

Review Article

Vitamin D Status and Fracture Healing in Patients with Long Bone Nonunion

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Abstract

Background: Vitamin D deficiency is common in orthopaedic populations and has been proposed as a modifiable contributor to impaired fracture healing and long bone nonunion.

Objective: To synthesise published evidence on vitamin D status in fracture and nonunion patients, underlying biological mechanisms, and outcomes of vitamin D supplementation.

Methods: Narrative review of observational cohorts, systematic reviews, a large fracture-registry study, mechanistic literature, and supplementation trials.

Findings: Deficiency prevalence ranges from roughly 40% in general fracture cohorts to over 80% in nonunion series; a registry of over 309,000 fractures identified deficiency as an independent nonunion predictor, and lower vitamin D levels correlate with prolonged healing time. Randomised supplementation data remain limited and inconsistent.

Conclusions: Vitamin D deficiency is prevalent and biologically plausible as a nonunion risk factor, but high-quality trial evidence for supplementation as definitive treatment is lacking, warranting screening and individualised correction pending further trials.

Keywords: Vitamin D; Fracture healing; Nonunion; Long bone; Bone metabolism

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Introduction

Long bone nonunion is an uncommon but disabling complication of fracture care, occurring in approximately 1.9–5% of fractures overall, with substantially higher rates after diaphyseal tibial and femoral injury and after open or high-energy trauma [1,2,3]. Beyond the direct cost of revision surgery, nonunion imposes lasting functional impairment, chronic pain, and delayed return to work relative to fractures that heal uneventfully [4,5]. Because established mechanical and biological risk factors — fracture personality, soft-tissue injury, infection, smoking, and fixation stability — do not fully account for individual variation in healing, attention has turned to correctable

metabolic and endocrine contributors. Among these, vitamin D deficiency has attracted particular interest, given its established role in mineral homeostasis and its high prevalence in trauma populations [6,7,8].

Vitamin D exists physiologically as 25-hydroxyvitamin D [25(OH)D], the storage form measured clinically, which is converted renally to the active hormone 1,25-dihydroxyvitamin D. This hormone increases intestinal calcium and phosphate absorption, modulates renal calcium handling in concert with parathyroid hormone, and directly regulates osteoblast differentiation and matrix mineralization [9,10]. Because adequate calcium-phosphate flux to the fracture site is required for endochondral ossification and mineralization of callus, disrupted vitamin D-calcium homeostasis provides a coherent mechanistic pathway by which deficiency could impair healing and predispose to nonunion, independent of purely observational associations [11].

This review synthesises the literature on vitamin D status and long bone fracture healing across four domains: the prevalence of hypovitaminosis D in fracture and nonunion cohorts, the biological mechanisms linking vitamin D to bone repair, observational evidence associating vitamin D status with nonunion risk and healing time, and the evidence base — and its limitations — for vitamin D (with or without calcium) supplementation as adjunct treatment.

Prevalence of Vitamin D Deficiency in Fracture and Nonunion Patients

Hypovitaminosis D is common even in orthopaedic patients presenting for elective surgery, with one single-centre analysis finding 43% of patients scheduled for orthopaedic procedures had insufficient serum 25(OH)D, with the highest rates among trauma and sports-medicine patients [7]. In dedicated trauma cohorts, prevalence estimates cluster similarly: a prospective

Dutch cohort of adult fracture patients found 40% met deficiency criteria and 11% were severely deficient, with smoking and winter presentation as independent risk factors [12]; a tertiary trauma centre cross-sectional survey of 124 hospitalised patients found comparable overall deficiency of roughly 44%, disproportionately affecting patients with multiple fractures and lower socioeconomic status [13]. A pooled meta-analysis of acute fracture cohorts reported a weighted prevalence of hypovitaminosis D of 70% (mean serum level 19.5 ng/mL), confirming that insufficiency, broadly defined, is the norm rather than the exception in this population [14].

