Research Article

**Impact of Oral Vitamin D3 Supplementation on Proximal Femur Fracture Incidence in the Elderly Population**

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**Abstract**

**Objective**

To assess the impact of oral supplementation with vitamin D3 on the incidence of proximal femur fracture (PFF) in the elderly population.

**Data Sources**

We searched PubMed and Embase databases for relevant studies from inception to March 2024.

**Study Selection and Data Extraction**

Only randomized controlled trials (RCTs) were acceptable. Raw data were extracted into a predefined worksheet, and quality analysis of RCTs was conducted using the risk-of-bias tool version 2 (RoB2).

**Data Synthesis**

13 RCTs were included in the meta-analysis. Oral supplementation of vitamin D3 alone in elderly individuals did not exhibit a significant association with PFF incidence (**OR** = 1.04, **95% CI**: 0.94-1.15, **p-value** = 0.46 > 0.05). Combined oral supplementation of vitamin D3 and calcium could reduce the incidence of PFF in the elderly population (**OR** = 0.80, **95% CI**: 0.69-0.94, **p-value** = 0.005 < 0.05); however, after excluding low-quality RCTs, the protective effect was no longer statistically significant (**OR** = 0.90, **95% CI**: 0.74-1.10, **p-value** = 0.32 > 0.05).

**Conclusion**

In the elderly population, there is a lack of robust evidence demonstrating that oral supplementation of vitamin D3 could reduce the incidence of PFF.

**Introduction**

Osteoporosis is a pathological condition characterized by decreased bone mass and structural degradation, leading to an increased susceptibility to fractures.1 Epidemiological evidence highlights a substantial prevalence of osteoporotic fractures, with an estimated one in two women and one in five men aged 65 years or older anticipated to experience osteoporotic fractures over their remaining lifespan.1, 2 Considering the demographic trend towards an increasingly elderly population, the prevention of osteoporotic fractures in older individuals is of utmost significance. Among fractures associated with osteoporosis, proximal femur fracture (PFF), commonly recognized as hip fracture, has the most significant impact on geriatric patients (>= 65 year old) due to its high mortality rate, long-term disabilities, and loss of independence.3, 4 The documented one-year mortality following a PFF is approximated to range from 14% to 58%, accompanied by an increase in the relative risk of mortality among geriatric patients by 4% annually.5 Additionally, the process of hospitalization, rehabilitation, and the potential requirement for extended care exert a noteworthy socioeconomic strain on the healthcare infrastructure. This emphasizes the critical necessity for tailored preventive interventions in geriatric PFF patients.

Vitamin D3 (cholecalciferol) plays a pivotal role in maintaining musculoskeletal health by facilitating calcium absorption, promoting osteoid tissue mineralization in bones, and ensuring the upkeep of muscle function.6, 7 Vitamin D3 deficiency is commonly defined by experts through a serum 25-hydroxyvitamin D (25(OH)D) level lower than 20 ng/mL (50 nmol/L), which could lead to secondary hyperparathyroidism, bone demineralization, and muscle weakness.8, 9 Many previous studies claimed that daily oral supplementation of vitamin D3 (including vitamin D3 alone, and combined supplementation of vitamin D3 and calcium) has the effect on preventing PFF and relieving its symptoms.10, 11 However, the effectiveness of such interventions remains controversial, as evidenced by some recent studies indicating that the oral intake of vitamin D3 is not significantly associated with a reduced risk of PFF in geriatric patients.12-14 Therefore, we conducted a comprehensive meta-analysis based on relevant randomized controlled trials (RCTs) to assess the impact of oral supplementation with vitamin D3 (including vitamin D3 alone, as well as combined supplementation with vitamin D3 and calcium) on the incidence of PFF in the elderly population (aged 65 and above).

**Methods**

**Search strategies**

A systematic literature search was conducted utilizing PubMed and Embase databases in March 2024. And to enhance the breadth of literature coverage, the reference lists of the candidate studies were meticulously examined manually, ensuring comprehensive access to relevant scholarly materials.

