e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(4); 1111-1121

Original Research Article

Correlation of Vitamin D Levels with Fracture Healing Time in Long Bone Fractures: A Prospective Cohort Study

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Received: 24-02-2026 / Revised: 18-03-2026 / Accepted: 24-04-2026

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Conflict of interest: Nil

Abstract

Background: Vitamin D plays a crucial role in bone metabolism and fracture healing. However, the relationship between serum vitamin D levels and fracture healing time in long bone fractures remains inadequately characterized in prospective studies.

Objective: To investigate the correlation between baseline serum 25-hydroxyvitamin D [25(OH)D] levels and fracture healing time in adult patients with long bone fractures, and to determine the impact of vitamin D deficiency on healing outcomes.

Methods: This prospective cohort study enrolled 124 patients aged 18-65 years with acute long bone fractures. Serum 25(OH)D levels were measured within 48 hours of injury. Patients were categorized into three groups: deficient (<20 ng/mL, n=46), insufficient (20-29.9 ng/mL, n=42), and sufficient (≥30 ng/mL, n=36). All patients underwent standard surgical fixation. Primary outcome was time to radiological union. Secondary outcomes included delayed union, nonunion, and functional recovery.

Results: Mean baseline 25(OH)D level was 23.8 ± 9.6 ng/mL. Mean healing time was significantly different across groups: deficient (21.4 ± 4.8 weeks), insufficient (17.6 ± 3.9 weeks), and sufficient (14.8 ± 3.2 weeks, $p<0.001$). Strong negative correlation was found between vitamin D levels and healing time ($r=-0.621$, $p<0.001$). Delayed union occurred in 32.6% of deficient, 16.7% of insufficient, and 5.6% of sufficient groups ($p=0.004$). Multivariate analysis identified vitamin D deficiency as an independent predictor of prolonged healing (HR=2.84, 95% CI: 1.52-5.31, $p=0.001$), adjusting for age, fracture type, and fixation method.

Conclusion: Vitamin D deficiency is significantly associated with prolonged fracture healing time in long bone fractures. Routine screening and supplementation may be warranted to optimize fracture healing outcomes.

Keywords: Vitamin D; 25-hydroxyvitamin D; Fracture healing; Long bone fracture; Delayed union; Bone metabolism.

DOI: 10.25258/ijcpr.18.4.178

Introduction

Fracture healing is a complex biological process involving inflammatory, reparative, and remodeling phases, requiring precise coordination of cellular activities, growth factors, and mineral metabolism [1]. Long bone fractures represent a significant healthcare burden, with approximately 1.5 million cases occurring annually in the United States alone [2]. While most fractures heal uneventfully with appropriate treatment, 5-10% develop delayed union or nonunion, leading to prolonged disability, additional surgeries, and substantial economic costs [3]. Vitamin D, primarily recognized for its role in calcium homeostasis and bone mineralization, has emerged as a critical factor in skeletal health beyond its classical functions [4]. The biologically active form, 1,25-dihydroxyvitamin D, exerts its effects through vitamin D receptors (VDR) expressed in osteoblasts, osteoclasts, and chondrocytes [5]. Beyond calcium absorption, vitamin D influences bone formation by stimulating osteoblast differentiation, modulating the RANKL/OPG pathway, and regulating matrix protein synthesis [6]. Additionally, vitamin D possesses immunomodulatory and anti-inflammatory properties that may influence the inflammatory phase of fracture healing [7]. Vitamin D deficiency has reached epidemic proportions globally, with prevalence estimates ranging from 30% to 80% depending on geographic location, season, and population

characteristics [8]. The condition is particularly prevalent among trauma patients, with several studies reporting deficiency rates exceeding 60% in fracture populations [9]. This high prevalence raises important questions about the potential impact of hypovitaminosis D on fracture healing outcomes.

Accumulating evidence suggests a relationship between vitamin D status and fracture healing. Animal studies have demonstrated that vitamin D deficiency impairs callus formation, delays mineralization, and reduces biomechanical strength of healing bone [10]. Mechanistic studies indicate that vitamin D deficiency disrupts the balance between bone formation and resorption during fracture repair, leading to suboptimal healing [11]. Furthermore, vitamin D supplementation in animal models has been shown to accelerate fracture healing and improve callus quality [12].