Table 1: Principal observational studies of vitamin D status in fracture and nonunion populations reviewed here [7,12,13,6,15,17,2].				
Study	Design	N	Population	Key finding
Bogunovic 2010	Cross-sectional	723	Elective orthopaedic surgery	43% had insufficient serum 25(OH)D
Gorter 2016	Prospective cohort	527	Adult fracture patients	40% deficient, 11% severely deficient
Gupta 2024	Cross-sectional survey	124	Hospitalised orthopaedic trauma	43.6% deficient; higher with multiple fractures
Brinker 2007	Metabolic screening series	37 of 683	Unexplained fracture nonunion	68% newly diagnosed vitamin D deficiency
Sleiman 2024	Retrospective cohort	94	Adult fracture nonunion	44.3% hypovitaminosis D
Anciano 2024	Retrospective case series	13	Foot/ankle arthrodesis nonunion	85% (11/13) low vitamin D level
Zura 2016	Registry analysis	309,330	Fractures across 18 bones	4.9% nonunion; vitamin D deficiency an independent predictor

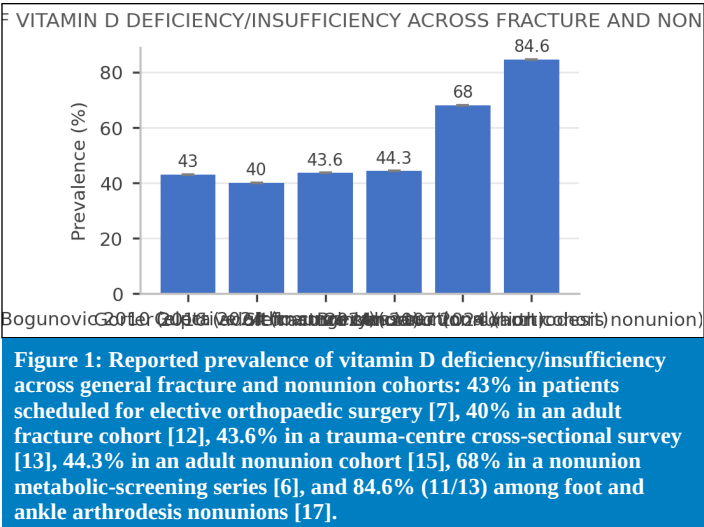


Figure 1: Reported prevalence of vitamin D deficiency/insufficiency across general fracture and nonunion cohorts: 43% in patients scheduled for elective orthopaedic surgery [7], 40% in an adult fracture cohort [12], 43.6% in a trauma-centre cross-sectional survey [13], 44.3% in an adult nonunion cohort [15], 68% in a nonunion metabolic-screening series [6], and 84.6% (11/13) among foot and ankle arthrodesis nonunions [17].

Prevalence rises further once nonunion has already developed. In the foundational metabolic screening series of 683 consecutive nonunion patients, 37 met criteria for endocrine referral, and vitamin D deficiency was the single most common newly diagnosed abnormality among these, present in 68% (25 of 37), with metabolic or endocrine abnormalities identified in 84% of the referred patients overall [6]. A more recent cohort of 94 nonunion patients corroborated this, finding hypovitaminosis D in 44.3%, alongside anaemia, elevated inflammatory markers, and low testosterone as other common derangements [15], while a focused endocrine-practice analysis likewise identified vitamin D and other metabolic disturbances as frequent findings warranting systematic screening in nonunion patients [16]. In site-specific series, deficiency appears even more concentrated: among patients with foot and ankle arthrodesis nonunion, 11 of 13 (85%) had low vitamin D levels, and correction followed by revision surgery was associated with union in four of five cases [17]. Figure 1 summarises reported deficiency/insufficiency prevalence across these general fracture and nonunion cohorts, and Table 1 details the design and key findings of the principal observational studies reviewed here [7,12,13,6,15,17,2].

Biological Mechanisms Linking Vitamin D to Bone

Repair

Fracture healing recapitulates much of embryonic endochondral bone formation, proceeding through an inflammatory phase, a soft callus phase dominated by chondrocyte proliferation, and a hard callus phase requiring mineralization of newly formed matrix before remodelling. Vitamin D contributes to each of these transitions primarily through its endocrine regulation of calcium and phosphate availability: active 1,25-dihydroxyvitamin D upregulates intestinal calcium transporters and, together with parathyroid hormone, maintains serum ionized calcium within the narrow range required for hydroxyapatite deposition in callus [18,10]. Independent of this endocrine axis, osteoblasts themselves express the vitamin D receptor and the enzymatic machinery (CYP27B1, CYP24A1) to synthesise and degrade active vitamin D locally, allowing autocrine and paracrine regulation of their own proliferation, differentiation, and mineralization activity that is superimposed on systemic vitamin D status [10]. Vitamin D signalling drives expression of osteoblast differentiation markers such as alkaline phosphatase while also inducing mineralization inhibitors such as osteopontin, indicating a finely tuned, stage-dependent role rather than a simple dose-dependent stimulus [9,10]. A systematic review of the human fracture-healing literature concluded that, while animal and cell-based data strongly support a mechanistic role for vitamin D in normal healing, clinical evidence directly linking deficiency to impaired human fracture repair was, at the time, still preliminary and heterogeneous in design [11]. Vitamin D also participates in innate immune modulation relevant to fracture-site infection, an important confounder of healing outcomes in open and severely contaminated injuries [19].

