EnM OPEN ACCESS
ENDOCRINOLOGY AND METABOLISM

Review Article

Endocrinol Metab 2026 Forthcoming.
https://doi.org/10.3803/EnM.2029.2938
pISSN 2093-596X · eISSN 2093-5978

Revisiting the Role of Vitamin D in Fracture Prevention in the Era of Mega-Trials

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For decades, vitamin D has been a cornerstone of preventive medicine. However, recent large-scale randomized controlled trials have failed to replicate the broad benefits previously observed in epidemiological studies, particularly with respect to fracture and fall prevention in vitamin D-replete populations. Moreover, growing evidence suggesting an increased fall risk associated with high-dose bolus administration has necessitated a re-evaluation of safety assumptions. This review synthesizes these discordant findings to propose a framework grounded in precision medicine. We explore the 'divergent threshold' hypothesis, whereby a serum 25-hydroxyvitamin D level of 20 to 30 ng/mL may be sufficient for skeletal health, whereas a higher threshold of 40 to 50 ng/mL appears necessary to achieve metabolic benefits, such as diabetes prevention in non-obese individuals. Ultimately, we advocate a shift away from a 'one-size-fits-all' paradigm toward targeted strategies that maximize efficacy while minimizing the risks associated with excess supplementation.

Keywords: Vitamin D; Fractures, bone; Vitamin D deficiency

INTRODUCTION

Vitamin D, often termed the 'sunshine hormone,' has been a cornerstone of musculoskeletal preventive medicine for decades. Beyond its classical role in calcium homeostasis and bone mineralization, the identification of vitamin D receptors (VDRs) in a wide range of tissues, including skeletal muscle, fueled enthusiasm for its potential role in maintaining muscle function and preventing falls [1,2]. Supported by this biological plausibility and by observational studies demonstrating a robust inverse association between serum 25-hydroxyvitamin D (25(OH)D) levels and the risk of fractures and falls, the medical community has witnessed a global surge in vitamin D screening and empiric supplementation over the past two decades [3]. During this period, correcting 'deficiency' emerged as a primary clinical objective, often applied indiscriminately to otherwise healthy individuals in the general population.

However, unexpected discordances have emerged in recent years. Although observational studies consistently suggested a protective effect, high-quality, large-scale randomized controlled trials (RCTs), often referred to as 'mega-trials,' have largely failed to reproduce these benefits. Landmark investigations, including the Vitamin D and Omega-3 Trial (VITAL), the Vitamin D3-Omega3-Home Exercise-Healthy Aging and Longevity (DO-HEALTH) study, and the D-Health trial, have reported 'largely null findings' with respect to fracture and fall

Received: 23 January 2026, **Revised:** 30 January 2026, **Accepted:** 3 February 2026

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prevention in vitamin D-replete populations [4-6]. Furthermore, updated systematic reviews and meta-analyses published in 2025 have reinforced the conclusion that vitamin D supplementation does not reduce fall risk among community-dwelling older adults, with some analyses even suggesting potential harm at higher doses [7-9].

These findings have necessitated a paradigm shift in clinical practice guidelines. Most notably, the 2024 Endocrine Society Clinical Practice Guideline now recommends against empiric vitamin D supplementation in healthy adults younger than 75 years, signaling a decisive transition from universal screening toward a more targeted, risk-based approach [10].

This review aims to critically synthesize evidence from recent mega-trials and updated meta-analyses while exploring the mechanistic pathways that may explain the discordance between observational and interventional findings. In addition, we discuss the clinical implications of these data by bridging global guideline recommendations with the distinct epidemiological context of South Korea, where vitamin D deficiency remains prevalent. Through this lens, we propose a framework for precision medicine in vitamin D therapy.

BIOLOGICAL PLAUSIBILITY AND OBSERVATIONAL EVIDENCE

The rationale for vitamin D supplementation in the prevention of fractures and falls is grounded in well-established physiological mechanisms. Vitamin D plays a central role in calcium and phosphate homeostasis, and its active metabolite, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), facilitates intestinal calcium absorption, which is essential for appropriate bone mineralization. In the setting of severe vitamin D deficiency, secondary hyperparathyroidism develops, leading to increased bone turnover and cortical bone loss and, consequently, a heightened risk of osteoporosis and fractures [11].

