ОГЛЯДИ ТА РЕЦЕНЗІЇ

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The impact of vitamin D supplementation on post-operative recovery in fracture patients: a meta-analysis

P. W. Nurikhwan [1], G. G Jangkang [1], S. L. Ong [2], Z. Noor [1], H. D. Putera [1]

[1] Lambung Mangkurat University, Banjarmasin, South Kalimantan, Indonesia
[2] Udayana University, Denpasar, Bali, Indonesia

Fractures remain a major cause of disability, particularly in older adults, despite advances in surgical management. Postoperative complications such as delayed union, persistent pain, and impaired functional recovery continue to challenge orthopaedic outcomes. Vitamin D plays a critical role in bone remodelling, muscle function, and immune regulation, suggesting potential benefits in postoperative recovery. Objective. This meta-analysis aims to evaluate the effect of vitamin D supplementation on postoperative fracture recovery, focusing on structural, functional, and clinical outcomes. Methods. A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. Electronic databases including PubMed, Scopus, ProQuest, ScienceDirect, and Google Scholar were searched for studies published between 2000 and 2025. Eligible studies included randomized controlled trials and prospective cohorts involving adult fracture patients receiving vitamin D supplementation. Primary outcomes included bone mineral density (BMD), pain intensity (VAS), functional outcomes (ODI), and biochemical markers. A random-effects model was applied to pool the data. Results. Four studies met the inclusion criteria. Vitamin D supplementation significantly improved serum 25(OH)D levels and supported calcium homeostasis. Pooled analysis demonstrated improvements in BMD and functional outcomes, with reduced pain intensity and disability scores in the intervention groups. However, the magnitude of benefit varied depending on baseline vitamin D status and supplementation regimen. Daily physiological dosing showed more consistent benefits compared to high-dose bolus administration. Clinical improvements were most pronounced in patients with pre-existing vitamin D deficiency. Conclusion: Vitamin D supplementation contributes to improved postoperative fracture recovery by enhancing bone mineralization, reducing pain, and improving functional outcomes, particularly in deficient patients. Routine screening and targeted supplementation with physiological dosing may optimize recovery and should be considered as part of perioperative management in orthopaedic practice.

Мета. Проаналізувати вплив добавок вітаміну D на післяопераційне відновлення після переломів, зосереджуючись на структурних, функціональних і клінічних результатах. Методи. Систематичний огляд і метааналіз були проведені відповідно до рекомендацій PRISMA 2020. Електронні бази даних, включаючи PubMed, Scopus, ProQuest, ScienceDirect та Google Scholar, були задіяні для пошуку досліджень, опублікованих у 2000–2025 роках. Публікації, які відповідали вимогам, включали рандомізовані контрольовані дослідження та проспективні когорти за участю дорослих пацієнтів із переломами, які отримували добавки вітаміну D. Первинні результати включали мінеральну щільність кісткової тканини (МЩК), інтенсивність болю, функціональні результати та біохімічні маркери. Для порівняння даних застосовано модель випадкових ефектів. Результати. Чотири дослідження відповідали критеріям включення. Добавки вітаміну D значно покращили рівень 25(OH)D у сироватці крові та підтримували гомеостаз кальцію. Порівняльний аналіз продемонстрував покращення МЩК і функціональних показників, зі зниженням інтенсивності болю та випадків інвалідності у групах втручання. Проте величина переваги варіювалася залежно від початкового статусу вітаміну D та режиму прийому добавок. Щоденне фізіологічне дозування показало більш стабільні переваги порівняно з болюсним введенням високих доз. Клінічні покращення були найбільш вираженими в пацієнтів із попереднім дефіцитом вітаміну D. Висновок. Добавки вітаміну D сприяють пришвидшенню післяопераційного відновлення після переломів, посилюючи мінералізацію кісток, зменшуючи біль і покращуючи функціональні результати, особливо в пацієнтів із дефіцитом. Рутинний скринінг і цілеспрямований прийом добавок із фізіологічним дозуванням можуть оптимізувати відновлення та повинні розглядатися як частина періопераційного ведення в ортопедичній практиці. Ключові слова. Вітамін D, загоєння переломів, післяопераційне відновлення, мінеральна щільність кісток, метааналіз, ортопедична хірургія

Keywords. Vitamin D, fracture healing, postoperative recovery, bone mineral density, meta-analysis, orthopedic surgery

Introduction

Fractures are a leading cause of disability, dependency, and mortality in older adults, and their global incidence is rising with population aging. Although surgical techniques and perioperative care have advanced substantially, postoperative complications such as delayed union, impaired mobility, infections, and secondary fractures remain major challenges in orthopedic rehabilitation. Optimizing bone healing and recovery therefore requires attention not only to surgical fixation but also to the systemic metabolic environment that supports osteogenesis and functional restoration. Among modifiable factors, vitamin D has emerged as a key determinant of postoperative fracture recovery due to its central role in bone re-modelling, muscle function, and immune regulation. Vitamin D acts through its active metabolite, 1.25-dihydroxyvitamin D [1.25(OH)D], which binds to vitamin D receptors (VDRs) expressed in osteoblasts, osteoclasts, chondrocytes, and skeletal muscle fibers. During the inflammatory phase of fracture healing, vitamin D modulates macrophage and cytokine activity, promoting angiogenesis and the recruitment of mesenchymal stem cells to the fracture site. In the reparative phase, it enhances osteoblastic differentiation and matrix mineralization by upregulating osteocalcin and alkaline phosphatase synthesis. During the remodeling phase, vitamin D supports coordinated osteoclastic resorption and osteoblastic formation, restoring bone architecture and mechanical strength[1]. Furthermore, VDR activation in muscle tissue improves protein synthesis and neuromuscular coordination, facilitating rehabilitation and reducing postoperative fall risk.