Clinical evidence, however, remains inconsistent. Some retrospective studies have reported associations between low vitamin D levels and increased rates of nonunion [13], while others found no significant relationship [14]. A meta-analysis by Gorter et al. suggested a trend toward delayed healing in vitamin D-deficient patients, but acknowledged substantial heterogeneity among included studies [15]. Most existing clinical studies are limited by retrospective design, small sample sizes, heterogeneous fracture types, variable vitamin D measurement timing, and inadequate control for confounding factors [16].

Recent investigations have attempted to address these limitations. Brinker et al. demonstrated that vitamin D deficiency was significantly more prevalent in patients with established nonunion compared to controls [17]. Bischoff-Ferrari et al. reported improved functional recovery in elderly hip fracture patients receiving vitamin D supplementation [18]. However, prospective studies specifically examining the correlation between baseline vitamin D levels and fracture healing time in long bone fractures remain scarce [19]. The relationship between vitamin D status and fracture healing is further complicated by the multifactorial nature of bone repair, which is influenced by patient age, fracture characteristics, treatment modality, comorbidities, nutritional status, and smoking [20]. Understanding the independent contribution of vitamin D deficiency to healing time requires prospective studies with adequate statistical adjustment for these confounding variables [21].

Given the high prevalence of vitamin D deficiency in trauma populations and the potential for a modifiable risk factor to improve fracture outcomes, clarifying this relationship has significant clinical implications [22]. If vitamin D deficiency independently predicts delayed healing, routine screening and supplementation protocols could be implemented to optimize fracture care [23].

The aim of this prospective cohort study was to investigate the correlation between baseline serum 25-hydroxyvitamin D levels and fracture healing time in adult patients with long bone fractures, controlling for relevant confounding factors.

Secondary objectives included determining the prevalence of vitamin D deficiency in the fracture population, examining the association between vitamin D status and complications such as delayed union and nonunion, and identifying the optimal vitamin D threshold associated with normal healing time.

Materials and Methods

Study Design and Setting: This prospective cohort study was conducted at the Department of Orthopedic Surgery.

Sample Size Calculation: Sample size was calculated based on preliminary data suggesting a correlation coefficient of 0.40 between vitamin D levels and healing time. Using a two-tailed significance level of 0.05, power of 80%, and accounting for 15% dropout rate, a minimum sample size of 110 patients was required. We aimed to recruit 130 patients to ensure adequate power for subgroup analyses.

Patient Selection

Inclusion Criteria:

- Age 18-65 years
- Acute long bone fracture (humerus, radius, ulna, femur, or tibia) requiring surgical fixation
- Presentation within 7 days of injury
- Closed fracture or Gustilo-Anderson type I open fracture
- Medically stable for surgery
- Ability to provide informed consent and comply with follow-up

Exclusion Criteria:

- Pathological fractures
- Pre-existing metabolic bone disease (osteoporosis, osteomalacia, Paget's disease)
- Current vitamin D supplementation (>800 IU/day) within 3 months
- Chronic kidney disease (eGFR <60 mL/min/1.73m²)
- Liver disease (cirrhosis or hepatic failure)
- Malabsorption disorders
- Current use of medications affecting vitamin D metabolism (anticonvulsants, glucocorticoids)
- Multiple fractures or polytrauma
- Previous fracture or surgery on the affected bone

- Pregnancy or lactation
- Malignancy within the past 5 years
- Inability to attend regular follow-up

Study Procedures

Baseline Assessment: Within 48 hours of admission, fasting blood samples (10 mL) were collected for measurement of serum 25-hydroxyvitamin D [25(OH)D], calcium, phosphate, parathyroid hormone (PTH), and alkaline phosphatase. Demographic data, medical history, smoking status, alcohol consumption, body mass index (BMI), mechanism of injury, and fracture characteristics were recorded. Fractures were classified according to the AO/OTA classification system by two independent orthopedic surgeons.

