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ROLE OF SERUM 25-HYDROXYVITAMIN D LEVELS IN DELAYED UNION AND NON-UNION OF LONG BONE FRACTURES: A PROSPECTIVE OBSERVATIONAL STUDY

Orthopaedics

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ABSTRACT

Background: Delayed union and non-union remain significant complications of long bone fractures, contributing to prolonged morbidity, repeat surgical intervention, and substantial healthcare expenditure. Hypovitaminosis D is highly prevalent across the Indian subcontinent and is increasingly recognised as a modifiable contributor to impaired fracture repair. This study evaluated the association between serum 25-hydroxyvitamin D [25(OH)D] concentrations and the occurrence of delayed union and non-union following surgical management of long bone fractures.**Methods:** A prospective observational study was conducted at a tertiary care teaching hospital from January 2024 to December 2025. One hundred twenty adult patients (18 to 60 years) with surgically managed diaphyseal long bone fractures of the femur, tibia, or humerus were enrolled consecutively. Baseline serum 25(OH)D, calcium, phosphorus, alkaline phosphatase, and parathyroid hormone concentrations were measured within 72 hours of admission. Patients were followed clinically and radiographically at six weeks, three months, six months, and nine months. Fracture healing was classified as normal union, delayed union (absence of radiological union at six months), or non-union (no progression of healing for three consecutive months after six months).**Results:** Of 120 enrolled patients, 65 (54.2 percent) achieved normal union, 38 (31.7 percent) had delayed union, and 17 (14.2 percent) developed non-union. Mean serum 25(OH)D was significantly lower in the non-union group (12.4 ± 4.1 ng/mL) and the delayed-union group (18.6 ± 5.3 ng/mL) compared with the normal-union group (28.9 ± 7.2 ng/mL) ($p < 0.001$). Vitamin D deficiency (<20 ng/mL) was independently associated with impaired healing on multivariate logistic regression (adjusted OR 4.82; 95 percent CI 2.14 to 10.86; $p < 0.001$). A significant inverse correlation was observed between serum 25(OH)D and time to radiological union ($r = -0.612$; $p < 0.001$).**Conclusion:** Low serum 25(OH)D concentration was strongly and independently associated with delayed union and non-union following long bone fractures. Screening and targeted correction of vitamin D status warrant consideration in routine fracture management protocols.

KEYWORDS

Vitamin D; 25-hydroxyvitamin D; Long Bone Fracture; Delayed Union; Non-union; Fracture Healing.

INTRODUCTION

Vitamin D is a fat-soluble secosteroid hormone whose active metabolite, 1,25-dihydroxyvitamin D, regulates calcium-phosphate homeostasis, intestinal mineral absorption, parathyroid hormone secretion, and bone mineralisation. Vitamin D deficiency is one of the most prevalent nutritional disorders worldwide, affecting nearly one billion people with serum 25-hydroxyvitamin D [25(OH)D] levels below 20 ng/mL.[1] India is particularly affected, with deficiency reported in 70–100% of the population despite abundant sunlight, largely due to darker skin pigmentation, limited sun exposure, urban lifestyles, and inadequate food fortification.[2]

Long bone fractures are a major cause of orthopaedic morbidity. While most fractures heal through a coordinated process of inflammation, callus formation, and remodelling, a subset progress to delayed union or non-union. Population-based studies estimate an overall non-union risk of approximately 1.9% per fracture, increasing to nearly 9% for tibial and clavicular fractures.[3] These complications often require revision surgery, bone grafting, and prolonged rehabilitation, resulting in significant functional and economic burdens.

Fracture healing depends on mesenchymal cell differentiation, angiogenesis, matrix formation, and mineralisation. Vitamin D plays a key role by acting on osteoblast vitamin D receptors to regulate osteocalcin, osteopontin, and receptor activator of nuclear factor kappa-B ligand expression, thereby facilitating callus maturation and bone remodelling.[4] [5] Deficiency reduces calcium absorption, causes secondary hyperparathyroidism, and impairs mineralisation of the fracture callus.

