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# Optimising Vitamin D Levels after Hip Fractures

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## Abstract

Older people presenting with hip fractures requiring surgery have a high prevalence of hypovitaminosis D, which is an important modifiable risk factor for falls and fractures. Inadequate sun exposure is the main reason for vitamin D deficiency in older people. Vitamin D supplements, with or without calcium, have been shown to reduce falls and fracture risk in this population. A small number of randomised controlled trials (RCTs) have shown that increased 25-OHD levels with a loading dose of vitamin D may improve falls and fractures. It is not previously known whether oral vitamin D replenishment using a loading dose is effective, and if it is, what is the interplay this is with patient characteristics, in particular lower limb mobility and 25-OHD levels. The results of a recent multisite randomised controlled trial (REVITAHIP) provide early evidence of the benefits of an early loading-dose oral vitamin D replenishment on functional mobility, falls, fractures, grip strength, health-related quality of life and mortality.

**Keywords:** Fragility fractures, femoral fractures, cholecalciferol, aged care, osteoporosis, rehabilitation, trauma surgery

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## 1. Introduction

Hip fractures and related disabilities are important public health issues for older people around the world. Despite the age-adjusted hip fracture rates reducing in countries such as Australia, Italy, France, Japan and the United States, the actual numbers of fractures are increasing steadily due to the increasing proportion of the elderly population [1]. Outcomes for people who survive hip fracture are of concern, with more than one-quarter dying within a two-year period [2] and most not recovering their previous level of function. For example, around half of the people surviving a hip fracture require long-term help with routine activities and cannot walk unaided, one quarter require full-time nursing-home care [3] and 16% reporting depressive symptoms [4]. Given that people require assistance to recover from a

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hip fracture, personal and societal costs are often incurred following surgery due to the need for rehabilitation, outpatient visits for follow-up treatment, temporary residential aged care facility placement if required and assistance with activities of daily living at home during the recovery period. Given these factors, the quest in improving function after a hip fracture has the potential to be of enormous benefit to elderly people by reducing disability and improving quality of life. This can then reduce direct treatment costs and costs of long-term community or residential aged care services. The ability to mobilise is the key activity underlying functioning and quality of life.

Low vitamin D levels are commonly associated with hip fracture in older people [4] and occur because of multiple factors such as decreased sun exposure with reduced skin production of vitamin D and low dietary D2/D3 intake. More importantly, the relationship between vitamin D and frailty is postulated to be largely mediated via the development of sarcopenia, a condition characterised by a combination of the reduction in muscle mass, plus either muscle strength or performance.

Whilst an independent relationship has not been established on vitamin D and frailty in observational studies, there is a dearth of interventional studies yielding a positive effect on frailty using supplemental vitamin D, mainly via improvements in the physical performance parameters [5]. Further, vitamin D replacement (with calcium) has been used successfully to prevent fractures as well as falls among older people [6], and those living in the community [7]. However, in the absence of preventive treatment, hypovitaminosis D following hip fracture may result in proximal muscle weakness, pain, reduced dynamic balance and performance speed [8] affecting mobilisation during the acute postoperative and rehabilitation periods. Further, there had been concern from one RCT with the safety data of 'megadose' vitamin D increasing the risk of falls and fractures in the first 3 months of treatment [9].

A pilot study examining the efficacy and effectiveness of moderate dose oral vitamin D therapy in maintaining 25-hydroxyvitamin D (25-OHD) levels following a hip fracture found that vitamin D levels significantly fall in the first 14 days following hip fracture despite regular oral vitamin D treatment (1000 IU daily) [10]. Whilst 1000 IU of cholecalciferol is an accepted dosage for maintenance therapy, this study found that the dose only raised levels by a small amount and took a longer timeframe to do so compared with loading doses.

As a further concern, mild but especially severe hypovitaminosis D can contribute to and exacerbate symptomatic hypocalcaemia occurring rarely but significantly following intravenous bisphosphonate (zoledronic acid), a first-line recommended treatment following hip fracture [11]. Whilst rare, hypocalcaemia may be life threatening and require immediate resuscitation and evaluation, often requiring hospitalisation to prevent additional morbidity and mortality risk from seizures, tetany, refractory hypotension or arrhythmias. Therefore, optimisation of vitamin D levels after hip fractures in older people can improve osteoporosis by providing an optimal environment for medications to act on the bone matrix, as well as improving non-skeletal factors such as ensuring adequate muscle function and controlling pain. The ability to simultaneously improve skeletal and non-skeletal factors using vitamin D replenishment techniques, therefore, has enormous potential to improve mobility and functional during the

post-acute and rehabilitation periods, as well as to prevent falls and further fractures in the medium and long term.