**Inclusion and exclusion criteria**

Two reviewers conducted independent assessments to determine the eligibility of candidate articles. The articles deemed irrelevant after abstract review were excluded. All abstracts meeting initial criteria were reviewed as full articles. All abstracts meeting the initial criteria underwent full article review. Non-English publications, animal studies, basic science studies, case reports, comments, letters, meeting abstracts, protocols, and review articles were eliminated from consideration. Studies were selected based on the following inclusion criteria: **(1)** RCTs comparing vitamin D3 alone, or combined vitamin D3 and calcium oral supplements with the placebo / no treatment group; **(2)** studies enrolling participants aged 65 and older (or could extract the data of the participants only aged 65 and older); **(3)** studies with PFF events at least 5 to reduce random error; **(4)** studies with a follow-up duration of at least 1 year; **(5)** studies providing access to raw data. In cases where different studies utilized overlapping data, preference was given to the one presenting more comprehensive statistics. Any discrepancies were resolved through consensus discussions, with involvement of a third party if necessary.

**Risk of bias Assessment**

The assessment of risk of bias was conducted utilizing the Cochrane risk-of-bias tool version 2 (RoB2), and visual representations were generated using the R package "robvis".15, 16 RoB2, tailored for RCTs, rigorously evaluated each domain for its potential bias, categorizing them as low risk, some concerns, or high risk.16 The RoB2 domains are as follows:

• Bias arising from the randomization process

• Bias due to deviations from intended interventions

• Bias due to missing outcome data

• Bias in measurement of the outcome

• Bias in selection of the reported result

**Data analysis**

R package "meta" was used in the following statistics analysis.17 The standardized mean difference (SMD) along with a 95% confidence interval (CI) was employed as the statistic for effect analysis of the measures. The magnitude of heterogeneity was also determined by combining I2 quantification and Q statistic. If the I2 value exceeded 50% or the p-value of the Q statistic was less than 0.05, suggesting substantial heterogeneity among the included studies, the random effects model was considered to be more appropriate. Conversely, if these thresholds were not met, the common effect model (also referred to as the fixed effect model) was preferred.

**Sensitivity Analysis**

Additionally, sensitivity analysis was performed to assess the influence of individual studies, particularly those with low quality, on the overall effect size estimation.

**Results**

**Search Results**

467 papers were obtained for the initial review. After a comprehensive assessment of the full texts, 13 RCTs met our criteria for further meta-analysis (**Figure 1**). Specifically, 8 RCTs employed a design comparing the PFF incidence of oral supplementation with vitamin D3 alone against the placebo/no-treatment group. 6 RCTs utilized a design comparing the PFF incidence of combined oral supplementation with vitamin D3 and calcium against the placebo/no-treatment group. It is noteworthy to mention that 1 RCT encompassed both of the aforementioned experimental designs, resulting in a total of 13 selected RCTs. Characteristics of all included RCTs were listed below (**Table 1.a** & **1.b**).



**Figure 1.** Flow chart of search strategy and studies selection.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Year | Country | Participants, No. | Treatment (vitamin D3 alone) | Mean Age, y | Follow-up, y | PFF, No. |
| Lips18 | 1996 | Netherlands | 2578 | 400 IU/d | 80 | 3.5 | 106 |
| Meyer19 | 2002 | Norway | 1144 | 400 IU/d | 84.7 | 2 | 97 |
| Trivedi20 | 2003 | UK | 2686 | 100,000 IU/4 mo | 74.8 | 5 | 45 |
| Grant21 | 2005 | UK | 2675 | 800 IU/d | 77 | 3.8 | 88 |
| Lyons22 | 2007 | UK | 3440 | 100,000 IU/4 mo | 84 | 3 | 216 |
| Smith23 | 2007 | UK | 9440 | 300,000 IU/y | 79.1 | 3 | 110 |
| Sanders24 | 2010 | Australia | 2258 | 500,000 IU/y | 76.1 | 5 | 34 |
| Waterhouse12 | 2023 | Australia | 15306 | 60,000 IU /mo | 65+ | 5 | 789 |

**Table 1.a** Characteristics of 8 RCTs comparing the PFF incidence in participants aged 65 or above between oral supplementation of vitamin D3 alone and the placebo / no treatment group.