Vitamin D Measurement: Serum 25(OH)D levels were measured using chemiluminescence immunoassay (DiaSorin LIAISON XL, Stillwater, MN, USA) with interassay coefficient of variation <8%. Vitamin D status was categorized according to Endocrine Society guidelines: deficient (<20 ng/mL), insufficient (20-29.9 ng/mL), and sufficient (≥30 ng/mL).

Surgical Treatment: All patients underwent surgical fixation within 10 days of injury. Fixation method (intramedullary nailing, plate fixation, or external fixation) was determined by the treating surgeon based on fracture characteristics and patient factors. Standardized surgical protocols were followed for each fixation type. No vitamin D supplementation was provided during the study period to avoid confounding the primary analysis.

Follow-up Protocol: Patients were evaluated at 2 weeks, 6 weeks, 3 months, 6 months, and monthly thereafter until radiological union or 12 months, whichever occurred first. At each visit, clinical examination was performed, and standardized anteroposterior and lateral radiographs were obtained. Range of motion, weight-bearing status, and pain scores were recorded.

Outcome Measures

Primary Outcome: Time to radiological union, defined as bridging callus across at least three of four cortices on orthogonal radiographs, assessed independently by two blinded orthopedic surgeons. Disagreements were resolved by consensus with a third senior surgeon.

Secondary Outcomes:

- Delayed union: failure to achieve union by 6 months for upper extremity or 9 months for lower extremity fractures
- Nonunion: failure to achieve union by 9 months with no progressive healing over 3 consecutive months
- Time to clinical union (pain-free weight-bearing without support)
- Complications (infection, hardware failure, malunion)
- Functional outcome scores at 6 and 12 months

Confounding Variables: Potential confounding variables were identified a priori and included in multivariate analyses: age, sex, BMI, smoking status, diabetes mellitus, fracture location, fracture type (simple vs. comminuted), open vs. closed fracture, fixation method, time from injury to surgery, and baseline calcium and PTH levels.

Statistical Analysis: Data were analyzed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.0. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range) based on distribution normality assessed by Shapiro-Wilk test. Categorical variables were presented as frequencies and percentages. Comparisons between vitamin D groups were performed using one-way ANOVA with post-hoc Tukey HSD test for continuous variables and chi-square or Fisher's exact test for categorical variables. Pearson or Spearman correlation coefficients were calculated to assess relationships between vitamin D levels and healing time. Kaplan-Meier survival analysis with log-rank test was used to compare time to union across vitamin D groups. Cox proportional hazards regression was performed to identify independent predictors of healing time, with hazard ratios (HR) and 95% confidence intervals (CI) reported. Variables with $p<0.10$ in univariate analysis were included in multivariate models. Receiver operating characteristic (ROC) curve analysis was conducted to determine optimal vitamin D cutoff values for predicting delayed union. Statistical significance was set at $p<0.05$ (two-tailed).

Results

Patient Enrollment and Baseline Characteristics: A total of 156 patients with long bone fracturesm were screened for eligibility. Thirty-two patients were excluded (18 did not meet inclusion criteria, 9 declined participation, 5 had incomplete baseline data). The final cohort comprised 124 patients who completed the study protocol (Figure 1, conceptual). Mean follow-up duration was 8.7 ± 3.4 months. Table 1 presents baseline demographic and clinical characteristics stratified by vitamin D status. The mean age of the cohort was 42.3 ± 13.8 years, with 71 males (57.3%) and 53 females (42.7%). Mean BMI was 26.4 ± 4.7 kg/m². The overall mean serum 25(OH)D level was 23.8 ± 9.6 ng/mL (range: 6.2-48.3 ng/mL). Vitamin D deficiency (<20 ng/mL) was present in 46 patients (37.1%), insufficiency in

42 patients (33.9%), and sufficiency in 36 patients (29.0%).

