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# CHOLECALCIFEROL AND CALCIFEDIOL ARE BOTH USEFUL TO IMPROVE VITAMIN D SERUM LEVELS IN HYPOVITAMINOSIS D: A RANDOMIZED CONTROLLED TRIAL

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**ABSTRACT** – ***Objective:*** Vitamin D deficiency is known to increase fracture risk, especially in elderly patients, being the primary cause of atraumatic vertebral and femoral neck fractures. The aim of our study was to compare the effects of calcifediol and cholecalciferol in hypovitaminosis D.

***Patients and Methods:*** This study compared the effects of calcifediol, administered daily and monthly, with those of cholecalciferol, taken every 15 days, focusing on bone densitometry values after a 12-month follow-up. Seventy-four patients were randomized into three groups, with a minimum of 20 subjects per group, according to the vitamin D supplementation regimen. We followed the CONSORT flowchart and conducted a statistical analysis to demonstrate the optimal outcomes of vitamin D intake.

***Results:*** There were no statistically significant differences observed in vitamin D dosage or in vertebral and femoral T-scores at the 12-month follow-up. In fact, all three groups reported a considerable increase in vitamin D levels, with averages within normal reference ranges (> 20 ng/mL). However, the daily intake of calcifediol led to a greater increase compared to the biweekly intake of cholecalciferol and the monthly intake of calcifediol; however, this was not statistically significant.

***Conclusions:*** Cholecalciferol and calcifediol are both useful to improve serum 25(OH)D levels in hypovitaminosis D patients. In this study, no statistically significant differences were observed among the three supplementation regimens in terms of serum vitamin D levels or vertebral and femoral T scores at 12 months.

**ClinicalTrials.gov:** NCT06138249.

**KEYWORDS:** Cholecalciferol, Calcifediol, Vitamin D, Hypovitaminosis D.

## INTRODUCTION

Vitamin D is essential for optimal bone health and muscle function[1,2]. However, an alarming prevalence of hypovitaminosis D in the global population, regardless of race, age, or ethnicity, has recently been reported[3-5].

Vitamin D deficiency increases fracture risk and reduces the effectiveness of anti-osteoporotic treatments, as well as negatively affecting clinical outcomes in patients undergoing orthopedic surgery[6-10].

Vitamin D deficiency (serum 25-hydroxyvitamin D < 30 nmol/L) accelerates bone turnover, bone loss, and the occurrence of osteoporotic fractures. These risks may be reduced by supplementation with 800 IU of vitamin D combined with adequate calcium intake, particularly in institutionalized elderly individuals or vitamin D-deficient subjects[2].

Women with hypovitaminosis D with 25(OH)D < 20 ng/mL are at increased risk of osteoporotic fractures[11,12]. Bone metabolism and serum 25(OH)D levels appear to play a role in the occurrence of recurrent vertebral compression fractures after kyphoplasty[13].

Hypovitaminosis D is also associated with prolonged hospitalization, poorer functional outcomes, increased preoperative and postoperative pain, and a higher rate of medical and surgical complications[14].

A high prevalence of secondary hyperparathyroidism due to hypovitaminosis D has been reported[15] in hospitalized elderly patients, both with and without hip fractures.

Vitamin D supplementation remains one of the most debated topics in the medical field, and there is still no consensus regarding the optimal supplementation strategy in terms of dosage, frequency, and duration of treatment. A daily dosage of 1,000-2,000 IU appears to be an effective strategy to improve skeletal health and reduce the risk of fractures or re-fractures.

Risk factors for osteoporosis and fractures include female sex, advanced age, renal or hepatic diseases, and long-term use of corticosteroids or heparin.

The literature remains inconclusive regarding which serum vitamin D levels or densitometric parameters are directly associated with fracture risk, and whether vitamin D supplementation alone can prevent fractures[16-21].

The aim of this study was to compare the effects of calcifediol administered daily and monthly, and cholecalciferol administered every 15 days, by evaluating biochemical and functional parameters related to bone health and possible side effects.

Therefore, this study evaluated three vitamin D supplementation regimens in patients with serum 25(OH)D levels < 20 ng/mL.

## PATIENTS AND METHODS

Seventy-four patients (52 females and 22 males) with hypovitaminosis D were recruited from our Osteoporotic Service between July 2023 and July 2024, and the follow-up period was 1 year.

Patients were randomized into three groups, with a minimum of 20 subjects per group, according to the vitamin D supplementation regimen:

- Group A: Calcifediol 0.266 cp once monthly (15,960 IU)
- Group B: Cholecalciferol 25,000 IU every 15 days
- Group C: Calcifediol 10 µg daily

Inclusion criteria were subjects with serum 25(OH)D levels < 20 ng/mL, age > 20 years, body mass index (BMI) between 20 and 30 kg/m², and femoral and vertebral T-scores > -2.5.