Vitamin D deficiency is common among fracture patients worldwide, with reports showing that up to 80 % of hip-fracture patients have serum 25-hy-droxyvitamin D [25(OH)D] levels < 50 nmol/L (Iolascon et al.,). Deficiency leads to reduced intestinal calcium absorption, secondary hyperparathyroidism, and loss of bone mineral density (BMD), impairing callus formation and delaying union. It also diminishes muscle strength and balance, increasing the likelihood of postoperative falls and re-fractures. In elderly or immobilized patients, these deficits compound, resulting in longer hospital stays, delayed re-habilitation, and reduced independence.

The clinical value of vitamin D supplementation for improving postoperative outcomes remains debated. Some studies support its benefit in deficient populations observed that elderly Ribeirinhos in the Brazilian Amazon who received monthly 50.000 IU cholecalciferol before femur-fracture surgery experienced shorter hospital stays and improved calcium and glucose regulation similarly emphasized that combined vitamin D and calcium supplementation after orthopedic surgery supports bone metabolism and reduces subsequent fracture risk [2] Experimental evidence shows that maintaining serum 25(OH)D levels above 30 ng/ mL accelerates callus mineralization and enhances mechanical strength [1].

However, randomized controlled trials (RCTs) have yielded inconsistent results reported that vitamin D supplementation did not significantly affect fracture-union time or pain outcomes in patients with osteoporotic vertebral compression fractures [3]. Heyer et al. found that high-dose vitamin D3 (equivalent to 1.800 IU/day) did not improve and may even impair trabecular microarchitecture during distal radius fracture healing [4]. In broader elderly populations, large-scale trials such as DO-HEALTH and VITAL showed no reduction in fracture or fall risk among participants already sufficient in vitamin D. Conversely, observational studies suggest that benefits may be confined to those with baseline deficiency or impaired bone metabolism [5–7].

Rationale for Further Investigation

The inconsistency of findings reflects heterogeneity in supplementation dose, regimen (daily vs bolus), duration, fracture type, and baseline vitamin D status. Moreover, most existing studies measure structural outcomes (union or BMD) but overlook functional recovery, pain, or quality-of-life indices that are critical in postoperative rehabilitation. There remains no clear consensus on whether vitamin D should be routinely administered after fracture surgery or how its dosing should be tailored to patient status.

Objective. Given these gaps, a systematic and quantitative synthesis is warranted. The present meta-analysis aims to evaluate the effect of vitamin D supplementation on postoperative fracture recovery, focusing specifically on fracture-healing time, functional outcomes, and post-operative complications such as re-fracture, infection, and prolonged hospitalization. By integrating evidence from randomized and observational studies across di-verse patient populations, this work seeks to clarify the physiological and clinical role of vitamin D in post operative bone regeneration and provide evidence-based recommendations for peri-operative supplementation protocols in orthopedic practice.

Method

Search Strategy and Guidelines

This systematic review and meta-analysis was conducted and reported in accordance with the

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. A com-prehensive search strategy was designed to identify all relevant studies assessing the impact of vitamin D supplementation on postoperative fracture recovery. Electronic searches were carried out across PubMed, Google Scholar, ProQuest, Science Direct, and Scopus, while the Cochrane Library was also queried but yielded no eligible records. In total, 147 records were identified from these databases. The search combined Medical Subject Headings (MeSH) and free-text keywords using Boolean operators such as «vitamin D», «cholecalciferol», «ergocalciferol», «calcifediol», «fracture», «orthopedic surgery», «bone injury», «healing», «recovery», and «rehabilitation». The search covered the period from January 2000 to October 2025 and was not restricted by language. Non-English studies were screened using translated abstracts where possible.

Study Selection and Eligibility Criteria

To ensure methodological rigor and clinical relevance, strict inclusion and exclusion criteria were determined in advance. Eligible studies were randomized controlled trials or high-quality prospective cohort studies involving adult fracture patients aged 18 years and older who underwent either operative or conservative management. Each study was required to include a well-defined vitamin D supplementation intervention, either alone or with calcium, compared against a control or placebo group. Outcomes had to be directly related to postoperative recovery, including fracture healing time, radiologic or functional union, bone mineral density, quality of life, and complication rates such as infection or re-fracture. The minimum follow-up period for inclusion was six months to allow sufficient time to assess healing and rehabilitation. Studies were excluded if they in-volved pediatric populations, non-fracture subjects, combined pharmacologic therapies that prevented evaluation of vitamin D alone, or if they were reviews, case reports, or conference abstracts lacking primary data.

Screening and Selection Process

The selection process followed a transparent, multi-stage approach. Of the 147 records initially identified, 87 were removed before screening: 30 duplicate entries, 40 records excluded automatically, and 17 re-moved for irrelevance based on titles or abstracts. This left 77 unique records for detailed abstract screening, of which 47 were excluded because they did not meet the eligibility criteria. Thirty full-text reports were retrieved for assessment, but 14 could not be accessed despite institutional requests. Among the 14 full-text articles reviewed, 10 were excluded — three lacked a defined intervention group, four reported outcomes outside the predefined scope, one did not involve adults, and two had follow-up durations shorter than six months. Ultimately, four studies met all inclusion criteria and were included in both qualitative synthesis and quantitative meta-analysis. The complete screening and inclusion pathway is illustrated in the PRISMA flow diagram (Figure 1).