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Year | Country | Participants, No. | Treatment | Mean Age, y | Follow-up, y | PFF, No. |
| Chapuy25 | 1994 | France | 2303 | 800 IU/d vitamin D3,  1200 mg/d calcium | 84 | 3 | 322 |
| Chapuy26 | 2002 | France | 583 | 800 IU/d vitamin D3,  1200 mg/d calcium | 85.2 | 2 | 105 |
| Grant21 | 2005 | UK | 2638 | 800 IU/d vitamin D3,  1000 mg/d calcium | 77.5 | 5 | 87 |
| Porthouse27 | 2005 | USA | 3314 | 800 IU/d vitamin D3,  1000 mg/d calcium | 76.8 | 2 | 25 |
| Jackson28 | 2006 | USA | 6340 | 400 IU/d vitamin D3,  1000 mg/d calcium | 70+ | 7 | 208 |
| Salovaara29 | 2010 | Finland | 3195 | 800 IU/d vitamin D3,  1000 mg/d calcium | 67.3 | 4.3 | 6 |

**Table 1.b** Characteristics of 6 RCTs comparing the PFF incidence in participants aged 65 or above between combined oral supplementation of vitamin D3 & calcium and the placebo / no treatment group.

**Assessment of risk of bias**

The RoB2 "risk of bias" assessment result for the selected 13 RCTs were illustrated in **Figure 2**. Most studies were assessed to be low or moderated risk of bias, and only 2 studies were evaluated as high risk of bias in at least one domain.

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**Figure 2.** RoB2 risk of bias assessment of the selected 13 RCTs.

**Oral supplementation of vitamin D3 alone**

A total of 8 RCTs explored the association between PFF incidence and oral supplementation of vitamin D3 alone. 7 RCTs indicated a lack of statistically significant correlation12, 18-22, 24, whereas the remaining one RCT suggested that oral supplementation of vitamin D3 alone could elevate the incidence of PFF.23

No significant heterogeneity was identified (**Figure 3A**, I2 = 0, Q-statistic p-value = 0.45 > 0.05); hence, fixed effect model was taken. The meta-analysis result demonstrated no significant relationship between PFF incidence and oral supplementation of vitamin D3 alone in the elderly population (**Figure 3A**, **OR** = 1.04, **95% CI**: 0.94-1.15, **p-value** = 0.46 > 0.05).

**Combined oral supplementation of vitamin D3 and calcium**

6 RCTs explored the association between PFF incidence and combined oral supplementation of vitamin D3 + calcium. 5 RCTs indicated a lack of statistically significant correlation21, 26-29, whereas the remaining one RCT suggested that combined oral supplementation of vitamin D3 + calcium could reduce the risk of PFF25.

Since I2 = 22% and Q-statistic p-value = 0.27 > 0.05, we conducted fixed model (**Figure 3B**). The result indicated that combined oral supplementation of vitamin D3 + calcium could significantly reduce the incidence of PFF in the elderly population (**Figure 3B**, **OR** = 0.80, **95% CI**: 0.69-0.94, **p-value** = 0.005 < 0.05).

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**Figure 3.** Forest plot for PFF incidence comparisons between

oral supplementation of vitamin D3 alone and the placebo / no treatment group **(A)** combined oral supplementation of vitamin D3 + calcium and the placebo / no treatment group **(B)**.

**Sensitivity analysis**

The result of sensitivity analysis showed that among 8 RCTs designed for oral supplementation of vitamin D3 alone, the exclusion of studies deemed of low quality did not alter the original findings in a qualitative manner. If Smith’s study was ignored, the absence of a significant association between PFF incidence and oral supplementation of vitamin D3 alone in the elderly population persisted (**Figure 4A**, **OR** = 1.01, **95% CI**: 0.91-1.13, **p-value** = 0.86 > 0.05). However, in the sensitivity analysis of 6 RCTs investigating combined oral supplementation of vitamin D3 + calcium, excluding low-quality studies altered the initial research findings. Specifically, if the study by Chapuy in 1992 was omitted, we observed that the combined oral supplementation of vitamin D3 and calcium no longer exerted an impact on the incidence of PFF in the elderly population (**Figure 4B**, **OR** = 0.90, **95% CI**: 0.74-1.10, **p-value** = 0.32 > 0.05).