Vitamin D Status as a Risk Factor for Nonunion and Delayed Healing

The strongest population-level evidence linking vitamin D

status to nonunion risk comes from a large United States trauma registry analysis of over 309,000 fractures across 18 bones, which found an overall nonunion rate of 4.9% and identified vitamin D deficiency among the independent clinical predictors of nonunion, alongside factors such as smoking, diabetes, and NSAID use [2]. This registry-scale association is reinforced by smaller but more granular clinical studies directly measuring 25(OH)D and healing time. A recent prospective study of lower-limb fractures found a significant inverse correlation between serum vitamin D level and time to union ($r = -0.62$), with mean union times of 14.8 weeks in vitamin D-sufficient patients, 16.7 weeks in insufficient patients, and 17.9 weeks in deficient patients ($p < 0.001$), and vitamin D remained an independent predictor of healing time after multivariable adjustment; delayed union rates were correspondingly higher in deficient patients [20], a dose-response relationship illustrated in Figure 2. Reviews of nonunion epidemiology and risk factors consistently list vitamin D deficiency among the modifiable, patient-related contributors alongside smoking, diabetes, and poor nutritional status that should prompt metabolic screening once mechanical and infective causes have been addressed [21,3].

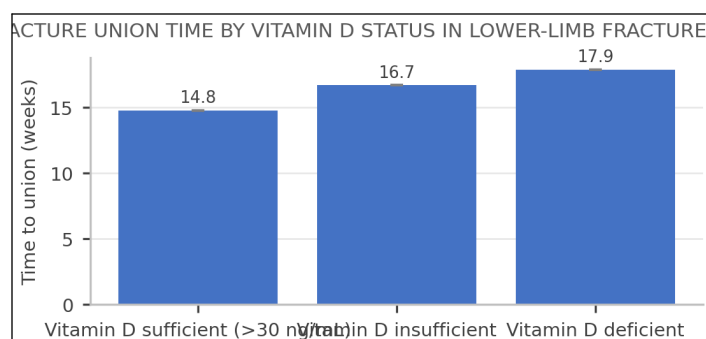


Figure 2: Mean time to fracture union in lower-limb fractures by vitamin D status: 14.8 weeks (sufficient), 16.7 weeks (insufficient), and 17.9 weeks (deficient), a significant inverse correlation ($r = -0.62$, $p < 0.001$) [20].

Vitamin D (and Calcium) Supplementation as Adjunct Treatment

Table 2: Key studies of vitamin D (or calcium/vitamin D) supplementation relevant to fracture and nonunion healing [22,14,23,24,25].				
Study	Design	N	Intervention	Key outcome
Haines 2017	RCT, double-blind, placebo-controlled	100	Single 100,000 IU vitamin D3 vs placebo	Nonunion 4% both groups; no union benefit
Sprague 2016	Systematic review/meta-analysis	Multiple studies	Vitamin D supplementation, varied dosing	70% pooled hypovitaminosis D prevalence; limited efficacy data
Gatt 2023	Systematic review	Multiple studies	Vitamin D supplementation	Safe and normalises levels; efficacy evidence inconclusive
Moone 2021	Case report	1	Vitamin D repletion	Union achieved after correcting deficiency
Kishore 2024	Cohort study	Not stated	Vitamin D supplementation	Improved radiographic/functional healing in osteoporotic fracture patients

Despite the strength of the observational and mechanistic case, prospective interventional evidence for vitamin D supplementation as a treatment for impaired fracture healing remains limited. The only adequately powered randomised trial to date enrolled 100 acute long bone fracture patients with hypovitaminosis D and randomised them to a single 100,000 IU dose of vitamin D3 or placebo within two weeks of injury; nonunion rates were low and statistically equivalent between groups (4% each), leading the authors to conclude that union was largely independent of this supplementation strategy, albeit in a population with a generally low baseline nonunion risk [22]. A broader systematic review of vitamin D supplementation trials for fracture-related bone healing found the existing evidence base small, heterogeneous in dosing and timing, and insufficient to draw firm conclusions about efficacy, while still supporting supplementation as safe and effective for normalising serum levels [23,14]. By contrast, case-based and small cohort experience in confirmed nonunion patients has been more encouraging: correction of vitamin D

deficiency, generally alongside other identified metabolic abnormalities and appropriate mechanical management, has been associated with subsequent union in individual case reports and small series [24,17,6], and a small study of vitamin D repletion in osteoporotic fracture patients reported improved radiographic and functional healing outcomes [25]. The Endocrine Society and Institute of Medicine guidelines provide a basis for defining deficiency (25(OH)D <20 ng/mL) and insufficiency (21–29 ng/mL) and for dosing repletion regimens, though neither guideline was developed specifically for the fracture or nonunion population [18,26]. Table 2 summarises the design and outcomes of the key supplementation and treatment studies discussed above [22,14,23,24,25].