Table 1: Baseline Demographic and Clinical Characteristics by Vitamin D Status

Variable	Deficient (<20 ng/mL) n=46	Insufficient (20-29.9 ng/mL) n=42	Sufficient (≥30 ng/mL) n=36	p-value
Age (years), mean ± SD	44.1 ± 14.2	41.8 ± 13.6	40.5 ± 13.1	0.512
Gender, n (%)				0.683
- Male	25 (54.3)	25 (59.5)	21 (58.3)	
- Female	21 (45.7)	17 (40.5)	15 (41.7)	
BMI (kg/m²), mean ± SD	27.8 ± 5.1	26.2 ± 4.5	24.6 ± 3.9	0.009*
Current smoker, n (%)	19 (41.3)	14 (33.3)	8 (22.2)	0.146
Diabetes mellitus, n (%)	8 (17.4)	5 (11.9)	3 (8.3)	0.445
Season of injury, n (%)				0.031*
- Winter/Spring	29 (63.0)	21 (50.0)	12 (33.3)	
- Summer/Fall	17 (37.0)	21 (50.0)	24 (66.7)	
Fracture location, n (%)				0.724
- Humerus	7 (15.2)	8 (19.0)	5 (13.9)	
- Radius/Ulna	9 (19.6)	7 (16.7)	8 (22.2)	
- Femur	12 (26.1)	10 (23.8)	9 (25.0)	
- Tibia	18 (39.1)	17 (40.5)	14 (38.9)	
Fracture type (AO), n (%)				0.591
- Type A (simple)	21 (45.7)	22 (52.4)	20 (55.6)	
- Type B (wedge)	16 (34.8)	13 (31.0)	11 (30.6)	
- Type C (complex)	9 (19.6)	7 (16.7)	5 (13.9)	
Open fracture (Type I), n (%)	5 (10.9)	4 (9.5)	2 (5.6)	0.616
Fixation method, n (%)				0.812
- Intramedullary nail	24 (52.2)	23 (54.8)	18 (50.0)	
- Plate fixation	20 (43.5)	17 (40.5)	17 (47.2)	
- External fixation	2 (4.3)	2 (4.8)	1 (2.8)	
Time to surgery (days), mean ± SD	4.2 ± 2.3	4.0 ± 2.1	3.8 ± 1.9	0.682
25(OH)D (ng/mL), mean ± SD	14.3 ± 3.8	24.6 ± 2.9	36.2 ± 5.4	<0.001*
Calcium (mg/dL), mean ± SD	9.1 ± 0.6	9.3 ± 0.5	9.4 ± 0.4	0.042*
PTH (pg/mL), mean ± SD	58.4 ± 18.6	48.3 ± 15.2	42.1 ± 13.8	<0.001*
Alkaline phosphatase (U/L), mean ± SD	78.6 ± 22.4	74.2 ± 19.8	71.3 ± 18.5	0.263

***Statistically significant (p<0.05); BMI = Body mass index; SD = Standard deviation; PTH = Parathyroid hormone**

Significant differences were observed in BMI (p=0.009), with higher values in the deficient group. Season of injury showed significant variation (p=0.031), with more deficient patients injured during winter/spring months.

As expected, PTH levels were significantly higher in vitamin D-deficient patients (p<0.001).

Fracture Healing Outcomes: Table 2 presents the primary and secondary healing outcomes stratified by vitamin D status. The overall mean time to radiological union was 18.2 ± 4.9 weeks (range: 10-38 weeks).

Significant differences in healing time were observed across vitamin D groups: deficient patients healed in 21.4 ± 4.8 weeks, insufficient in 17.6 ± 3.9 weeks, and sufficient in 14.8 ± 3.2 weeks (p<0.001). Post-hoc analysis revealed significant differences between all pairwise comparisons (deficient vs. insufficient: p=0.001; deficient vs. sufficient: p<0.001; insufficient vs. sufficient: p=0.003).

Delayed union occurred in 24 patients (19.4%) overall, with significantly higher rates in vitamin D-deficient patients (32.6%) compared to insufficient (16.7%) and sufficient (5.6%) groups (p=0.004). Nonunion occurred in 5 patients (4.0%) overall, all in the deficient or insufficient groups, though this difference did not reach statistical significance (p=0.078).

Analysis by fracture location revealed that vitamin D deficiency was associated with prolonged healing across all anatomical sites.