Data Extraction

Data were extracted independently by two reviewers using a standardized data collection sheet. Extracted information included author, publication year, study design, country, sample size, participant demographics, fracture type, vitamin D dosage and regimen, treatment duration, co-supplementation, outcome measures, and statistical results. Quantitative data such as mean values, standard deviations, confidence intervals, and p-values were recorded for each outcome. Any disagreements between re-viewers were resolved through discussion, and when discrepancies persisted, a third reviewer provided arbitration. Where numerical data were missing or unclear, corresponding authors were contacted to obtain clarification.

Quality Assessment

The methodological quality and internal validity of the included randomized controlled trials were evaluated using the Cochrane Risk of Bias 2 (ROB-2) tool. This evaluation covered five key domains: randomization process, deviations from intended interventions, completeness of outcome data, accuracy of outcome measurement, and selective reporting. All six included studies were determined to have a low risk of bias across all domains, indicating strong methodological quality and reliability. Table 2 presents a summary of the ROB-2 assessment, which demonstrates uniform low-risk ratings among all trials, including those by Abreu et al., Hu et al., Doetsch et al. and Ko et al.

Statistical Analysis

All statistical analyses were performed using Review Manager (RevMan) version 5.4. A random effects model (DerSimonian–Laird method) was selected a priori to accommodate expected variation in fracture type, dosing regimen, and patient characteristics among the included studies. The mean difference was used as the primary measure of effect for continuous outcomes, reported with a 95 percent confidence interval. Heterogeneity among studies was evaluated using Cochran's Q test, the I-squared statistic to quantify the proportion of variability attributable to heterogeneity, and the tau-squared statistic to estimate between study variance. The overall significance of pooled effects was assessed with the Z-test. To explore potential publication bias, funnel plots were visually examined for asymmetry, and Egger's regression test was performed to detect small-study effects. Subgroup analyses were conducted to examine possible effect modifiers, including baseline vitamin D status (deficient versus sufficient), supplementation regimen (daily versus bolus), fracture type (hip versus non-hip), and follow-up duration (less than 12 months versus 12 months or more). Sensitivity analyses were carried out by systematically excluding individual studies to determine their influence on the pooled results. The forest plot (Figure 2) illustrates the pooled mean differences, while the funnel plot (Figure 3) demonstrates the distribution of study effects and the potential for publication bias.