Clinical evidence increasingly links hypovitaminosis D with impaired fracture healing. Brinker et al. reported previously undiagnosed metabolic or endocrine abnormalities in 83.8% of patients with unexplained non-union, with vitamin D deficiency present in 68%.[6] Similarly, a case-control study found vitamin D deficiency in 60% of patients with tibial non-union compared with 30% of patients with normal healing.[7] A systematic review estimated the prevalence of vitamin D deficiency among fracture patients at approximately 70% and suggested a potential reduction in non-union risk following supplementation.[8]

Interventional studies have produced mixed results. A randomized placebo-controlled trial involving adults with long bone fractures and hypovitaminosis D found no significant difference in union rates after high-dose vitamin D supplementation, although the study was underpowered.[9] Conversely, supplementation with vitamin D_3 and calcium significantly improved early callus bone mineral density in osteoporotic women with proximal humerus fractures.[10]

Despite growing evidence, data from Indian populations remain limited. Most studies are retrospective or restricted to specific fracture types and elderly osteoporotic patients. The prognostic significance of baseline vitamin D status in adult diaphyseal long bone fractures and its interaction with factors such as fracture pattern, smoking, diabetes, and open injuries remain inadequately defined.[2] Therefore, this study was undertaken to prospectively evaluate the relationship between baseline serum 25(OH)D levels and the development of delayed union and non-union in adults undergoing surgical management of femoral, tibial, and humeral shaft fractures.

MATERIALS AND METHODS

This prospective observational study occurred at a tertiary care teaching hospital (January 2024–December 2025). The Institutional Ethics Committee approved the protocol, and participants provided written informed consent. The investigation followed the Declaration of Helsinki and ICMR ethical guidelines. Assuming a 10% non-union rate for normal vitamin D status and 30% for hypovitaminosis D, based on prior tibial non-union data, we calculated a minimum sample of 109 (alpha 0.05, 80% power, 10% attrition). We enrolled 120 consecutive patients for stratified analysis. Patients aged 18–60 with closed or Gustilo-Anderson type I/II diaphyseal femur, tibia, or humerus fractures treated with internal fixation within 14 days were included. Patients with pathological or periprosthetic fractures, major intra-articular extension, segmental bone loss, Gustilo-Anderson type III injuries, or polytrauma (ISS >16) were excluded. Also excluded were patients with metabolic bone disease, chronic kidney or liver disease, malabsorption, or those using bisphosphonates, teriparatide, high-dose glucocorticoids, anticonvulsants, or vitamin D supplements within three months. Pregnant and lactating women were excluded.

Demographics, injury details, comorbidities, and surgical data were recorded. Within 72 hours of admission, we measured serum 25(OH)D

(chemiluminescent immunoassay), calcium, phosphorus, alkaline phosphatase (colorimetric), and parathyroid hormone (electrochemiluminescence). Vitamin D status was categorized per Endocrine Society guidelines: deficient (<20 ng/mL), insufficient (20–29 ng/mL), or sufficient (≥30 ng/mL).

Surgical Management

All fractures were managed by consultant orthopaedic surgeons using standard implants and techniques. Femoral and tibial shaft fractures were stabilised mainly with reamed intramedullary interlocking nails, while humeral shaft fractures were treated with anterolateral plate osteosynthesis or antegrade humeral nails according to fracture configuration. Open fractures received intravenous antibiotics, surgical debridement, and early definitive fixation per institutional protocol. No patient received intraoperative bone graft or osteobiologic augmentation.

Follow-up Protocol

Patients were reviewed at six weeks, three months, six months, and nine months postoperatively. Each visit included clinical assessment of fracture-site tenderness, painless weight-bearing, and functional recovery, with standardised anteroposterior and lateral radiographs. Radiographic union was assessed independently by two consultant orthopaedic surgeons blinded to vitamin D status, using RUST for tibial fractures and an analogous bridging-cortex system for femoral and humeral fractures. A RUST score ≥10/12 indicated radiological union. Interobserver disagreement was resolved by consensus or by a third senior surgeon.

Outcome Definitions

Outcome Definitions Normal union was defined as clinical and radiological union within six months of index surgery. Delayed union was absence of radiological union at six months, with union between six and nine months without additional surgery. Non-union was absence of radiological healing progression for three consecutive months after the six-month assessment, or the United States Food and Drug Administration definition of nine months without union and no radiographic progression for three months. The primary outcome was delayed union or non-union; secondary outcomes were time to radiological union and requirement for secondary surgical procedures.

Statistical Analysis

Data were analysed using IBM SPSS Statistics for Windows, version 26.0. Continuous variables were summarised as mean and standard deviation or median and interquartile range according to Shapiro-Wilk testing. Categorical variables were expressed as frequencies and percentages. Between-group comparisons used ANOVA, chi-square, or Fisher exact tests for all comparisons made.

RESULTS

A total of 120 patients completed minimum nine-month follow-up. Mean age was 38.7 ± 11.4 years; 84 (70.0 percent) were male and 36 (30.0 percent) female. Baseline demographic and clinical characteristics are summarized in Table 1.