Beyond skeletal health, vitamin D is also essential for muscle function. VDRs are expressed in human skeletal muscle tissue, and mechanistic studies suggest that $1,25(OH)_2D$ promotes *de novo* protein synthesis in muscle cells while modulating calcium transport within the sarcoplasmic reticulum, a process critical for effective muscle contraction [12]. Clinically, profound vitamin D deficiency is associated with proximal muscle weakness and preferential atrophy of type II muscle fibers, which play a key role in fall prevention [13]. As demonstrated in biopsy studies by Glerup et al. [13], deficiency is associated with a marked reduction in the cross-sectional area of these fibers, which are integral to the 'righting reflex' required to prevent falls. Importantly, although supplementation can restore type II fiber morphology in deficient individuals, this effect reflects correction of a pathological deficit rather than enhancement beyond the physiological baseline. This so-called 'ceiling effect' suggests that, in vitamin D-replete individuals, additional supplementation is unlikely to confer further ergogenic benefits for muscle function [13]. Furthermore, at the molecular level, although genomic VDR signaling supports muscle structure, the rapid non-genomic pathway regulates intracellular calcium influx; overstimulation of this pathway by high doses has been hypothesized to disrupt calcium homeostasis, potentially impairing neuromuscular stability rather than improving it [2].

Consistent with these biological mechanisms, numerous observational studies have reported a strong inverse association between serum 25(OH)D concentrations and the risk of adverse musculoskeletal outcomes. Meta-analyses of prospective cohort studies have demonstrated that individuals in the lowest quartile of serum 25(OH)D levels experience a significantly higher risk of hip fractures and falls compared with those in the highest quartile [14,15]. Nevertheless, causal inference from these associations remains challenging because of the potential influence of confounding factors and reverse causality. For example, frailty, poor overall health, and reduced mobility often lead to decreased outdoor activity and sunlight exposure, thereby lowering vitamin D levels. In this context, low vitamin D status may function more as a marker of underlying ill health than as an independent causal driver of fractures and falls [16].

MUSCULOSKELETAL HEALTH: PARADOX OF FRACTURES AND FALLS

The translation of biological plausibility into clinical efficacy has proven far more complex than initially anticipated. Although the rationale for vitamin D supplementation in fracture and fall prevention appeared robust on the basis of observational data, the transition to large-scale RCTs has revealed a striking paradox (Table 1). This section critically examines the persistent null findings for fracture prevention alongside the emerging U-shaped risk curve for falls, integrating evidence from recent mega-trials and updated meta-analyses to challenge the long-held dogma of universal supplementation.

For decades, the prevailing clinical assumption held that higher serum 25(OH)D levels would correlate linearly with increased bone density and a reduced risk of fractures. However, recent mega-trials conducted in community-based populations

Table 1. Summary of Key Randomized Controlled Trials

Study	No. of population	Intervention vs. Control	Baseline 25(OH)D	Primary outcome	Key findings
VITAL	USA, ≥50 yr (*n*=25,871)	2,000 IU/day vs. placebo	30.8 ng/mL	Fractures (total, hip, vertebral)	No effect regardless of baseline levels
DO-HEALTH	Europe, ≥70 yr (*n*=2,157)	2,000 IU/day vs. placebo	22.4 ng/mL	Non-vertebral fractures	No effect in active seniors
D-Health	Australia, 60–84 yr (*n*=21,315)	60,000 IU/mo vs. placebo	~25–30 ng/mL	Total fractures	No effect
D2d	USA, prediabetes (*n*=2,423)	4,000 IU/day vs. placebo	27.7 ng/mL	Incident diabetes	No effect in the total population Benefit observed in severe deficiency (<12 ng/mL) and high intratrial levels (40–50 ng/mL)

25(OH)D, 25-hydroxyvitamin D; VITAL, Vitamin D and Omega-3 Trial; IU, international unit; DO-HEALTH, Vitamin D3-Omega3-Home Exercise-Healthy Aging and Longevity; D2d, Vitamin D and Type 2 Diabetes.

have dismantled this model, instead supporting a 'threshold hypothesis.' The VITAL trial, which enrolled over 25,000 adults in the United States, served as a definitive test of this assumption. Despite its rigorous design, daily supplementation with 2,000 IU of vitamin D_3 failed to reduce the risk of total, non-vertebral, or hip fractures when compared with placebo [4]. Crucially, this absence of benefit persisted even among participants with lower baseline 25(OH)D concentrations (<20 ng/mL). These findings were subsequently corroborated by the DO-HEALTH study conducted in Europe [5] and the D-Health trial in Australia [6], both of which similarly demonstrated no significant reduction in fracture risk among vitamin D-replete older adults.