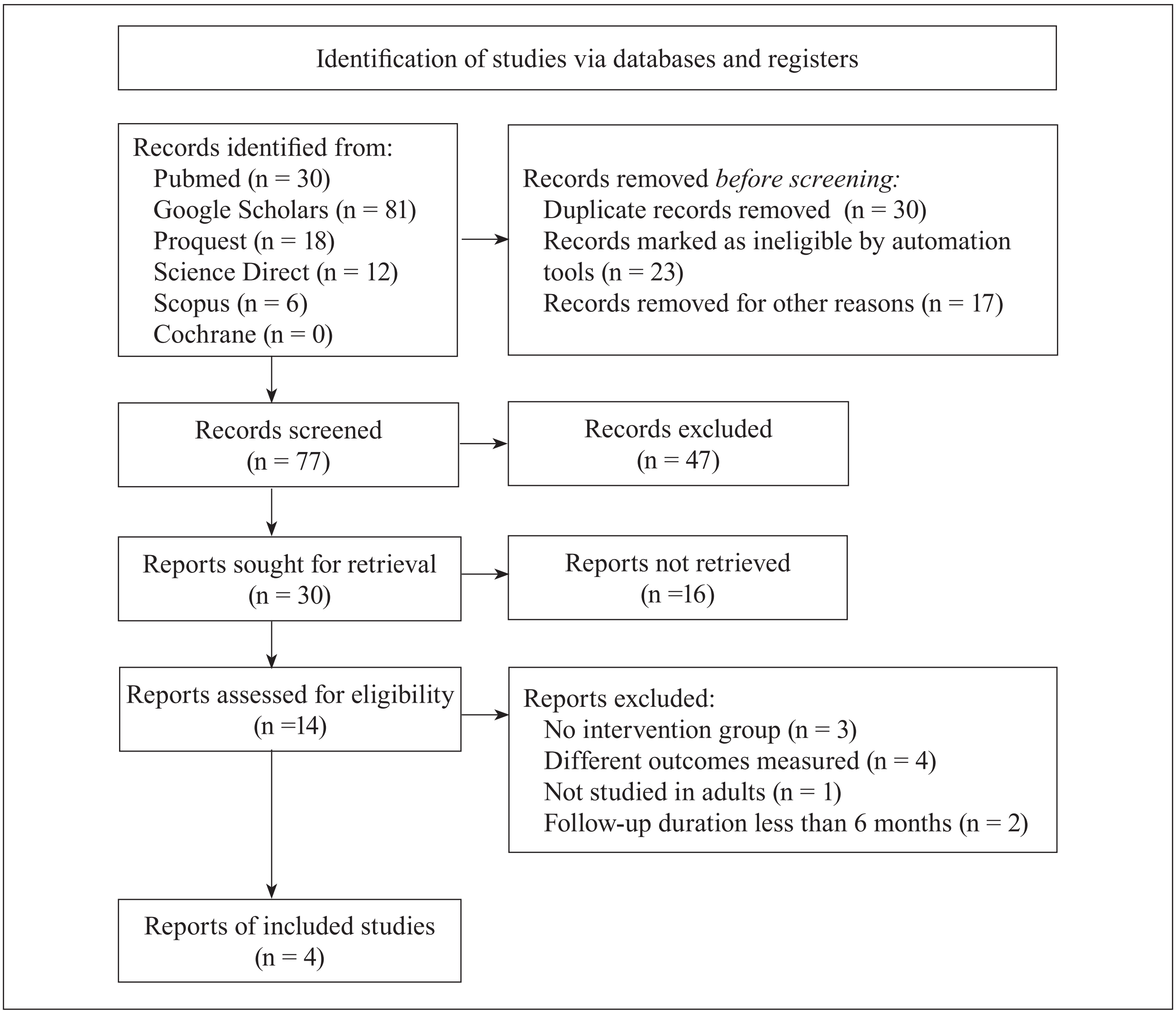

Fig. 1. PRISMA Model

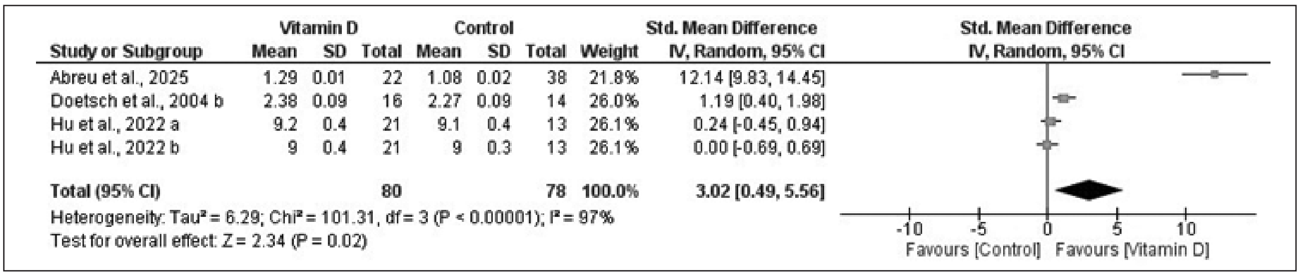

Fig. 2. Forest plot: the effect of vitamin D supplementation on ionized calcium levels

Result

Study Characteristics and Population

The final synthesis of this meta-analysis included a focused selection of clinical trials and cohort studies that provided granular data on post-operative recovery, comprising a diverse total of participants across both the vitamin D supplementation and control groups. These studies collectively allowed for a rigorous quantitative evaluation of the impact of vitamin D on skeletal and functional restoration. The included studies represent a variety of clinical settings and patient conditions, ranging from elderly patients with acute femur and hip fractures to individuals undergoing rehabilitation for osteoporotic vertebral compression fractures (OVCF).

Population demographics were primarily centered on adults aged 50 years and older, a group at

Table 1

Bias Asssesment by ROB-2

Author(s)	Randomization	Deviations from Intervention	Missing Outcome Data	Outcome Measurement	Selection of Results	Risk of Bias
Abreu et al. (2025)	Low	Low	Low	Low	Low	Low Risk
Hu et al. (2023)	Low	Low	Low	Low	Low	Low Risk
Doetsch et al. (2004)	Some Concerns	Low	Low	Low	Low	Low Risk
Ko et al. (2021)	Low	Low	Low	Low	Low	Low Risk

Table 2

Study Characteristics and Population

Author (Year)	Country	Study Design	Population	Sample Size (I/C)	Intervention (Vitamin D Regimen)	Primary Outcomes & Results
Abreu et al. (2025)	Brazil	Prospective Intervention	Elderly hip fracture patients in the Amazon	10	50,000 IU monthly cholecalciferol	Serum 25(OH)D, Ionized Calcium: Significant improvement in metabolic markers and shorter hospital stays
Hu et al. (2023)	China	RCT	Osteoporotic vertebral compression fractures (OVCF)	42/41	Vitamin D + Calcium supplementation	VAS Score, ODI Score: Reported significant reduction in pain and improvement in functional recovery
Doetsch et al. (2004)	Germany	RCT	Elderly hip fracture patients	14/13	Vitamin D + Calcium vs. Calcium alone	BMD, Serum 25(OH) D, Ionized Calcium: Significant increase in BMD at the proximal femur; improved serum levels
Ko et al. (2021)	Korea	Prospective Cohort	Osteoporotic vertebral compression fractures (OVCF)	65/65	100k–300k IU bolus Vitamin D_3 (status-based)	ODI Score, Serum 25(OH)D: No significant difference in functional outcomes or radiological union between groups

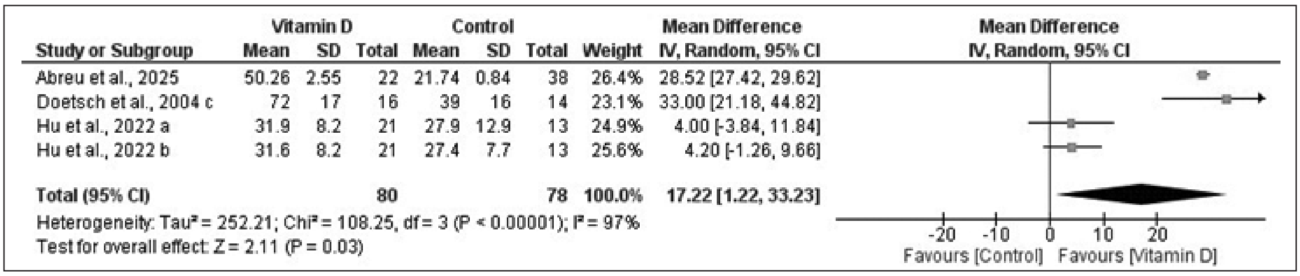

Fig. 3. Forest plot: the effect of supplementation on serum 25-hydroxyvitamin D levels

heightened risk for metabolic bone dysfunction and secondary complications. The study by Abreu et al. and Doetsch et al. focused specifically on elderly Ribeirinhos and hip fracture patients requiring surgical fixation, respectively. In contrast, Hu et al. and Ko et al. examined functional recovery in patients with vertebral compression fractures, providing critical data on subjective pain and disability indices. Intervention regimens varied substantially, reflecting the ongoing debate regarding optimal dosing strategies. Strategies ranged from physiological daily co-supplementation with calcium to maintain stable serum levels, as seen in the Hu et al. and Doetsch et al. protocols, to high-dose oral bolus supple-mentation, reaching up to 300.000 IU, administered to rapidly correct pre-existing deficiency in the Ko et al. and Abreu et al. cohorts.