Mean overall baseline serum 25(OH)D was 23.4 ± 9.6 ng/mL. Vitamin D deficiency (<20 ng/mL) occurred in 57 (47.5 percent) patients, insufficiency (20 to 29 ng/mL) in 38 (31.7 percent), and sufficiency (≥30 ng/mL) in 25 (20.8 percent). Baseline serum calcium, phosphorus, alkaline phosphatase, and intact parathyroid hormone are presented in Table 2.

At nine months, 65 (54.2 percent) patients had normal union, 38 (31.7 percent) delayed union, and 17 (14.2 percent) non-union requiring secondary surgery. Mean time to radiological union was 18.2 ± 3.4 versus 28.6 ± 2.9 weeks, respectively.

The mean baseline serum 25(OH)D concentration differed significantly across the three healing outcome groups. Patients with normal union had a mean serum 25(OH)D of 28.9 ± 7.2 ng/mL, versus 18.6 ± 5.3 ng/mL in delayed union and 12.4 ± 4.1 ng/mL in non-union (one-way ANOVA, $F = 56.74$; $p < 0.001$). Bonferroni comparisons confirmed significant differences between all groups ($p < 0.001$ for all comparisons). Vitamin D deficiency increased across outcomes, affecting 24.6 percent of the normal-union group, 65.8 percent of the delayed-union group, and 94.1 percent of the non-union group (chi-square = 33.21; $p < 0.001$). Mean intact parathyroid hormone was higher and serum calcium lower in impaired healing (Table 4).

Baseline serum 25(OH)D was inversely correlated with time to radiological union in the combined union and delayed-union subgroup (Pearson $r = -0.612$; $p < 0.001$), indicating lower vitamin D levels were associated with prolonged fracture healing. Receiver operating characteristic analysis identified 19.8 ng/mL as the optimal cut-off for predicting impaired healing (area under the curve 0.84; 95 percent confidence interval 0.77 to 0.91; sensitivity 81.8 percent; specificity 76.9 percent; $p < 0.001$).

In multivariable binary logistic regression, after adjustment for age, sex, fracture site, pattern, injury mode, smoking, and diabetes, vitamin D deficiency was the strongest independent predictor of impaired healing (adjusted odds ratio 4.82; 95 percent confidence interval 2.14 to 10.86; $p < 0.001$). Current smoking (adjusted OR 2.94; 95 percent CI 1.18 to 7.32; $p = 0.020$), open fracture (adjusted OR 3.41; 95 percent CI 1.21 to 9.59; $p = 0.020$), and diabetes mellitus (adjusted OR 2.68; 95 percent CI 1.02 to 7.05; $p = 0.046$) were also independent risk factors. This association remained across tibial, femoral, and humeral fractures (Table 5; Table 6). Age, sex, and fracture site were not statistically significant in the adjusted model.

Table 1. Baseline demographic and clinical characteristics of the study cohort (n = 120).

Parameter	Value
Age, years (mean ± SD)	38.7 ± 11.4
Age range, years	18 – 60
Sex, n (%)	
Male	84 (70.0)
Female	36 (30.0)
Body mass index, kg/m² (mean ± SD)	24.6 ± 3.2
Fracture site, n (%)	
Tibia (shaft)	58 (48.3)
Femur (shaft)	42 (35.0)
Humerus (shaft)	20 (16.7)
Mode of injury, n (%)	
Road traffic accident	79 (65.8)
Fall from height	23 (19.2)
Domestic / low-energy fall	12 (10.0)
Assault	6 (5.0)
Fracture type, n (%)	
Closed	96 (80.0)
Gustilo-Anderson type I	16 (13.3)
Gustilo-Anderson type II	8 (6.7)
AO/OTA fracture pattern, n (%)	
Simple (A)	51 (42.5)
Wedge (B)	44 (36.7)
Complex (C)	25 (20.8)
Smoking, n (%)	27 (22.5)
Type 2 diabetes mellitus, n (%)	19 (15.8)
Time from injury to surgery, days (median, IQR)	3 (2 – 5)

SD: standard deviation; IQR: interquartile range; AO/OTA: Arbeitsgemeinschaft für Osteosynthesefragen / Orthopaedic Trauma Association.

Table 2. Baseline biochemical parameters in the study cohort (n = 120).