Discussion and Clinical Implications

Taken together, the literature supports a coherent but incompletely proven picture: vitamin D deficiency is highly prevalent in patients with fractures and even more so in those who develop nonunion, plausible mechanistic pathways connect vitamin D status to the mineralization-dependent steps of fracture repair, and population-level data associate deficiency with both nonunion risk and prolonged healing time [2,20,6]. What remains unresolved is whether correcting deficiency changes healing trajectories in a clinically meaningful way, since the single adequately powered randomised trial did not demonstrate a union benefit in a low-risk acute fracture population [22], and no equivalently powered trial has been conducted specifically in established nonunion. Current practice, informed largely by metabolic screening series, favours routine 25(OH)D testing in patients with nonunion or delayed union, and repletion using accepted endocrine dosing, on the rationale that correcting a common, safe-to-treat abnormality is reasonable even where union-specific trial evidence is still maturing [6,15,16].

Conclusion

Vitamin D deficiency is a frequent, biologically plausible, and readily correctable metabolic abnormality in patients with long bone fractures and nonunion, supported by mechanistic data on osteoblast function and mineralization and by large observational and registry studies linking deficiency to nonunion risk and delayed healing. Definitive randomised evidence that supplementation improves union rates in established nonunion is still lacking. Pending further trials targeted specifically at the nonunion population, screening for and correcting vitamin D deficiency represents a low-risk, guideline-concordant adjunct to standard mechanical and biological nonunion management.

References

1. Mills, L.A., Aitken, S.A., Simpson, A.H.R.W. (2017) The risk of non-union per fracture: current myths and revised figures from a population of over 4 million adults. *Acta Orthopaedica*, 88(4): 434-439.
2. Zura, R., Xiong, Z., Einhorn, T., Watson, J.T., Ostrum, R.F., Prayson, M.J., Della Rocca, G.J., Mehta, S., McKinley, T., Wang, Z., Steen, R.G. (2016) Epidemiology of Fracture Nonunion in 18 Human Bones. *JAMA Surgery*, 151(11): e162775.
3. Rupp, M., Biehl, C., Budak, M., Thormann, U., Heiss, C., Alt, V. (2018) Diaphyseal long bone nonunions - types, aetiology, economics, and treatment recommendations. *International Orthopaedics*, 42(2): 247-258.
4. Tay, W.H., de Steiger, R., Richardson, M., Gruen, R., Balogh, Z.J. (2014) Health outcomes of delayed union and nonunion of femoral and tibial shaft fractures. *Injury*, 45(10): 1653-1658.
5. Ekegren, C.L., Edwards, E.R., de Steiger, R., Gabbe, B.J. (2018) Incidence, Costs and Predictors of Non-Union, Delayed Union and Mal-Union Following Long Bone Fracture. *International Journal of Environmental Research and Public Health*, 15(12): 2845.
6. Brinker, M.R., O'Connor, D.P., Monla, Y.T., Earthman, T.P. (2007) Metabolic and endocrine abnormalities in patients with nonunions. *Journal of Orthopaedic Trauma*, 21(8): 557-570.
7. Bogunovic, L., Kim, A.D., Beamer, B.S., Nguyen, J., Lane, J.M. (2010) Hypovitaminosis D in patients scheduled to undergo orthopaedic surgery: a single-center analysis. *Journal of Bone and Joint Surgery American*, 92(13): 2300-2304.
8. Hood, M.A., Murtha, Y.M., Della Rocca, G.J., Stannard, J.P., Volgas, D.A., Crist, B.D. (2016) Prevalence of Low Vitamin D Levels in Patients With Orthopedic Trauma. *American Journal of Orthopedics*, 45(7): E522-E526.
9. van Driel, M., van Leeuwen, J.P.T.M., van den Bemd, G.J.C.M., Pols, H.A.P. (2001) Vitamin D control of osteoblast function and bone extracellular matrix mineralization. *Critical Reviews in Eukaryotic Gene Expression*, 11(1-3): 199-226.
10. van Driel, M., van Leeuwen, J.P.T.M. (2023) Vitamin D and Bone: A Story of Endocrine and Auto/Paracrine Action in Osteoblasts. *Nutrients*, 15(3): 480.
11. Gorter, E.A., Hamdy, N.A.T., Appelman-Dijkstra, N.M., Schipper, I.B. (2014) The role of vitamin D in human fracture healing: a systematic review of the literature. *Bone*, 64: 288-297.
12. Gorter, E.A., Krijnen, P., Schipper, I.B. (2016) Vitamin D deficiency in adult fracture patients: prevalence and risk factors. *European Journal of Trauma and Emergency Surgery*, 42(3): 369-378.
13. Gupta, A. (2024) Prevalence of Vitamin D Deficiency in Orthopedic Trauma Patients: A Cross-Sectional Survey From a Tertiary Care Trauma Center. *Cureus*, 16(9): e69174.
14. Sprague, S., Petrisor, B., Scott, T., Devji, T., Phillips, M., Spurr, H., Bhandari, M., Slobogean, G.P. (2016) What Is the Role of Vitamin D Supplementation in Acute Fracture Patients? A Systematic Review and Meta-Analysis of the Prevalence of Hypovitaminosis D and Supplementation Efficacy. *Journal*