The REVITAHIP multisite randomised controlled trial was conducted over three sites in Sydney and the Central Coast of Australia, evaluating the effect of an initial loading dose of vitamin D to improve rehabilitation outcomes following hip fractures. The study examined the impact of a loading dose of the vitamin D on physical performance measures designed to measure mobility-related disability. The results of this trial in relationship to other available trials on the effectiveness of optimisation strategies of vitamin D levels following hip fracture and its implication on public health will be discussed in this chapter.

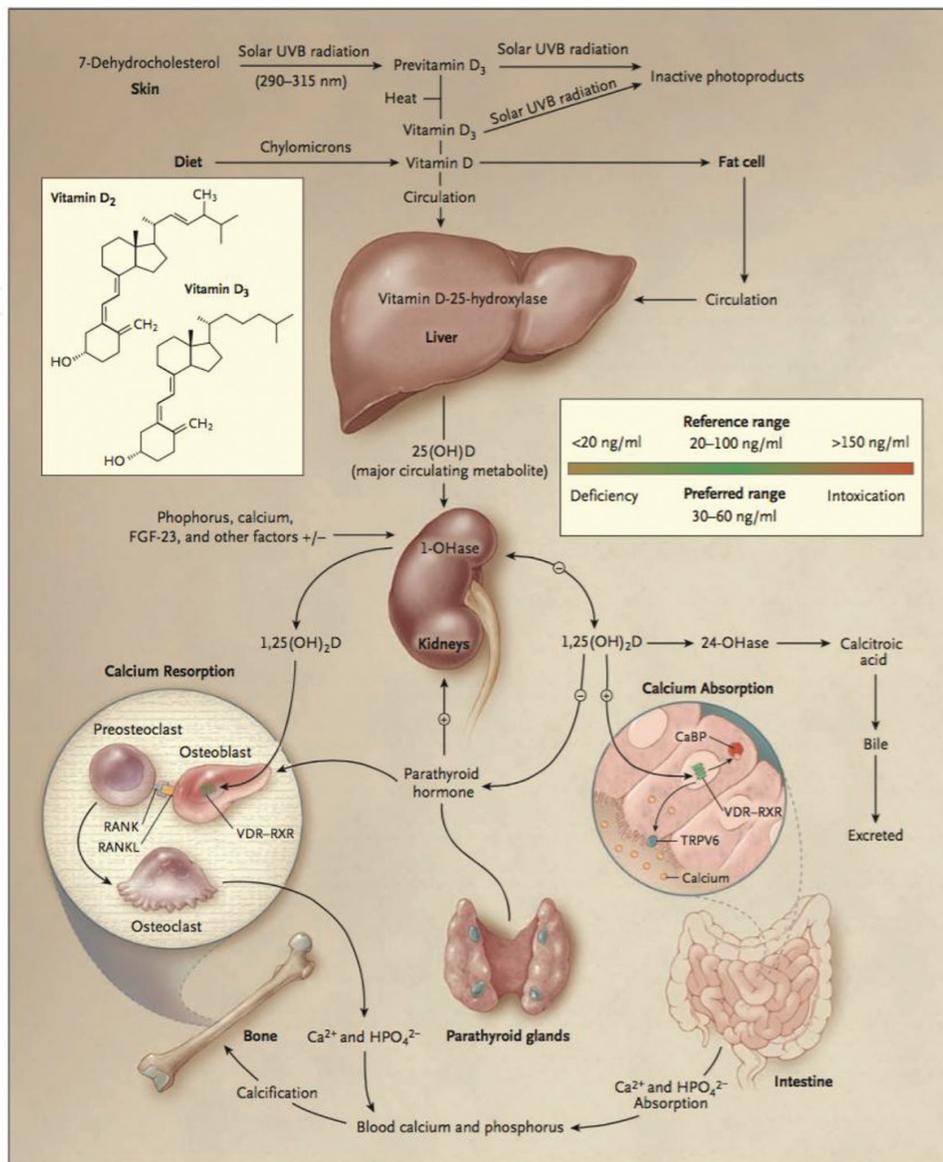
## 2. Hypovitaminosis D, hip fracture surgery and old people