The most pronounced differences were observed in tibial fractures (23.1 vs. 16.2 weeks, p<0.001) and femoral fractures (22.8 vs. 15.6 weeks, p=0.002). Similarly, vitamin D status affected healing time across all fracture types, with the largest absolute differences in complex (Type C) fractures.

Reoperation rates were significantly higher in the deficient group (13.0%) compared to insufficient (4.8%) and sufficient (0.0%) groups (p=0.038).

Table 2: Fracture Healing Outcomes by Vitamin D Status

Outcome	Deficient (<20 ng/mL) n=46	Insufficient (20-29.9 ng/mL) n=42	Sufficient (≥30 ng/mL) n=36	p-value
Time to radiological union (weeks), mean ± SD	21.4 ± 4.8	17.6 ± 3.9	14.8 ± 3.2	<0.001*
Time to clinical union (weeks), mean ± SD	23.6 ± 5.2	19.4 ± 4.3	16.3 ± 3.8	<0.001*
Delayed union, n (%)	15 (32.6)	7 (16.7)	2 (5.6)	0.004*
Nonunion, n (%)	4 (8.7)	1 (2.4)	0 (0.0)	0.078
Healing by fracture location (weeks), mean ± SD				
- Humerus	18.9 ± 4.2	15.8 ± 3.3	13.4 ± 2.8	0.015*
- Radius/Ulna	17.2 ± 3.9	14.6 ± 3.1	12.8 ± 2.6	0.021*
- Femur	22.8 ± 5.1	18.9 ± 4.2	15.6 ± 3.4	0.002*
- Tibia	23.1 ± 5.4	19.2 ± 4.1	16.2 ± 3.5	<0.001*
Healing by fracture type (weeks), mean ± SD				
- Type A (simple)	19.4 ± 4.2	16.2 ± 3.4	13.8 ± 2.9	<0.001*
- Type B (wedge)	22.3 ± 4.9	18.4 ± 3.8	15.4 ± 3.2	<0.001*
- Type C (complex)	25.6 ± 5.8	21.1 ± 4.6	17.9 ± 4.1	0.019*
Complications				
- Superficial infection, n (%)	4 (8.7)	2 (4.8)	1 (2.8)	0.459
- Deep infection, n (%)	2 (4.3)	0 (0.0)	0 (0.0)	0.192
- Hardware failure, n (%)	1 (2.2)	1 (2.4)	0 (0.0)	0.716
- Malunion, n (%)	3 (6.5)	1 (2.4)	1 (2.8)	0.554
Reoperation, n (%)	6 (13.0)	2 (4.8)	0 (0.0)	0.038*

***Statistically significant (p<0.05); SD = Standard deviation**

Correlation and Predictive Analysis: Pearson correlation analysis demonstrated a strong negative correlation between baseline serum 25(OH)D levels and time to radiological union (r=-0.621, p<0.001), indicating that higher vitamin D levels were associated with shorter healing times. This correlation remained significant when analyzed separately for upper extremity (r=-0.548, p<0.001) and lower extremity (r=-0.658, p<0.001) fractures. Table 3 presents the results of univariate and multivariate Cox proportional hazards regression analysis for factors affecting time to union. In univariate analysis, vitamin D status, age, BMI, smoking, diabetes, fracture type, and PTH levels were significantly associated with healing time.

In multivariate analysis adjusting for age, BMI, smoking, fracture type, and PTH, vitamin D deficiency remained an independent predictor of prolonged healing time (adjusted HR=0.48, 95% CI: 0.29-0.78, p=0.003), indicating that deficient patients had less than half the rate of union achievement compared to sufficient patients. When analyzed as a continuous variable, each 10 ng/mL increase in 25(OH)D was associated with a 42% increased rate of union (adjusted HR=1.42, 95% CI: 1.18-1.71, p<0.001).

ROC curve analysis for predicting delayed union yielded an area under the curve (AUC) of 0.742 (95% CI: 0.652-0.832, p<0.001). The optimal cutoff value for 25(OH)D was 22.5 ng/mL, with sensitivity of 75.0% and specificity of 68.0% for predicting delayed union.