- of Orthopaedic Trauma, 30(2): 53-63.
15. Sleiman, A., Revelt, N., Thuppai, S., Bejcek, C., Beason, A., Besserman, K., Delfino, K., Gardner, M.P. (2024) Metabolic abnormalities underlying nonunion in the adult fracture patient. *Journal of Orthopaedics, Trauma and Rehabilitation*, 31(1): 48-54.
 16. Bergin, P.F., Rothberg, D.L., Spitler, C.A., Chrea, B., Miles, D.T., Yener, U., Bhanat, E., Frederiksen, H.G., Graves, M.L. (2022) The Prevalence of Metabolic and Endocrine Disturbances on Fracture Nonunion. *Endocrine Practice*, 28(6): 599-602.
 17. Anciano, V., Tran, S.K., Carr, J.B., Edwards, C., Russell, D., Reid, R.T., Park, J. (2024) Incidence of Vitamin D Deficiency in Foot and Ankle Arthrodesis Nonunions. *Cureus*, 16(3): e57028.
 18. Holick, M.F., Binkley, N.C., Bischoff-Ferrari, H.A., Gordon, C.M., Hanley, D.A., Heaney, R.P., Murad, M.H., Weaver, C.M. (2011) Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. *Journal of Clinical Endocrinology & Metabolism*, 96(7): 1911-1930.
 19. Jha, G., Dhanjal, R., Hamza, A. (2025) Vitamin D Supplementation in Orthopedic Trauma: Influence on Immune Modulation, Fracture Healing, and Infection Outcomes. *Cureus*, 17(11): e97842.
 20. Memon, R., Raj, P., Sheoran, M., Singh, S.K., Kamra, P., Bhavadharani. (2025) Correlation between Vitamin D Levels and Healing Time in Lower Limb Fractures. *Journal of Orthopaedic Case Reports*, 15(10): 379-385.
 21. Gharu, E., John, B. (2024) Nonunion of Fractures: A Review of Epidemiology, Diagnosis, and Clinical Features in Recent Literature. *Indian Journal of Orthopaedics*, 58(12): 1680-1685.
 22. Haines, N., Kempton, L.B., Seymour, R.B., Beebe, M.J., Watson, D., Sanders, R.W., Mir, H.R. (2017) The effect of a single early high-dose vitamin D supplement on fracture union in patients with hypovitaminosis D: a prospective randomised trial. *Bone & Joint Journal*, 99-B(11): 1520-1525.
 23. Gatt, T., Grech, A., Arshad, H. (2023) The Effect of Vitamin D Supplementation for Bone Healing in Fracture Patients: A Systematic Review. *Advances in Orthopedics*, 2023: 6236045.
 24. Moonen, L., Gorter, E., Schipper, I. (2021) The importance of vitamin D in treatment of fracture non-union: A case report. *Nutrition*, 87-88: 111192.
 25. Kishore, D.R., Nandini, H., Karri, N. (2024) Impact of Vitamin D Supplementation on Bone Healing Post-Fracture in Osteoporotic Patients. *SSR Institute of International Journal of Life Sciences*, 10(4): 6088-6094.
 26. Institute of Medicine, Committee to Review Dietary Reference Intakes for Vitamin D and Calcium (2011) *Dietary Reference Intakes for Calcium and Vitamin D*. National Academies Press, Washington, DC.