### 2.1. Vitamin D synthesis (in older people)

Vitamin D is recognised to have a wide role as a prohormone, with many cells in the body having receptors for its active form. The key source of vitamin D in humans is its synthesis from sunlight, and dietary sources are less significant. The daily recommended dietary allowance (RDA) of vitamin D is 600 IU (International Units) for children and adults less than 70 years of age and 800 IU for those aged over 70 years [12].

Vitamin D from diet and the skin is metabolised to 25-hydroxyvitamin D (25-OHD) in the liver, and it is in this form that 25-OHD is used to determine one's vitamin D status. Then in the kidneys, 25-OHD is metabolised by the enzyme 25-OHD-1 $\alpha$ -hydroxylase (CYP27B1) to its active form 1,25-dihydroxyvitamin D (1,25-OHD). The renal production of 1,25-OHD is regulated tightly by plasma parathyroid hormone (PTH) levels, as well as serum calcium and phosphorus levels [6, 7]. Furthermore, there is a strong negative feedback regulation by 1,25-OHD itself in its own production (**Figure 1**). Inadequate sun exposure is the main reason for vitamin D deficiency in older people [13].

Humans obtain vitamin D from exposure to sunlight, from their diet and from dietary supplements (as above). Whilst theoretically a diet rich in oily fish helps to improve 25-OHD levels and prevents vitamin D deficiency, in reality this is challenging to achieve, in particular for older people and those with dietary restrictions. Solar ultraviolet B radiation (wavelength, 290–315 nm) traverses the skin and converts 7-dehydrocholesterol to previtamin D<sub>3</sub>, which is rapidly converted to vitamin D<sub>3</sub>. Because any excess previtamin D<sub>3</sub> or vitamin D<sub>3</sub> is destroyed by sunlight, there is also reversible conversion to inactive sterols in the skin, and excessive exposure to sunlight does not cause vitamin D<sub>3</sub> intoxication [14]. Despite this, practical attempts for supervised 'sunlight therapy' in residential aged care have only produced mild 25-OHD improves, did not reach optimal levels and depended on the season of exposure [15]. On a pragmatic level, excessive ultraviolet exposure is the main cause of skin cancer, including cutaneous malignant melanoma, basal cell carcinoma and squamous cell carcinoma [16], and the general advice is 'avoid too much sun. Use sun protection. Do not use sunbeams'.



**Figure 1.** Synthesis and metabolism of vitamin D in the regulation of calcium, phosphorus and bone metabolism (from Holick [8]).

Age is the most important factor in vitamin D synthesis. The capacity of older people to synthesise vitamin D after UVB exposure has been investigated in laboratory and clinical studies. MacLaughlin and Holick [17] showed decreasing concentrations of 7-dehydrocholesterol with age and when irradiated, ageing skin had decreased capacity to produce previtamin D. With the ageing process, the ability to synthesise vitamin D from sunlight is reduced. Further, the ability of vitamin D to be activated to 1,25-OHD in the kidney also decreases with age. Finally, elderly people (especially those who stay mainly at home) are less likely to engage in regular exercise in the outdoor setting.

## 2.2. Definition of vitamin D deficiency

The optimal level of vitamin D has been subject to considerable debate, but a serum 25-OHD level of  $\geq 50$  nmol/L at the end of winter (with a 10–20 nmol/L higher level at the end of summer

to allow for the winter decrease) is required for optimal musculoskeletal health. 25-OHD levels are inversely associated with PTH levels until the former reach 30–40 ng/mL (75–100 nmol/L), at which point PTH levels begin to level off (at their nadir) [18]. The Working Group recommended that although higher levels are likely to play a role in other diseases, ‘there is insufficient evidence from randomised controlled trials to recommend higher targets’ [19]. The Working Group also defined vitamin D status according to levels of serum 25-OHD:

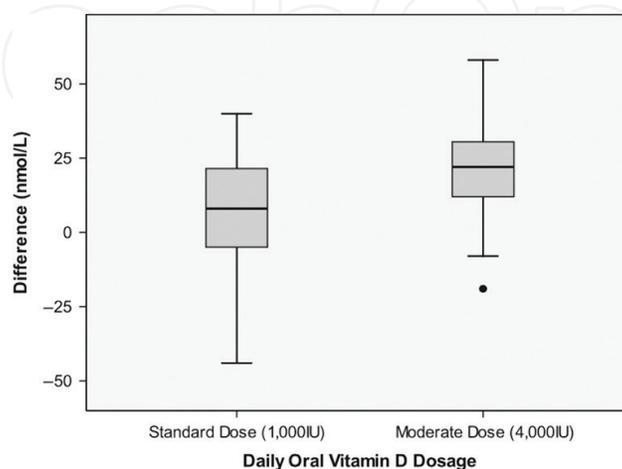
- Vitamin D adequacy:  $\geq 50$  nmol/L (at end of winter).
- Mild vitamin D deficiency: 30–49 nmol/L.
- Moderate vitamin D deficiency: 12.5–29 nmol/L.
- Severe vitamin D deficiency:  $< 12.5$  nmol/L.

### 2.3. Prevalence of vitamin D deficiency following hip fracture surgery

The reported prevalence of vitamin D deficiency following hip fracture, dependent on racial groups and gender, ranges from 65.8 to 96.7% [20, 21] and, in up to 32% of cases, is complicated by secondary hyperparathyroidism ( $PTH > 5.25$  pmol/L in the presence of hypovitaminosis D). Furthermore, soon after hip fracture surgery (at 2 weeks), 25-OHD levels can decrease after hip fracture despite standard oral vitamin D treatment (of 1000 IU daily) compared with higher replacement doses (Figure 2 [10]).

### 2.4. Correction of vitamin D deficiency in older people following hip fracture surgery

There have been several studies looking at the optimal method in replenishing 25-OHD levels following hip fracture surgery. A moderate oral dose (4000 IU daily) replacement approach can significantly improve and maintain 25-OHD levels within 2 weeks after a hip fracture, with a mean vitamin D increase in  $22.4 \pm 18.3$  nmol/L and up to 88.9% of participants with optimal 25-OHD levels [10]. de Jong et al. [22] found that substitution with 50,000 IU oral cholecalciferol daily for 7 days increased 25-OHD levels rapidly, safely and consistently. Finally,



**Figure 2.** Differences in 25-hydroxyvitamin D levels 14 days after hip fracture according to daily oral vitamin D protocol ( $n = 66$ ); 37.5% of participants on 1000 IU vitamin D reduced 25-OHD levels, from Mak et al. [10].

Lyles et al. [23], in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) Recurrent Fracture Trial, successfully utilised the strategy of a loading dose of either vitamin D3 or D2 (at a dose of 50,000–125,000 IU given orally or intramuscularly) 14 days before first infusion of a study drug. This was followed by daily supplementation with oral calcium (1000–1500 mg) and vitamin D (800–1200 IU). Whilst these studies highlight the various strategies that can be utilised to replenish vitamin D (oral/intramuscular), loading dose followed by regular daily or interval dosing, there has been a sparsity of outcomes data including lower limb function, falls and fractures and mortality.

### 3. REVITAHIP Study

The Replenishment of Vitamin D in Patients with Hip Fracture (REVITAHIP) Trial was a multicenter, randomised, double-blind and placebo-controlled trial involving patients with recent hip fracture [24]. Patients were randomly assigned to receive either an oral loading dose of cholecalciferol (at a dose of 250,000 IU vitamin D3) or placebo, followed by daily supplementation with oral vitamin D (800 IU) and calcium (600 mg). Deviation from this protocol occurred for any participants with an initial serum 25-hydroxyvitamin D level of 10 nmol/L or less due to the known risks. Such cases received a 14-day loading dose of vitamin D3 (at a dose of 4000 IU given orally), continuing on as per other patients for the remainder of the trial. Patients were monitored for up to 26 weeks with telephone interviews or clinic/home visits at 2, 4, 12 (telephone interview only) and 26 weeks. All study procedures were approved by the local institutional review board at each participating site (HREC Number 10/HARBR/14).