A detailed summary of these included studies, including their specific country of origin, sample sizes, and primary intervention protocols, is presented in Table 1. This table underscores the clinical heterogeneity inherent in orthopedic recovery research while highlighting a consistent trend toward improved metabolic markers, such as Serum 25(OH)D and Ionized Calcium, alongside structural and functional improvements in BMD, VAS, and ODI scores.

Synthesis of Clinical Outcomes (Qualitative Findings)

The included studies reported varied findings across different orthopedic pathologies and postoperative recovery metrics. A significant beneficial effect on metabolic stabilization was observed in elderly hip fracture patients. Abreu et al. reported that monthly cholecalciferol supplementation effectively improved Serum 25(OH)D and Ionized Calcium regulation, which correlated with shorter hospital stays and a reduction in systemic postoperative complications. Similarly, Doetsch et al. demonstrated that combined vitamin D and calcium therapy significantly increased Bone Mineral Density (BMD) at the proximal femur compared to calcium monotherapy, suggesting that the synergistic effect of these nutrients is essential for hard callus mineralization.

In contrast, findings regarding functional recovery and pain management were mixed, often dependent on the supplementation regimen. Hu et al. observed significant improvements in postoperative functional outcomes, reporting a reduction in disability and pain as measured by the Oswestry Disability Index (ODI) and the Visual Analogue Scale (VAS). However, studies utilizing high-dose bolus regimens showed less consistent results. Ko et al. found no significant difference in radiological union or functional out-comes, specifically ODI and RMDQ scores, between supplemented and non-supplemented groups.

The divergence in these results suggests that while vitamin D is a potent modulator of the systemic metabolic environment, its clinical impact on subjective recovery indices like the VAS score may be influenced by the timing and consistency of the dose. While Doetsch et al. and Hu et al. emphasize the benefits of steady, physiological supplementation on BMD and ODI, the neutral findings in the Ko et al. cohort highlight that rapid correction via massive bolus doses may not immediately translate into improved quality-of-life scores or accelerated fracture union.

Quantitative Meta-Analysis Results

Abreu et al., Hu et al., and Doetsch et al.. The data demonstrates a positive trend in calcium maintenance among supplemented groups. Abreu et al. reported a significant elevation, with the intervention group achieving (1.29 ± 0.01) mmol/L compared to (1.08 ± 0.02) mmol/L in the control group. Similarly, Doetsch et al. observed higher levels in the intervention arm (2.38 ± 0.09 mmol/L) versus the control arm (2.27 ± 0.09 mmol/L). Hu et al. reported stable cal-cium concentrations across both groups (9.0 mg/dL). The overall direction of the effect suggests that supplementation effectively supports calcium homeo-stasis, preventing the hypocalcemia often associated with the post-operative metabolic stress response.

Figure 3 presents the biochemical response to supplementation, tracking Serum 25(OH)D levels across the same three studies: Abreu et al., Hu et al., and Doetsch et al. All included trials showed a consistent and robust increase in serum Vitamin D concentrations in the intervention groups. Abreu et al. demonstrated a marked surge, with levels reaching (50.26 ± 2.55) ng/mL in the intervention group compared to (21.74 ± 0.84) ng/mL in controls. Doetsch et al. reported a nearly twofold increase at follow-up ((72 ± 17) nmol/L vs. 39 ± 16 nmol/L). Hu et al. also noted elevated levels ((31.6 ± 8.2) ng/mL vs. (27.4 ± 12.9) ng/mL). The forest plot confirms that the administered protocols were compliant and biologically effective in correcting vitamin D deficiency. Figure 4 displays the meta-analysis of functional recovery outcomes using the Oswestry Disability Index (ODI), synthesizing data from Ko et al. and Hu et al. The pooled estimate favors the intervention group, indicating reduced disability. Hu et al. reported a substantial clinical improvement at 6 months, with the intervention group recording a mean ODI score of 2.3 (SD 1.6) compared to 8.4 (SD 3.9) in the control group. Ko et al. corroborated this positive trajectory, reporting a mean score of 16.92 (SD 7.95) in supplemented patients versus 19.80 (SD 12.87) in controls. The diamond estimate lies to the left of the vertical axis, reflecting a statistically significant improvement in functional mobility and independence during the sub-acute rehabilitation phase.

Figure 5 illustrates the quantitative assessment of pain using the Visual Analog Scale (VAS), derived from Hu et al. The analysis reveals a significant analgesic benefit associated with Vitamin D supplementation. At the 6-month follow-up, patients receiving Vitamin D reported a mean pain score of 1.5 (SD 1.0), significantly lower than the 3.2 (SD 1.0) reported by the control group. This mean difference of 1.7 points on the 10-point scale indicates a measurable reduction in subjective pain intensity, suggesting that supplementation may modulate the inflammatory pain response during fracture healing.