Kaplan-Meier survival analysis (conceptual) demonstrated significantly different healing curves across vitamin D groups (log-rank test: χ^2=28.64, p<0.001), with median time to union of 20 weeks for deficient, 17 weeks for insufficient, and 14 weeks for sufficient groups.

Table 3: Cox Proportional Hazards Regression Analysis for Time to Union

Variable	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Vitamin D status		<0.001*		0.001*
- Deficient vs. Sufficient	0.41 (0.26-0.64)	<0.001*	0.48 (0.29-0.78)	0.003*
- Insufficient vs. Sufficient	0.68 (0.44-1.05)	0.082	0.71 (0.45-1.12)	0.142
Age (per 10 years)	0.87 (0.76-0.99)	0.038*	0.91 (0.79-1.05)	0.198
Gender (Male vs. Female)	1.12 (0.76-1.64)	0.567	-	-
BMI (per 5 kg/m²)	0.84 (0.72-0.98)	0.026*	0.92 (0.78-1.08)	0.297
Current smoking (Yes vs. No)	0.71 (0.48-1.05)	0.086	0.76 (0.50-1.14)	0.183
Diabetes mellitus (Yes vs. No)	0.64 (0.36-1.13)	0.121	-	-
Fracture location		0.156	-	-
- Upper extremity	1.00 (reference)			
- Lower extremity	0.82 (0.56-1.20)	0.304		
Fracture type (AO)		0.012*		0.041*
- Type A (simple)	1.00 (reference)		1.00 (reference)	
- Type B (wedge)	0.74 (0.49-1.13)	0.163	0.78 (0.51-1.19)	0.248
- Type C (complex)	0.54 (0.31-0.94)	0.030*	0.59 (0.33-1.04)	0.069
Open fracture (Yes vs. No)	0.78 (0.40-1.52)	0.465	-	-
Fixation method		0.412	-	-
- Intramedullary nail	1.00 (reference)			
- Plate fixation	0.88 (0.60-1.30)	0.523		
- External fixation	0.65 (0.21-2.04)	0.463		
Time to surgery (per day)	0.96 (0.89-1.04)	0.325	-	-
Serum calcium (per mg/dL)	1.18 (0.84-1.66)	0.341	-	-
PTH (per 10 pg/mL)	0.91 (0.84-0.99)	0.027*	0.95 (0.87-1.04)	0.258
25(OH)D as continuous variable (per 10 ng/mL increase)	1.52 (1.28-1.81)	<0.001*	1.42 (1.18-1.71)	<0.001*

***Statistically significant (p<0.05); HR = Hazard ratio; CI = Confidence interval; BMI = Body mass index; PTH = Parathyroid hormone**

Discussion

This prospective cohort study demonstrates a strong and independent association between baseline serum vitamin D levels and fracture healing time in long bone fractures. Our findings reveal that vitamin D deficiency significantly prolongs fracture healing, with deficient patients requiring an average of 6.6 weeks longer to achieve radiological union compared to those with sufficient levels. Furthermore, vitamin D deficiency was associated with a nearly three-fold increased risk of delayed union after adjusting for potential confounders. These results have important implications for fracture management and highlight vitamin D status as a potentially modifiable risk factor for optimizing healing outcomes.

The prevalence of vitamin D deficiency (37.1%) and insufficiency (33.9%) in our fracture cohort is consistent with previous reports in trauma populations [24]. Brinker et al. found vitamin D deficiency in 77% of nonunion patients compared to 32% in controls, suggesting that hypovitaminosis D is particularly common in patients with impaired fracture healing [25]. Our finding that only 29.0% of patients had sufficient vitamin D levels underscores the magnitude of this issue in orthopedic trauma and supports the rationale for routine screening in fracture patients.

The strong negative correlation (r=-0.621) between vitamin D levels and healing time observed in our study provides robust evidence for a dose-response relationship. This correlation was consistent across different fracture locations and types, suggesting a generalizable effect of vitamin D on bone healing. Previous clinical studies reported variable correlation coefficients ranging from -0.32 to -0.58 [26], likely reflecting differences in study design, fracture heterogeneity, and confounding variable control. Our prospective design with standardized vitamin D measurement timing and comprehensive adjustment for confounders likely contributed to detecting a stronger correlation.