Recent systematic reviews and meta-analyses have synthesized these trial-level findings to provide a more definitive consensus. The 2024 evidence review underpinning the U.S. Preventive Services Task Force (USPSTF) draft recommendation concluded that vitamin D supplementation confers 'no net benefit' for the primary prevention of fractures in community-dwelling postmenopausal women or men [9]. Collectively, this body of evidence supports the interpretation of vitamin D as a threshold nutrient, whereby once a sufficient physiological level (likely around 20 ng/mL) is achieved, additional supplementation yields no further skeletal benefit. Consequently, low serum 25(OH)D concentrations observed in epidemiological studies are increasingly interpreted as markers of underlying ill health, reflecting reverse causality rather than acting as independent drivers of fracture risk [16].

If the fracture data primarily suggest futility, the evidence concerning falls raises a more concerning signal, including the possibility of harm. The relationship between vitamin D status and fall risk appears to follow a U-shaped curve, in which both deficiency and excess are associated with increased risk. This paradox was most clearly illustrated in the study by Sanders et al. [17], in which administration of a high-dose annual bolus (500,000 IU) was associated with a significant increase in both falls and fractures.

Crucially, the mode of vitamin D administration appears to be a key determinant of safety. A comprehensive meta-analysis [18] provided important insight into this dose-response relationship. By stratifying studies according to dosing interval, the authors demonstrated that daily supplementation with 800 to 1,000 IU was associated with a modest reduction in fall risk, whereas intermittent or high-dose bolus regimens failed to demonstrate benefit and, in some contexts, trended toward harm. These findings are consistent with results from the Study To Understand Fall Reduction and Vitamin D in You (STURDY) trial, which showed that higher daily doses (≥1,000 IU) conferred no greater benefit than a low dose (200 IU) and exhibited a trend toward increased falls [19]. Furthermore, a recent systematic review and meta-analysis by Torres-Lopez et al. [7], focusing on community-dwelling older adults, reinforced this conclusion by reporting no overall reduction in fall risk with supplementation (odds ratio, 0.99; 95% confidence interval [CI], 0.95 to 1.03). This finding aligns with the 2024 USPSTF evidence review, which similarly identified no net benefit of vitamin D supplementation for fall prevention in this population [9].

The biological underpinnings of this 'fall paradox' likely involve disruption of neuromuscular homeostasis, particularly in the context of high-dose or bolus regimens that have been associated with increased risk. One leading mechanism involves

neuromuscular dysregulation mediated through non-genomic signaling pathways. Rapid elevations in circulating $1,25(OH)_2D$ following high-dose administration may overstimulate these pathways, resulting in an acute influx of intracellular calcium [20]. This transient calcium overload may interfere with nerve signal transmission, thereby impairing the rapid reaction times required to recover from an unexpected perturbation [7,15]. Concurrently, it has been hypothesized that elevated intracellular calcium levels may blunt muscle spindle sensitivity, delaying the stretch reflex that is critical for postural correction. In addition to these physiological mechanisms, a behavioral component described as 'activity-dependent risk' has been proposed. Improvements in subjective well-being following supplementation may encourage frail individuals to increase physical activity; paradoxically, this heightened mobility may expose them to a greater number of fall opportunities before sufficient gains in strength and balance have occurred [16].

EXTRASKELETAL HEALTH: METABOLIC OUTCOMES

Beyond its classical skeletal roles, vitamin D has long been implicated in metabolic health, particularly with respect to improving insulin resistance and preserving pancreatic beta-cell function [21-23]. The Vitamin D and Type 2 Diabetes (D2d) study, funded by the U.S. National Institutes of Health (NIH), was designed as a definitive investigation to determine whether vitamin D supplementation could prevent progression from prediabetes to overt diabetes [24]. The study enrolled 2,423 adults meeting established criteria for prediabetes and randomized them to receive either 4,000 IU of vitamin D_3 daily or a placebo. A critical aspect of the trial design was the absence of selection based on vitamin D deficiency; notably, the mean baseline serum 25(OH)D level was 27.7 ng/mL, indicating a largely vitamin D-replete cohort. In the primary intention-to-treat analysis conducted over a median follow-up of 2.5 years, the vitamin D group exhibited a 12% reduction in the risk of developing diabetes compared with the placebo group (hazard ratio [HR], 0.88; 95% CI, 0.75 to 1.04). However, this difference did not reach statistical significance (P=0.12) [24], leading to the conclusion that vitamin D supplementation does not provide a preventive benefit in the general population of adults with prediabetes.