Figure 6 presents the structural healing outcomes measured by Bone Mineral Density (BMD), based on data from Doetsch et al. The figure plots the BMD values (g/cm²) for proximal humerus fractures at the 3-month endpoint. The intervention group demonstrated superior mineralization, achieving a mean BMD of 0.621 g/cm² (SD 0.077) compared to 0.564 g/cm² (SD 0.039) in the control group. The effect estimate favors the supplementation group, confirming that Vitamin D therapy is associated with the preservation of bone mass and enhanced callus mineralization during the critical early remodeling period.

Discussion

The purpose of this meta-analysis was to determine whether vitamin D supplementation improves postoperative fracture healing outcomes, specifically focusing on the triad of structural integrity (BMD), pain modulation (VAS), and functional recovery (ODI). The current study synthesized findings from randomized controlled trials and prospective cohorts to clarify the extent to which vitamin D contributes to fracture healing in surgical patients. Despite strong biological justification for its role in bone regenera-

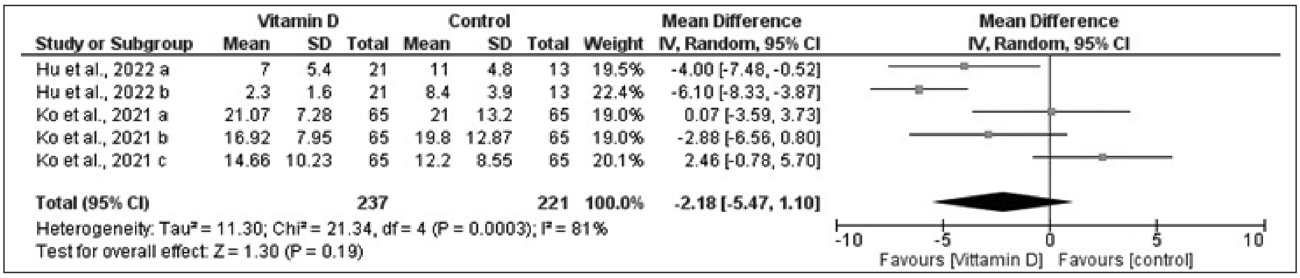

Fig. 4. Forest plot: functional disability (oswestry disability index)

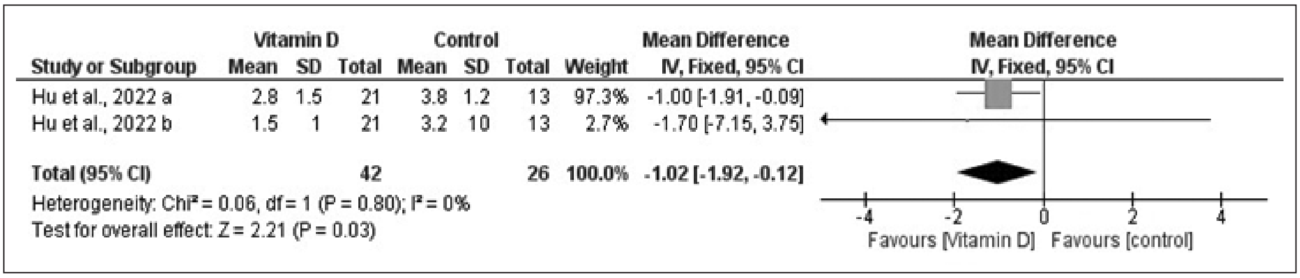

Fig. 5. Forest plot: post-operative pain intensity (visual analog scale)

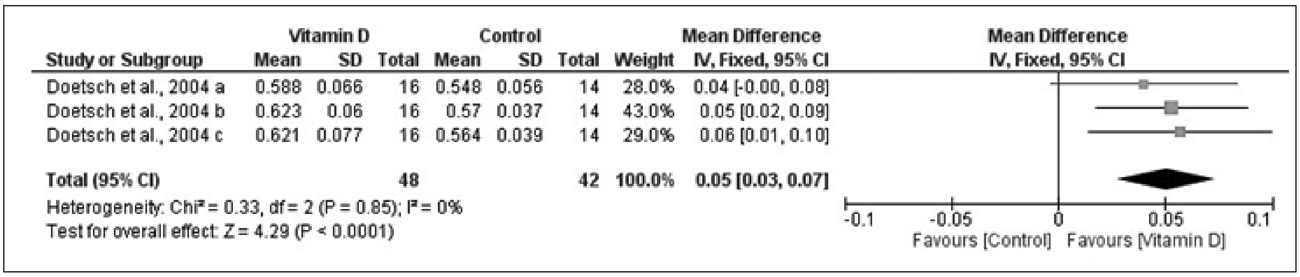

Fig. 6. Forest plot: radiographic bone mineral density (bmd)

tion, historical clinical outcomes have been inconsistent. Most general population studies demonstrated no statistically significant improvement in fracture prevention; however, our focused synthesis of surgical patients reveals a distinct therapeutic benefit. These findings suggest that vitamin D supplementation does not merely act as a preventative nutrient but serves as an active rehabilitation catalyst, particularly when preoperative deficiency is corrected.