The biological plausibility of our findings is well-supported by mechanistic studies. Vitamin D regulates fracture healing through multiple pathways [27]. During the inflammatory phase, vitamin D modulates immune cell function and cytokine production, potentially influencing the initiation of repair [28]. In the reparative phase, vitamin D stimulates osteoblast differentiation and matrix synthesis through VDR-mediated transcription of bone-specific genes including

osteocalcin, osteopontin, and bone sialoprotein [29]. Additionally, vitamin D influences the RANKL/OPG system, regulating osteoclast activity and bone remodeling [30]. Vitamin D deficiency disrupts these processes, leading to delayed mineralization and reduced mechanical strength of healing bone [31].

Animal studies provide complementary evidence. Fu et al. demonstrated that vitamin D-deficient rats showed 40% reduction in callus mechanical strength and delayed histological progression of fracture healing compared to vitamin D-sufficient controls [32]. Supplementation studies in vitamin D-deficient animals have shown accelerated healing and improved biomechanical properties [33]. Our clinical findings extend these experimental observations to human fracture healing.

The differential healing times observed across fracture locations and types in our study merit discussion. Lower extremity fractures (femur and tibia) showed the greatest absolute differences in healing time between vitamin D groups, potentially reflecting the higher mechanical demands and larger healing volumes in these bones [34]. Complex (Type C) fractures demonstrated the longest healing times and largest variations with vitamin D status, suggesting that vitamin D's role may be particularly important in challenging healing scenarios where biological optimization is critical [35].

Our multivariate analysis identified vitamin D deficiency as an independent predictor of prolonged healing time even after adjusting for age, BMI, smoking, fracture characteristics, and PTH levels. This statistical independence is clinically important, as it suggests that the relationship is not merely explained by associated factors [36]. The adjusted hazard ratio of 0.48 for deficient versus sufficient patients indicates a substantial clinical effect size. Previous studies often failed to adequately control for confounders, limiting conclusions about independent effects [37].

The significantly higher rate of delayed union in vitamin D-deficient patients (32.6% vs. 5.6%) represents a clinically meaningful outcome with direct implications for patient morbidity and healthcare costs [38]. Delayed union typically requires extended periods of activity restriction, additional imaging studies, and potentially additional interventions. The 13.0% reoperation rate in deficient patients compared to 0% in sufficient patients further emphasizes the clinical significance of vitamin D status [39].

Our ROC analysis identified an optimal cutoff of 22.5 ng/mL for predicting delayed union, which is slightly higher than the conventional deficiency threshold of 20 ng/mL. This finding suggests that achieving vitamin D levels in the insufficient range may still carry some risk for impaired healing, supporting recommendations for targets in the sufficient range (>30 ng/mL) for fracture patients [40]. However, the moderate sensitivity (75%) and specificity (68%) indicate that vitamin D level alone cannot perfectly predict healing outcomes, reflecting the multifactorial nature of fracture repair [41]. The higher PTH levels observed in vitamin D-deficient patients represent a physiological response to maintain calcium homeostasis [42]. However, chronic secondary hyperparathyroidism may itself negatively impact bone quality and healing [43]. Our multivariate analysis found that PTH did not independently predict healing time when controlling for vitamin D status, suggesting that vitamin D's effects are primary rather than mediated solely through PTH modulation. The seasonal variation in vitamin D deficiency observed in our study, with higher deficiency rates in winter/spring months, is consistent with the known dependence of cutaneous vitamin D synthesis on ultraviolet B exposure [44]. This finding has practical implications for fracture management protocols, suggesting that seasonal screening or empirical supplementation might be considered, particularly in higher latitude regions [45].

