70 ng/mL. Only 2 patients in the high-dose group and 1 patient in the low-dose group developed mild hypercalcemia, which was transient and asymptomatic in all 3 cases. Therefore, our high-dose vitamin D supplementation protocol is safe and effective for the treatment of hypovitaminosis D in fragility hip fracture patients.

In settings where there is limited access for serum vitamin D measurement, physicians can therefore preliminarily prescribe a high-dose vitamin D2 (60,000 IU per week) for 12 weeks and then switch to a maintenance dose of vitamin D2 (10,000 or 20,000 IU per week). It is important to emphasize that a maintenance dose of vitamin D is required after a period of high-dose vitamin D supplementation to maintain sufficient vitamin D status [10]. Bacon CJ *et al.* [26] reported the long-term sustainability of
serum 25(OH)D level via a maintenance dose of vitamin D3 of 50,000 IU per month following a single bolus dose of vitamin D3 500,000 IU.

There is a trend toward increased serum vitamin D measurement worldwide [27]. This increased number of laboratory tests substantially impact healthcare expenditures [28]. In Australia, the cost of vitamin D measurement increased an average of 59% each year, with a forecasted total cost of vitamin D measurement of A$95.6 million in 2010 [29]. In the United States, there was an 83-fold increase in the reimbursement volume for serum 25(OH)D tests from 2000 to 2010 [30]. Similarly – in the UK, the measurement of serum vitamin D was increased approximately 50-fold from 2005 to 2015 [31]. Since the laboratory cost of vitamin D measurement is quite high, the protocol to check serum vitamin D, both pre- and post-treatment, has burdened many medical centers. At our center, the cost of each serum 25(OH)D test is approximately US$30. With an estimated 42,000 hip fractures in Thailand in 2018 [32], evaluating serum vitamin D before and after supplementation would cost approximately US$2,520,000 per year. Since our preliminary high-dose vitamin D supplementation is effective and safe, this protocol is a cost-effective strategy for treating low vitamin D status in elderly patients with hip fracture without measuring serum vitamin D level.

There were some limitations in this study. First, several confounders, such as dietary vitamin D intake and sunlight exposure, were not evaluated or controlled. However, patients with advancing age, lack of physical activity, various comorbidities, and frailty are likely to reduce their exposure to sunlight [33]. We, therefore, assumed sunlight exposure not to be a major factor for changes in serum 25(OH)D level in this patient population. Second, there was a high drop-out rate in this study as expected, which is common among geriatric patients. Nevertheless, there were no differences in baseline patient demographics and clinical characteristics between patients who withdrew and those who completed the study. Third, there are a number of techniques to measure serum 25(OH)D level, and high performance liquid chromatography (HPLC) is considered a standard method [34]. However, the ECL technique used in our study showed good agreement with HPLC, and has been widely used in many centers [35]. Fourth, the follow-up duration in this study was only 12 weeks in duration, so it is possible that a longer-term analysis may have shown a change in serum vitamin D level after switching patients to a maintenance dose. Last, the average baseline serum 25(OH)D level in this study was not extremely low (baseline mean serum 25(OH)D around 18–20 ng/mL); therefore, our high-dose vitamin D supplementation protocol might achieve lower vitamin D status if patients have an initial 25(OH)D level less than that of our study population.

Conclusions

Vitamin D supplementation in patients with fragility hip fracture is essential. In settings where measurement of serum 25(OH)D is not available, a short period of high-dose vitamin D supplementation is a safe and effective protocol in elderly hip fractures. Based on the results of this study, we recommend treating all elderly hip fracture patients with ergocalciferol 60,000 IU per week for 12 weeks, and then switching them to a maintenance dose of 10,000 to 20,000 IU per week.
Abbreviations

25(OH)D: 25-hydroxyvitamin D  IU: international unit  eGFR: estimated glomerular filtration rate

AST: aspartate aminotransferase  ALT: alanine aminotransferase  ECL: electrochemiluminescence

PTH: parathyroid hormone  EQ-VAS: EuroQol-visual analogue scale

ADLs: activities of daily living  SD: standard deviation  HPLC: high performance liquid chromatography

Declarations

Ethics approval and consent to participate

The protocol of this study was approved by the Institutional Review Board (IRB) (certificate of approval no. Si 421/2016) and all procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration. All patients provided written informed consent before participation.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

No funding was received for this study.

Authors’ contributions

AJ contributed to the conceptual design of the study, conducted the methodological support, data analysis, and wrote the manuscript. SP contributed to the conceptual design of the study and provided data collection. PC and AU contributed to the conceptual design of the study, conducted the methodological support, critical reviewing, and revised the manuscript. All authors have read and approved the manuscript.
Acknowledgements

The authors gratefully acknowledge Ms. Wachirapan Narktang of the Division of Research, Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital and Mr. Suthipol Udompunthurak of the Division of Clinical Epidemiology, Department of Health Research and Development, Faculty of Medicine Siriraj Hospital for their assistance with data collection and statistical analysis.

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Figures
Figure 1

Consolidated Standards of Reporting Trials (CONSORT) diagram showing the flow of patients in the study
Figure 2

Graphs showing mean serum 25(OH)D (A) and mean serum calcium (B) level at baseline and at the 12-week follow-up.
**Figure 3**

Graphs showing mean Barthel Index (A) and mean EuroQol-visual analog scale (EQ-VAS) (B) at baseline and at the 12-week follow-up

**Supplementary Files**

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- VitaminDCONSORTChecklist.doc