#### 3.1. Results of the REVITAHIP Study

The REVITAHIP cohort included 220 participants, with a mean age of 83.9 years (SD 7.1) and 77.1% women. The REVITAHIP study [25, 26] found that in these patients following a hip fracture (within 7 days, median 3.3), a loading dose of 250,000 IU vitamin D3 compared with placebo (the 'Active' method) resulted in higher 25-OHD levels and a greater percentage with target 'sufficient' 25-OHD levels (>50 nmol/L [31]), with no significant differences in gait velocity at 4 weeks. A significantly reduced incidence of falls was also noted in the active group compared with placebo over the study period. This is surprising because in the study cohort the baseline level of 25-OHD is higher than in other studies of patients with hip fracture, and the differences in 25-OHD at weeks 2 and 4, between the active and placebo groups, whilst significant, were not large. Further, there was a significant reduction in falls and non-significant reduction in mortality (**Figure 3**).

#### 3.2. Limitations to the REVITAHIP trial

There were several limitations to this research. The REVITAHIP study patients were slightly younger with less unhealthy than are patients with hip fracture in the general population, as suggested by data regarding 1-year mortality. Despite this, patients in our study ranged widely in age (up to 101 years), with a significant percentage having cognitive impairment. Perhaps due to inclusion and exclusion criteria, there was under-recruitment of people with

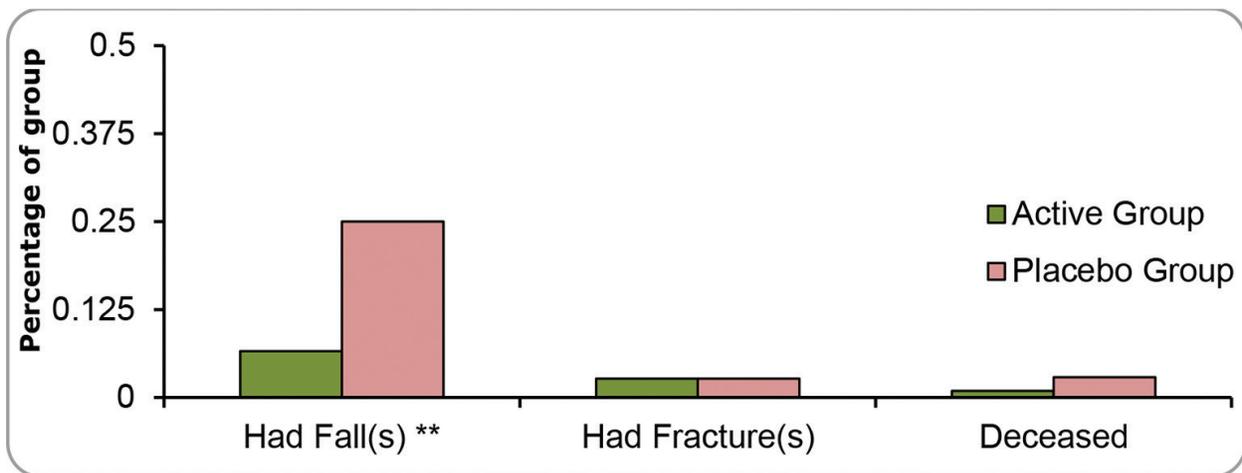


Figure 3. Fall, fractures and deaths over 4 weeks by intervention group in the REVITAHIP trial ( $p = 0.024$ ).

severe pre-existing disability compared to the usual population with hip fractures: (1) low number of participants from residential aged care facility (10%) and (2) participants with fewer total comorbidities. The REVITAHIP participants did have relatively good function with moderate independence prior to their hip fracture, most likely due to the inclusion and exclusion criteria. However, the study team argued that this could be considered a strength, as it alerts clinicians to potential problems (e.g. in ADLs, mobility, high psychotropic medication use) even in a relatively well-functioning cohort.

The REVITAHIP participants had higher levels of baseline 25-OHD compared to previous cohorts (e.g. the ICHIBAN cohort [26] had a lower baseline 25-OHD levels than the REVITAHIP ( $44.1 \pm 23.2$  vs  $53.1 \pm 24.2$  nmol/L)), likely owing to a less frail participant population. Another limitation was that the planned sample size of 450 could not be achieved due to less efficient than expected participant recruitment. Nevertheless, as 25-OHD levels in the REVITAHIP trial were higher than usual levels, it may have underestimated its effects on falls, fractures and death. It was also noted that the falls reduction effects at week 4 were higher than expected from other studies.