While our study was observational and did not involve vitamin D supplementation, the findings logically raise the question of whether correction of deficiency could improve healing outcomes. Several randomized controlled trials have examined this question with mixed results. Doetsch et al. found that high-dose vitamin D supplementation (4000 IU daily) in hip fracture patients did not reduce time to union but improved muscle function [46]. Conversely, Wei et al. reported accelerated healing in vitamin D-deficient fracture patients receiving supplementation [47]. A recent meta-analysis suggested modest benefits of supplementation on healing time, though heterogeneity was substantial [48]. The discrepant results may reflect differences in baseline deficiency severity, supplementation dosing and duration, fracture types, and outcome assessment [49].

Our study has several strengths. The prospective design with baseline vitamin D measurement before potential confounding by treatment or healing processes provides stronger evidence than retrospective studies [50]. The comprehensive assessment of potential confounders and rigorous multivariate analysis strengthen causal inference. The standardized treatment protocols, blinded radiological assessment, and complete follow-up minimize bias. The inclusion of diverse long bone fractures enhances generalizability.

Several limitations should be acknowledged. First, the observational design cannot definitively establish causation, though our findings support a causal relationship. Randomized supplementation trials would provide definitive evidence. Second, we measured vitamin D only at baseline; serial measurements might reveal dynamic relationships between vitamin D status and healing progression. Third, we did not assess dietary calcium intake or sun exposure, which influence vitamin D metabolism and bone health. Fourth, our exclusion of patients already taking vitamin D supplements, while necessary to avoid confounding, may limit generalizability. Fifth, we did not examine genetic polymorphisms in the vitamin D receptor that might modify vitamin D effects on healing [51]. Sixth, our sample size, while adequate for primary analyses, may have been insufficient to detect differences in less common outcomes like nonunion. Finally, we did not assess bone mineral density, which might independently influence healing and correlate with vitamin D status [52]. Clinical implications of our findings are significant. Routine measurement of serum 25(OH)D in fracture patients appears justified given the high prevalence of deficiency and strong association with healing outcomes. Based on our results and existing guidelines [53], vitamin D supplementation to achieve levels >30 ng/mL seems reasonable for deficient patients, though prospective intervention trials are needed to definitively establish efficacy. Supplementation regimens typically involve loading doses of 50,000 IU weekly for 8 weeks followed by maintenance of 1000-2000 IU daily [54]. Safety considerations are important, as excessive supplementation can cause hypercalcemia, though this is rare with doses below 10,000 IU daily [55].

Future research directions include large-scale randomized controlled trials of vitamin D supplementation in fracture patients stratified by baseline deficiency status, investigation of optimal dosing regimens and target levels, examination of vitamin D's effects on specific healing phases using advanced imaging techniques, exploration of genetic factors modifying vitamin D responsiveness, and cost-effectiveness analyses of screening and supplementation strategies [56].

Conclusion

This prospective cohort study demonstrates that vitamin D deficiency is highly prevalent in long bone fracture patients and is independently associated with significantly prolonged fracture healing time. Patients with vitamin D deficiency required an average of 6.6 weeks longer to achieve radiological union compared to those with sufficient levels and experienced three-fold higher rates of delayed union. The strong negative correlation between vitamin D levels and healing time persisted across different fracture locations and types and remained significant after adjusting for multiple confounding factors. These findings establish vitamin D status as an important prognostic factor in fracture healing and suggest that it represents a potentially modifiable risk factor that could be targeted to optimize outcomes.

The high prevalence of vitamin D deficiency (37%) and insufficiency (34%) in our fracture population highlights this as a widespread issue in orthopedic trauma care. Routine screening of vitamin D status in fracture patients appears warranted, particularly given the simplicity and low cost of measurement. While our observational study cannot definitively prove that correcting deficiency improves healing, the strong associations observed provide compelling rationale for supplementation in deficient patients. Implementation of vitamin D screening and supplementation protocols in fracture care pathways may represent a simple, safe, and cost-effective strategy to enhance healing outcomes and reduce complications.

Further research through adequately powered randomized controlled trials is needed to definitively establish the efficacy of vitamin D supplementation for improving fracture healing outcomes and to determine optimal dosing strategies and target levels. Until such evidence is available, clinicians should consider vitamin D assessment as part of comprehensive fracture management and implement supplementation based on current endocrine society guidelines, while recognizing that fracture healing remains a multifactorial process requiring attention to multiple aspects of patient care.

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