Exclusion criteria included hepatic and renal diseases, osteoporosis, sarcoidosis, malabsorption syndrome, primary hyperparathyroidism, calcium levels > 2.6 mmol/L, alcoholism, blood donation, candidates for immediate surgical intervention, and subjects using drugs interfering with vitamin D metabolism. We performed simple randomization of the recruited patients, assigning one of the three letters (A, B or C) at random. The letters A, B, and C referred to the three treatment groups.

Group A included 18 females and 10 males, Group B included 22 females and 4 males, and Group C included 12 females and 8 males.

Bone mineral density was assessed using dual-energy X-ray absorptiometry (DEXA) in all subjects at baseline (T0) and after 12 months. The exam was performed using the Horizon WI model, class IIb, number series 300294M, by HOLOGIC INC, Bradford, MA, USA.

All patients were asked to measure vitamin D levels after one month of supplementation; these data were collected through telephone interviews.

No statistically significant differences were observed in baseline 25(OH)D levels among the three groups ($p = 0.24$). Similarly, no statistically significant differences were detected in vitamin D levels after one month of treatment ($p = 0.48$).

Similarly, no statistically significant differences were observed when comparing vertebral and femoral T-scores among the three groups ($p = 0.23$ and $p = 0.18$, respectively).

These findings were confirmed after 12 months of vitamin D supplementation.

## Ethics Approval

The study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki. All patients provided informed consent for the anonymous publication of their data. Our study was approved by the local Ethics Committee (Comitato Etico Indipendente Azienda Ospedaliero-Universitaria "Consorziale Policlinico" of Bari) on 9th March 2022 (approval number 7170), and all patients provided informed consent for the use of their clinical data in statistical analyses.

The clinical study was registered on ClinicalTrials.gov with ID No.: NCT06138249.

## Statistical Analysis

An *a priori* sample size calculation performed in Stata/MP 15 (StataCorp, College Station, TX, USA) indicated a minimum of 60 participants to achieve 85% power at a two-sided $\alpha = 0.01$; ultimately, 74 patients were enrolled.

Continuous variables were summarized as mean ± SD. Statistical analysis was performed using Microsoft Excel and IBM SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA). Between-group comparisons of continuous variables were performed using one-way ANOVA, with $\alpha = 0.05$, after checking normality (Shapiro-Wilk) and homoscedasticity (Levene's test). When assumptions were violated, Mann-Whitney U or Kruskal-Wallis tests were applied. Categorical variables were compared using $\chi^2$ or Fisher's exact tests, as appropriate. Associations between osteoporosis severity and serum 25(OH)D levels and densitometric measures were explored using Pearson's correlation, according to distribution. A $p$-value < 0.05 was considered statistically significant.

## RESULTS

Demographic data and laboratory parameters such as 25(OH)D serum levels, serum calcium, parathyroid hormone, and urinary calcium were evaluated at baseline (T0) and after 4 weeks.

Femoral and vertebral DEXA scans were performed at the time of consultation.

Group A included 28 patients (18 females and 10 males) with a mean age of 56 years. Mean baseline vitamin D was 13.1 ng/mL and increased to 24.6 ng/mL after one month. Vertebral and femoral T-scores were -0.6 SD and -0.7 SD, respectively.

Group B included 26 patients (22 females and 4 males) with a mean age of 51 years. Mean baseline 25(OH)D was 13.3 ng/mL and increased to 20.6 ng/mL after one month. Vertebral and femoral T-scores were -1.7 SD and -1.5 SD, respectively.

Group C included 20 patients (12 females and 8 males) with a mean age of 34 years and 6 months. Mean baseline vitamin D was 17.4 ng/mL and increased to 37.2 ng/mL after one month. Vertebral and femoral T-scores were -1.2 SD and -1.0 SD, respectively (Table 1).

**Table 1.** Baseline characteristics and clinical outcomes of participants across the three treatment groups.

| | Total | Males | Females | Serum 25(OH)D baseline (ng/mL), mean ± SD | Serum 25(OH)D 1 month (ng/mL) mean ± SD | 95% CI (1 month) | Age mean ± SD | Vertebral T-score baseline, mean ± SD | Vertebral T-score 12 months, mean ± SD | Femoral T-score baseline, mean ± SD | Femoral T-score 12 months, mean ± SD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group A | 28 | 10 | 18 | 13.0±3.9 | 24.6±5.1 | [22.7-26.5] | 56.0±8.4 | -0.6±1.4 | -0.5±1.1 | -0.7±1.3 | -1.0±1.2 |
| Group B | 26 | 4 | 22 | 13.3±5.5 | 20.6±6.2 | [18.2-23.0] | 51.0±10.2 | -1.7±1.5 | -2.0±1.3 | -1.5±1.2 | -1.4±1.0 |
| Group C | 20 | 8 | 12 | 17.4±3.2 | 37.2±7.8 | [33.8-40.6] | 34.5±12.1 | -1.2±1.1 | -0.9±0.9 | -1.0±0.9 | -0.6±0.8 |

No statistically significant differences were observed in baseline or one-month serum vitamin D levels among the three groups ($p$ = 0.24 and $p$ = 0.48, respectively), although Group C showed a greater mean increase (19.8 ng/mL).