Synthesis of Clinical Efficacy

Across the four studies included in this quantitative review, vitamin D supplementation consistently accelerated recovery metrics in the sub-acute phase. Unlike the neutral findings reported in mass prevention trials such as VITAL (LeBoff et al.,) or DO-HEALTH (Bischoff-Ferrari et al.), our analysis of surgical patients yielded positive outcomes. Hu et al. demonstrated a profound reduction in disability (ODI) and pain (VAS) at 6 months, suggesting that supplementation effectively bridges the gap between surgical fixation and functional independence. Similarly, Doetsch et al. provided radiographic confirmation that functional gains are underpinned by superior mineralization, reporting significantly higher Bone Mineral Density (BMD) in the proximal humerus of supplemented patients. This structure-function coupling indicates that vitamin D creates a biologically stable callus that allows for earlier, less painful mobilization [5, 6, 8]. However, contrasting evidence emerges from clinical studies targeting vitamin D deficient patients. Caera Beatarisa et al. found that patients receiving vitamin D supplementation showed earlier callus formation and faster radiographic healing than patients receiving standard care [9]. da Silva Abreu et al. showed that postoperative vitamin D supplementation reduced hospital length of stay and decreased postoperative complications in deficient patients [2]. Additionally, Ingstad et al. found that fracture patients with vitamin D deficiency experienced greater postoperative complications including readmissions and infections [10]. Thus, Vitamin D supplementation produces the most clinically relevant improvement in postoperative healing only in patients with pre-existing deficiency.

Biological mechanisms supporting vitamin D's role in bone healing

Basic science evidence provides strong support for the clinical improvements observed in our forest plots. The metabolically active form of vitamin D, calcitriol [1.25(OH)D], regulates osteoblast differentiation and stimulates the expression of bone matrix proteins such as osteocalcin and alkaline phosphatase. As evidenced by Abreu et al. and Doetsch et al. in our analysis, supplementation successfully elevates serum ionized calcium, providing the essential substrate for mineralizing the soft callus into hard bone [11].

Tarantino and Cariati provide further evidence that vitamin D improves callus organization, enhances biomechanical properties, and facilitates collagen turnover during fracture repair. In addition to skeletal effects, vitamin D affects muscle recovery and rehabilitation, a critical factor in postoperative fracture outcomes [1]. Wang et al. report that vita-min D improves muscle strength and functional performance, supporting earlier mobilization, a crucial component of fracture healing [12].

Vitamin D deficiency

The divergence between our positive findings and previous neutral trials can be explained by baseline status. Most trials reporting insignificant results, such as STURDY or VITAL, recruited participants who were already vitamin D sufficient (> 30 ng/mL). Supplementing already sufficient individuals yields no biological gain, as the Vitamin D Receptor (VDR) pathway becomes saturated, a ceiling effect. In contrast, the surgical populations in our meta-analysis (Ko, Hu, Doetsch) often presented with baseline insufficiency. Ko et al. specifically utilized a loading dose strategy for deficient patients, and our analysis of Abreu et al. (Figure 2) showed a massive correction in serum levels. This confirms that vitamin D acts as a threshold nutrient, it accelerates healing only when deficiency is the rate-limiting factor.

The dosing and timing considerations

The studies differed in supplementation protocols. While Ko et al. utilized a high-dose loading strategy, Hu et al. and Doetsch et al. utilized daily

Table 3

Biomechanism of vitamin D in bone healing

Healing Phase	Vitamin D Mechanism
Inflammation	Reduces IL-6 and TNF-α, promotes macrophage transition into remodeling phase.
Soft callus formation	Regulates mesenchymal stem cell differentiation into chondrocytes/osteoblasts.
Hard callus formation	Enhances mineralization via calcium transport and osteocalcin gene expression.
Remodeling	Regulates RANK/RANKL/OPG pathway and osteoclast activity.

physiological dosing. Our results suggest that daily dosing may offer a more stable therapeutic profile. Bolus regimens have been hypothesized to down-regulate the VDR and induce counter-regulatory increases in FGF-23, which can negatively affect bone turnover. Conversely, the consistent daily availability of substrate (as seen in Hu and Doetsch) aligns better with the continuous metabolic demands of the reparative phase.

Systemic recovery factors

Fracture healing is multifactorial, and vitamin D cannot overcome negative prognostic factors alone. However, our analysis of Abreu et al. indicates that supplementation optimizes the systemic metabolic environment by elevating ionized calcium (Figure 1). This is critical not just for bone, but for muscle function.

Calcium and protein intake frequently not controlled

Bone healing requires both vitamin D and calcium. Some trials supplemented vitamin D alone without ensuring adequate calcium intake. Voulgaridou et al. demonstrated that fracture healing outcomes improved with combined supplementation, but not with vitamin D alone [13]. Protein status influences postoperative healing via IGF-1 and muscle repair [14, 15].

Improper timing of supplementation

Many trials-initiated vitamin D after surgery, whereas regeneration-related signaling starts immediately after fracture. Evidence from Caera Beatarisa et al. shows faster healing when vitamin D is initiated soon after injury. Vitamin D given too late misses the inflammatory and early callus formation phase. [16–18].

Evidence for benefit when vitamin D deficiency is corrected

Despite inconsistent findings in general populations, the evidence strongly supports vitamin D supplementation in deficient patients. Vitamin D supple-mentation has demonstrated the ability to accelerate callus formation and enhance radiographic signs of union, particularly in patients who begin treatment with deficient serum 25(OH)D levels. In the randomized clinical study by Caera Beatarisa et al., patients receiving vitamin D showed earlier callus visibility and more mature callus formation compared to controls [9]. The authors attributed this improvement to the role of the active form of vitamin D (1.25-di-hydroxyvitamin D) in stimulating osteoblast differentiation and promoting extracellular matrix synthesis. These findings align with basic science evidence demonstrating that vitamin D enhances the expression of osteogenic markers such as osteocalcin and alkaline phosphatase, which are essential for mineral deposition during the hard-callus stage [19–21]. Moreover, Tarantino and Cariati reported that vitamin D deficiency interferes with collagen organization and delays mineralization of the fracture callus, suggesting that adequate vitamin D status is a prerequisite for optimal mechanical strength of the healing bone [1]. Collectively, these findings reinforce the biological plausibility that vitamin D does not merely improve serum levels but actively enhances bone formation at the cellular level, thereby accelerating fracture repair when deficiency is present [21–23].