Furthermore, due to technical difficulties with obtain accurate fall diaries over a longer term, the data for fall rates of participants at week 12 and 26 could not be utilised and were therefore not able to be included in the presentation of the data. This is mainly due to the limited funds available resulting in limited to no administrative assistance with the trial. Documentation of various patient outcomes would have been improved with such help. Consequently, results of health services and community service utilisation and the economics analyses were not reported in the trial as data were incomplete, and analyses were not able to be done.

Finally, there was no direct comparison in this study between a loading dose and a high daily dose of vitamin D, so absolute conclusions cannot be drawn on optimal dosing regimen. The advantages of the loading dose were good compliance and likely rapid increase in 25OHD, both of which are likely to be helpful in this setting. But there are some disadvantages of loading doses, as opposed to daily doses of vitamin D [27], so the dosing issue is unclear.

Nevertheless, the study appears to indicate that a higher D status in this group of patients is beneficial for overall outcomes.

#### **4. Implications of research findings**

It has been generally established that vitamin D, usually with calcium supplement, decreases falls and fractures in older people from aged care facilities [28] but has not been proven convincingly in post-menopausal women in large meta-analyses. Following a hip fracture, vitamin D levels are universally low, and its levels may drop as early as 2 weeks following hip fracture [10]. Poor adherence to vitamin D therapy has been shown to compromise the efficacy of this treatment for fracture reduction and to increase medical costs [29]; such findings have been particularly notable in frail older adults [30]. Vitamin D deficiency is frequently observed in older patients and is associated with an increased risk of hypocalcaemia when intravenous bisphosphonates are administered before a normal vitamin D level has been achieved [8].

The REVITAHIP study was the first to show that treatment with 250,000 IU cholecalciferol within 7 days after hip fracture surgery (followed by regular maintenance vitamin D) is associated with higher percentage of replete 25-OHD and may reduce the rate of falls. However, the positive results occurred despite the group of participants having a higher baseline 25-OHD (with a resultant smaller than expected gain in 25-OHD levels), and the recruitment numbers were smaller than initially planned for a sample size to detect a difference in gait velocity. Thus, in practical terms, the use of the Active REVITAHIP vitamin D replenishment method would appear to be an efficient (through ease of administration) and effective means of optimising vitamin D levels for the older patients following hip fracture surgery. Indeed, several meta-analyses of studies of vitamin D supplementation, usually with calcium supplementation, have shown an overall benefit on falls and fracture reductions [31]. The intervention also had an optimal safety profile (one case of hypercalcaemia) and was relatively inexpensive to administer.

#### **5. Recommendations of research findings**

Currently, Australia is unique in that it does not have a 50,000 IU oral vitamin D tablet, readily available compared to other countries. Whilst (1) a liquid form of cholecalciferol exists (OsteVit-D) which potentially can be administered in higher doses; (2) preparations such as Fosamax Plus D (containing a weekly dose of 5600 IU daily); and (3) higher-dose formations of vitamin D manufactured from compounding pharmacists, the former (1) may be liable to accurate dosage; (2) may not be practical to administer whilst hip fractured patients are recovering in the post-acute period; and (3) the universal reliability of compounding pharmacist cannot be guaranteed. The approval of higher-dose vitamin D such as from the Active REVITAHIP method should be made readily available through Australian Government subsidies, and vitamin D manufacturers from overseas be supported to import such products into Australia.

For most other countries, higher dosage vitamin D formulations are available both in oral and injectable formats.

Finally, the author advocates that the outcomes of the Active REVITAHIP method of vitamin D replenishment be disseminated, and adaptation into local guidelines be considered.

## 6. Conclusion

The studies reviewed in this chapter provides an overall positive view on vitamin D replacement (which is deemed necessary) and showed that treatment with 250,000 IU cholecalciferol after hip fracture surgery in older patients (followed by regular daily maintenance vitamin D) is associated with higher percentage of replete 25-OHD and reduced rate of falls in the short term. Recognition of these factors may also improve the delivery of post-hip fracture surgical and rehabilitation care in this often vulnerable population. The author recommends further confirmation of the results of this latest research using a larger number of participants (with a higher diversity in ethnic populations who may be likely to have higher prevalence of hypovitaminosis D) in future studies.

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