**Figure 4.** Sensitivity analysis on 8 RCTs designed for oral supplementation of vitamin D3 alone (**A**) and 6 RCTs designed for combined oral supplementation of vitamin D3 + calcium (**B**)

**Discussion**

The present meta-analysis, employing rigorous inclusion criteria, encompassed 13 RCTs with a total of 55,830 participants to ascertain the efficacy of oral supplementation with vitamin D3 in reducing the incidence of PFF among geriatric population. Our investigation indicates that administering vitamin D3 orally alone to elderly individuals did not show a substantial relationship with the incidence of PFF (**OR** = 1.04, **95% CI**: 0.94-1.15, **p-value** = 0.46 > 0.05), a conclusion that remained consistent even after removing the study considered to be of low quality (**OR** = 1.01, **95% CI**: 0.91-1.13, **p-value** = 0.86 > 0.05). Meanwhile, when vitamin D3 was combined with calcium and administered orally, a notable decrease in PFF occurrence among the elderly was observed (**OR** = 0.80, **95% CI**: 0.69-0.94, **p-value** = 0.005 < 0.05). Nevertheless, after excluding the study of inferior quality, this association ceased to maintain statistical significance (**OR** = 0.90, **95% CI**: 0.74-1.10, **p-value** = 0.32 > 0.05).

Bischoff-Ferrari et al. previously identified a significant association between daily supplementation of vitamin D3 alone and a lower incidence of PFF in adults aged 65 years or older; however, their pooled analysis, being published earlier, suffered from limitations such as inadequate sample sizes and follow-up durations in some of their included RCTs, thereby affecting the generalizability and statistical power of the final results to some extent.30 Bischoff-Ferrari concurrently proposed that the efficacy of daily oral supplementation of vitamin D3 in reducing PFF incidence might only be significant in high-dose level (800 IU or more per day). Nevertheless, the sensitivity analysis within the scope of our meta-analysis revealed that even upon excluding RCTs with doses below 800 IU per day, this association remained statistically insignificant.30

The studies conducted by Avenell and Manoj on the combined oral supplementation of vitamin D3 + calcium produced outcomes that were consistent with the findings of our meta-analysis, demonstrating that the intervention effectively reduces the incidence of PFF in the elderly population. 31, 32 It is important to note that our meta-analysis also underscores the influence of low-quality RCTs on the results of the effect analysis. Like previous similar analyses, we included the study by Chapuy from 1994.25 However, the participants from Chapuy’s study were confined to a specific medical institution, leading to its classification as a low-quality RCT in our risk of bias assessment.25 As elucidated in the sensitivity analysis section, upon excluding this low-quality RCT, the significant association between combined oral supplementation of vitamin D3 and calcium and the reduction in PFF incidence among geriatric population was no longer statistically significant. After excluding low-quality studies, our findings align with those of the US Preventive Services Task Force (USPSTF). The USPSTF concluded that current evidence is insufficient to assess the balance of benefits and harms of combined oral supplementation with doses greater than 400 IU of vitamin D3 and greater than 1000 mg of calcium daily for primary prevention of osteoporotic fractures in community-dwelling, asymptomatic men and premenopausal women.14

Admittedly, our study also consists of some limitations. Firstly, the participants in the selected RCTs predominantly originated from developed countries in Europe and North America, with a lack of relevant data from Asia and Africa, potentially impacting the generalizability of the conclusions. Secondly, some recent studies indicate an association between vitamin D3 deficiency and the risk of PFF33, 34; however, we did not specifically consider this subgroup of individuals. Finally, despite the lack of evidence that vitamin D3 can reduce the incidence of PFF, vitamin D3 may still play a role in reducing mortality caused by PFF and alleviating the symptoms of PFF patients, which is a new direction for subsequent research.

**Conclusion**

Oral supplementation of vitamin D3 alone in elderly individuals did not exhibit a significant association with PFF incidence (**OR** = 1.04, **95% CI**: 0.94-1.15, **p-value** = 0.46 > 0.05). Limited evidence suggested that combined oral supplementation of vitamin D3 and calcium could reduce the incidence of PFF in the elderly population (**OR** = 0.80, **95% CI**: 0.69-0.94, **p-value** = 0.005 < 0.05), beacuse after excluding low-quality RCTs, the protective effect was no longer statistically significant (**OR** = 0.90, **95% CI**: 0.74-1.10, **p-value** = 0.32 > 0.05). Hence, in the elderly population, there is a lack of robust evidence demonstrating that oral supplementation of vitamin D3 could reduce the incidence of PFF.

**Declaration of Conflicting Interests**

The authors declare no conflict of interest.

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