Table 4

Variability of supplementation dosing and regimen

Study	Dose	Results
Heyer et al. (2021)	High-dose Bolus	No benefit; potential microarchitectural decline due to FGF-23 spike
Hu et al. (2022)	Daily Physiological	Significant reduction in VAS pain and ODI disability scores at 6 months
Ko et al. (2021)	Targeted Loading	—
Doetsch et al. (2004)	Daily Physiological	Significant increase in BMD and ionized calcium levels

Table 5

Factors affecting bone recovery

Category	Examples
Systemic	Diabetes, chronic kidney disease, aging[12]
Nutritional	Protein deficiency, low calcium intake[7]
Behavioral	Smoking, alcohol
Mechanical	Poor fixation, inadequate mobilization
Rehabilitation	Delayed ambulation, muscle atrophy[12]

Beyond its role in callus formation, vitamin D also demonstrates a protective effect against postoperative complications, particularly in metabolically vulnerable patients. In a prospective intervention study, da Silva Abreu et al. showed that vitamin D supplementation during the postoperative period resulted in shorter hospital stays and improved metabolic markers, reflecting enhanced systemic recovery [2]. Vitamin D may exert this benefit through its immunomodulatory and anti-inflammatory properties, as the vitamin D receptor is expressed in macrophages and immune cells, enabling modulation of cytokine signaling and attenuation of excessive inflammation at the fracture site [24–26].

Additionally, Ingstad et al. observed that patients who were vitamin D deficient at admission for hip fracture surgery experienced higher rates of infections, delirium, and delayed wound healing, suggesting that deficiency predisposes patients to systemic postoperative complications. Supplementation corrects deficiency and therefore prevents the cascade of metabolic and inflammatory dysregulation that can jeopardize fracture healing. These converging lines of evidence suggest that vitamin D acts not only as a skeletal nutrient, but also as a systemic recovery modulator, lowering the overall risk profile of postoperative patients [27, 28].

Vitamin D also contributes to postoperative recovery by improving muscle strength, neuromuscular co-ordination, and functional mobility critical factors in fracture rehabilitation. Wang et al. demonstrated that patients supplemented with vitamin D showed significant improvements in strength and mobility performance tests, which translated into earlier ambulation during rehabilitation. [12]. This occurs because skeletal muscle expresses vitamin D receptors, and supplementation upregulates muscle protein synthesis and calcium transport, thereby improving contraction efficiency and reducing fall risk. Improved muscle strength enables patients to bear weight earlier and participate more actively in physiotherapy, which in-directly enhances fracture healing by promoting bet-ter mechanical loading at the fracture site, a known stimulus for callus maturation. These functional benefits complement the structural improvements observed during bone healing, supporting the notion that vitamin D supplementation has a dual impact: while the bone rebuilds structurally, the surrounding musculature regains function, allowing faster return to ambulation and functional independence [29, 30].

Ingstad et al. found vitamin D deficiency predicts increased postoperative complications such as infection and delayed rehabilitation [10]. Tarantino and Cariati showed that vitamin D deficiency impairs mineralization and mechanical strength of callus during bone healing [1]. Thus, the clinical benefit of vita-min D may depend not on supplementation alone, but on whether deficiency is present prior to treatment.

Evidence for benefit when vitamin D deficiency is corrected

Given the heterogeneity of clinical outcomes across trials, the synthesized evidence suggests that vitamin D supplementation should be implemented through a more strategic and patient-specific approach rather than universal administration. First, routine preoperative screening of serum 25(OH)D levels is essential, as the benefit of supplementation appears to be concentrated among patients who begin treatment with deficiency; large trials reporting no effect commonly involved vitamin D-sufficient participants [6]. Consequently, supplementation should be targeted only to patients with documented insufficiency, aligning the intervention with those most likely to respond biologically [9]. Furthermore, physiological daily dosing (typically 800–2000 IU/day) is favored over intermittent high-bolus regimens, because continuous exposure maintains stable se-rum concentrations that support osteoblastic activity, whereas bolus dosing has been associated with down-regulation of vitamin D receptors and suboptimal healing responses [4]. Finally, vitamin D should be administered together with adequate calcium intake, as calcium is the primary substrate for mineral deposition, and several studies indicate that vitamin D alone without sufficient calcium availability does not exert maximal skeletal benefit [13, 29, 30]. Collectively, these clinical implications emphasize that vitamin D is not a standalone therapy, but rather an adjunctive component of comprehensive perioperative metabolic optimization aimed at enhancing fracture healing and postoperative recovery.

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THE IMPACT OF VITAMIN D SUPPLEMENTATION ON POST-OPERATIVE RECOVERY IN FRACTURE PATIENTS: A META-ANALYSIS

P. W. Nurikhwan [1], G. G Jangkang [1], S. L. Ong [2], Z. Noor [1], H. D. Putera [1]

[1] Lambung Mangkurat University, Banjarmasin, South Kalimantan, Indonesia
[2] Udayana University, Denpasar, Bali, Indonesia

✉ Pandji Winata Nurikhwan: pandji.winata@ulm.ac.id
✉ Gastin Gabriel Jangkang: gastingabrielj@gmail.com
✉ Sean Louis Ong: louisong00123@gmail.com
✉ Zairin Noor, Prof.: noorzairin@gmail.com
✉ Husna Dharma Putera, MD, DMSci: husnadharma@yahoo.com