No statistically significant differences were observed in vertebral or femoral T-scores among the three groups ($p$ = 0.23 and $p$ = 0.18). However, Group C was the only group showing a slight improvement in both T-scores.

The overall mean increase in serum vitamin D levels across the three groups was 12.2 ng/mL.

## DISCUSSION

The main finding of this study is the absence of statistically significant differences among the different oral vitamin D supplementation regimens. All formulations effectively increased vitamin D levels. However, daily supplementation resulted in a slightly higher mean increase in vitamin D levels and a more favorable trend in T-score values, but it is not statistically relevant.

These results may suggest improved absorption of vitamin D when administered daily and/or a greater response in younger patients, as Group C had a lower mean age (34 years) compared with Groups A and B (51 *vs.* 56). Therefore, this statement should be considered only as a favorable trend without statistical significance.

Vitamin D plays a crucial role in the pathophysiology and healing of fragility fractures, as well as in post-fracture rehabilitation. Correction of vitamin D deficiency should be a primary objective of fracture liaison services[4].

Vitamin D supplementation at doses of 700-1,000 IU/day has been shown to reduce fall risk among older individuals by approximately 19%, with efficacy comparable to active vitamin D forms[6].

Low serum 25(OH)D levels are associated with several musculoskeletal and non-musculoskeletal conditions[2], and deficiency is highly prevalent among patients with fragility fractures[7].

Vitamin D therapy improved vitamin 25(OH)D levels in most patients, although normalization was not achieved in all cases, highlighting the need for careful monitoring of low serum vitamin 25(OH)D[14]. Patients with initial deficiency showed the greatest improvement (Group C).

Vitamin D exerts pleiotropic effects on bone metabolism depending on physiological and pathological conditions[1].

Optimal vitamin D repletion appears necessary to maximize the response to anti-resorptive therapies in terms of bone mineral density and fracture prevention[22].

Associations between *VDR* gene polymorphisms, vitamin D receptor activation, and sarcopenia have been reported[9].

Combined osteoporosis drug therapy with calcium and vitamin D supplementation has been associated with reduced re-fracture rates and lower all-cause mortality[23].

In a study[20], 25% of younger men with high-energy fractures had vitamin D insufficiency, whereas women with fractures exhibited low vitamin D levels regardless of age or fracture mechanism.

Rapid normalization of serum 25(OH)D levels has been reported with all oral cholecalciferol regimens[17].

Targeting high-risk patients for vitamin D supplementation may reduce falls and fractures, although the optimal dose remains uncertain[18].

Calcifediol supplementation has been shown to rapidly and safely increase serum 25(OH)D levels in older adults[21-25].

Meta-analyses[10] support calcium plus vitamin D supplementation to reduce fracture risk in both community-dwelling and institutionalized middle-aged or older patients.

Vitamin D and calcium supplementation may prevent hip or any type of fracture[11,12,16].

Despite extensive research and trials, evidence supporting vitamin D and calcium supplementation for fracture treatment remains limited[26].

Densitometry was performed at the beginning of the study and after 12 months because intermediate densitometries are not informative and pose a significant radiation risk. We planned to measure 25(OH)D serum levels at 6 and 12 months of follow-up, but most participants declined the exam.

Although daily calcifediol intake appeared more effective, monthly vitamin D supplementation may be more convenient and cost-effective for patients.

A major strength of this study is the strict application of inclusion and exclusion criteria. Enrolled patients had a 25(OH) vitamin D level < 20 ng/mL and no fragility fractures.

A limitation of the study is the relatively small sample size and the younger age in group C, which may affect the results. Future studies could include additional measurements of 25(OH) vitamin D at 6 and 12 months. An additional vitamin D dose may further improve serum vitamin D levels.

## CONCLUSIONS

Vitamin D supplementation is essential for preventing fragility fractures. Both cholecalciferol and calcifediol rapidly increase serum 25(OH)D levels. In this study, no statistically significant differences were observed among the three supplementation regimens in terms of serum vitamin D levels or vertebral and femoral T-scores at 12 months.

All groups showed substantial increases in 25(OH)D levels, reaching mean values within the normal reference range (> 20 ng/mL). Daily calcifediol administration, however, resulted in a greater increase compared with biweekly cholecalciferol and monthly calcifediol supplementation. This observation could also be due to group C's younger age.

### Ethics Approval and Informed Consent:

This study was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki. All patients provided written informed consent for the anonymous publication of their data. The study was approved by the Ethics Committee of Azienda Ospedaliero-Universitaria "Consorziale Policlinico" of Bari (approval number 7170) on 9th March 2022.

### Conflict of Interest:

All authors declare that they have no conflict of interest.

### AI Disclosure:

No form of generative artificial intelligence was used for writing the manuscript.

### Authors' Contributions:

Silvana De Giorgi drafted the paper; Davide Bizzoca performed the statistical analysis and reviewed the paper; Alessandro Geronimo and Patrizia Spataro entered the data into the database; and Angela Notarnicola and Giuseppe Solarino corrected the final version of the manuscript.

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