However, prespecified and *post hoc* analyses of the D2d trial offer important insights into which subgroups may benefit and the magnitude of supplementation required, thereby supporting a more targeted approach [25]. First, among a small subgroup of participants with severe baseline vitamin D deficiency (<12 ng/mL), supplementation was associated with a 62% reduction in diabetes risk (HR, 0.38; 95% CI, 0.18 to 0.80), suggesting that correction of a profound deficit may confer substantial metabolic benefit. Second, analyses stratified by achieved serum 25(OH)D concentrations revealed a dose-response relationship. Participants who maintained mean serum levels of 40 to 50 ng/mL during the trial experienced a 52% lower risk of diabetes compared with those maintaining levels of 20 to 30 ng/mL, with risk reduction increasing to 71% among those exceeding 50 ng/mL [25]. Third, the preventive effect was markedly more pronounced in non-obese participants (body mass index <30 kg/m^2). In contrast, among obese individuals, the lipophilic nature of vitamin D may promote sequestration within adipose tissue, thereby reducing its bioavailability and attenuating increases in circulating 25(OH)D levels despite high-dose supplementation [25,26].

Taken together, these findings demonstrate that vitamin D is not a universal solution for diabetes prevention; instead, they support a threshold-based model. Crucially, this model implies that the optimal serum threshold for metabolic health may differ from that required for skeletal outcomes. While serum 25(OH)D levels of 20 to 30 ng/mL may be sufficient for fracture prevention, metabolic benefits, including improvements in insulin sensitivity, may require a higher threshold, potentially in the range of 40 to 50 ng/mL. Consequently, vitamin D supplementation may represent an effective precision strategy for selected populations, particularly non-obese individuals with prediabetes and low baseline vitamin D status, rather than a generalized recommendation applicable to all adults (Fig. 1).

DIFFERENCES IN CURRENT GUIDELINES

Although the null findings from mega-trials have prompted health authorities worldwide to reassess and revise clinical practice guidelines, the direction of these revisions has diverged substantially according to regional epidemiological context. This divergence underscores the importance of adapting global evidence to local population characteristics and nutritional realities.

In the United States, where food fortification strategies (such as fortification of milk and cereals) are widely implemented, the prevalence of vitamin D deficiency in the general population is comparatively low. As a result, recent guideline updates have emphasized reducing low-value care and avoiding unnecessary medicalization. The USPSTF, in its 2024 draft recommendation, issued a grade D statement against vitamin D supplementation for the primary prevention of fractures and falls in community-

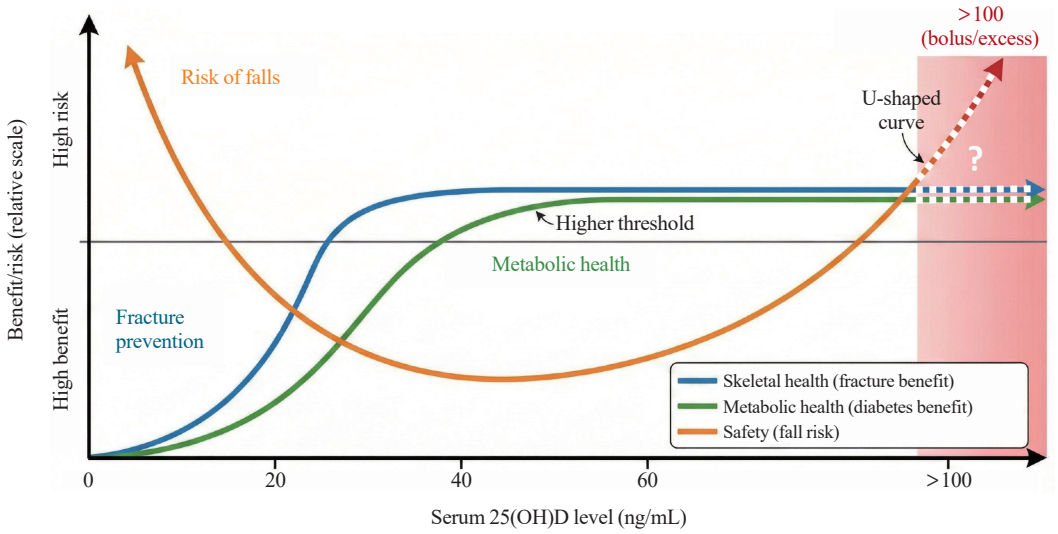

Fig. 1. Conceptual model of divergent thresholds and safety zones for vitamin D supplementation. This diagram illustrates the theoretical relationship between serum 25-hydroxyvitamin D (25(OH)D) concentrations and clinical outcomes based on current evidence. Skeletal health (blue line): Benefits for fracture prevention increase steeply at low concentrations and plateau at approximately 20 ng/mL, supporting the conventional threshold hypothesis. Metabolic health (green line): Extraskeletal benefits, including improvements in insulin sensitivity and diabetes prevention, may require a higher threshold in the range of 40 to 50 ng/mL to achieve maximal effect. Safety/fall risk (orange line): Fall risk follows a U-shaped relationship, with elevated risk at severe deficiency, a nadir within the physiological range, and a potential increase at excessive levels, particularly in the context of high-dose bolus administration. The dotted lines and question mark within the pink shaded region (>60 ng/mL) denote areas of uncertainty, reflecting limited and inconclusive evidence regarding toxicity and precise dose-response relationships at supraphysiological serum concentrations.

dwelling adults [9]. This recommendation reflects the assessment that potential harms, including nephrolithiasis, combined with the absence of net benefit observed in trials such as VITAL, outweigh any marginal advantages in a largely vitamin D-sufficient population.

Similarly, the 2024 Endocrine Society Clinical Practice Guideline advises against empiric vitamin D supplementation in healthy adults younger than 75 years and discourages routine screening of serum 25(OH)D levels [10]. Nevertheless, supplementation is recommended for selected subgroups, including adults aged 75 years and older, pregnant individuals, and those at elevated metabolic risk, such as patients with prediabetes. Importantly, consistent with safety concerns related to falls, the guideline explicitly favors daily low-dose supplementation over intermittent high-dose bolus regimens [10].

In contrast, South Korea faces a distinct epidemiological challenge. Despite its status as a developed nation, the prevalence of vitamin D deficiency remains strikingly high. Data from the Korea National Health and Nutrition Examination Survey (KNHANES) indicate that deficiency, defined as serum 25(OH)D levels below 20 ng/mL, affects approximately 65.7% of Korean men and 76.6% of Korean women [27]. This high prevalence has been attributed to lifestyle factors, including limited outdoor activity, widespread sunscreen use, and dietary patterns that provide relatively low vitamin D intake [27].

Against this backdrop, the Korean Society for Bone and Mineral Research (KSBMR) maintains a more proactive set of clinical recommendations [28]. The society advises a daily intake of 800 to 1,000 IU of vitamin D for all adults older than 50 years and for postmenopausal women. In addition, it recommends maintaining serum 25(OH)D levels above 20 ng/mL for general prevention and above 30 ng/mL for individuals with osteoporosis or those receiving pharmacological therapy [28]. This more intervention-oriented strategy reflects recognition that the baseline nutritional status of the Korean population differs fundamentally from that of the largely vitamin D-replete cohorts enrolled in Western mega-trials.

CONCLUSIONS

The scientific understanding of vitamin D is evolving from a period of enthusiasm toward one of evidence-based precision. Recent mega-trials have clarified that vitamin D is not a universal solution for all clinical outcomes. At the same time, these tri-

als have reinforced that vitamin D remains an essential therapeutic agent for individuals with true deficiency.

First, with respect to skeletal health, the evidence confirms that additional supplementation provides no fracture benefit in individuals who are already vitamin D-replete. Second, from a safety standpoint, and in order to circumvent the paradox of increased falls, clinical practice should pivot away from high-dose intermittent bolus regimens in favor of consistent daily low-dose administration, such as 800 to 1,000 IU. Lastly, regarding metabolic outcomes, a higher serum threshold of 40 to 50 ng/mL may be required to elicit extraskeletal benefits such as diabetes prevention, an approach that appears to be particularly effective in non-obese individuals with prediabetes.

Clinicians must now move decisively from a 'one-size-fits-all' strategy toward targeted precision medicine. In regions with adequate nutritional status, such as the United States, de-implementation of routine screening and empiric supplementation is appropriate. By contrast, in countries with endemic deficiency, including South Korea, identifying high-risk populations—such as young women and older adults—and ensuring physiological sufficiency through safe dosing regimens remains a critical public health priority. By bridging global trial evidence with local epidemiological realities, clinicians and policymakers can optimize the therapeutic value of this 'sunshine hormone' while minimizing unnecessary risks.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

This study was funded by the Korean Endocrine Society.

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