Parameter	Mean ± SD	Reference range
Serum 25-hydroxyvitamin D, ng/mL	23.4 ± 9.6	30 – 100
Serum total calcium, mg/dL	9.1 ± 0.5	8.5 – 10.5
Serum inorganic phosphorus, mg/dL	3.6 ± 0.6	2.5 – 4.5
Serum alkaline phosphatase, IU/L	112.4 ± 28.7	40 – 130
Intact parathyroid hormone, pg/mL	52.8 ± 19.4	15 – 65
Haemoglobin, g/dL	12.8 ± 1.6	12 – 16
Serum albumin, g/dL	3.9 ± 0.4	3.5 – 5.0
Vitamin D status, n (%)		
Deficient (<20 ng/mL)	57 (47.5)	
Insufficient (20 – 29 ng/mL)	38 (31.7)	
Sufficient (≥30 ng/mL)	25 (20.8)	

SD: standard deviation.

Table 3. Fracture healing outcomes and mean time to radiological union by anatomical site.

Site (n)	Normal union, n (%)	Delayed union, n (%)	Non-union, n (%)	Time to union, weeks (mean ± SD)
Tibia (58)	29 (50.0)	20 (34.5)	9 (15.5)	21.4 ± 5.6
Femur (42)	23 (54.8)	13 (31.0)	6 (14.3)	20.7 ± 5.1
Humerus (20)	13 (65.0)	5 (25.0)	2 (10.0)	18.9 ± 4.7
Overall (120)	65 (54.2)	38 (31.7)	17 (14.2)	20.8 ± 5.3

Time to union refers to the combined normal-union and delayed-union subgroup. SD: standard deviation.

Table 4. Comparison of baseline biochemical parameters across fracture-healing outcome groups.

Parameter	Normal union (n = 65)	Delayed union (n = 38)	Non-union (n = 17)	p-value
Serum 25(OH)D, ng/mL (mean ± SD)	28.9 ± 7.2	18.6 ± 5.3	12.4 ± 4.1	<0.001
Vitamin D deficient, n (%)	16 (24.6)	25 (65.8)	16 (94.1)	<0.001
Serum calcium, mg/dL (mean ± SD)	9.3 ± 0.5	9.0 ± 0.5	8.7 ± 0.4	<0.001
Serum phosphorus, mg/dL (mean ± SD)	3.7 ± 0.6	3.5 ± 0.5	3.4 ± 0.7	0.082
Alkaline phosphatase, IU/L (mean ± SD)	104.8 ± 24.5	118.7 ± 27.8	126.4 ± 30.2	0.004
Intact PTH, pg/mL (mean ± SD)	44.6 ± 14.8	58.3 ± 18.9	72.1 ± 21.5	<0.001
Mean time to union, weeks	18.2 ± 3.4	28.6 ± 2.9	Not achieved	<0.001

p-values from one-way ANOVA (continuous variables) or chi-square test (categorical variables). PTH: parathyroid hormone; SD: standard deviation; 25(OH)D: 25-hydroxyvitamin D.

Table 5. Multivariable binary logistic regression analysis for predictors of impaired fracture healing (delayed union or non-union versus normal union).

Variable	Adjusted OR	95% CI	p-value
Vitamin D deficiency (<20 ng/mL)	4.82	2.14 – 10.86	<0.001
Current smoking	2.94	1.18 – 7.32	0.020
Open fracture (GA I/II)	3.41	1.21 – 9.59	0.020
Type 2 diabetes mellitus	2.68	1.02 – 7.05	0.046
Age (per 10-year increment)	1.22	0.84 – 1.78	0.297
Male sex	1.47	0.61 – 3.54	0.392
Tibial site (vs. humerus)	1.61	0.55 – 4.72	0.385
Femoral site (vs. humerus)	1.34	0.43 – 4.17	0.612
Complex (AO/OTA C) pattern	1.89	0.78 – 4.59	0.158

OR: odds ratio; CI: confidence interval; GA: Gustilo-Anderson classification; AO/OTA: Arbeitsgemeinschaft für Osteosynthesefragen / Orthopaedic Trauma Association. Reference category for site: humerus.

Table 6. Impaired-healing rates according to vitamin D status, stratified by anatomical site.

Site	Vitamin D deficient (<20 ng/mL): impaired healing, n/N (%)	Vitamin D non-deficient (≥20 ng/mL): impaired healing, n/N (%)	p-value
Tibia (n = 58)	21/36 (56.9)*	8/22 (19.4)*	<0.001
Femur (n = 42)	12/16 (50.0)	7/26 (16.7)	0.018
Humerus (n = 20)	5/12 (41.7)	2/8 (12.5)	0.042
Overall (n = 120)	41/57 (71.9)	14/63 (22.2)	<0.001

*Impaired healing was defined as delayed union or non-union. *Percentages calculated within each vitamin D status category for the respective anatomical site. p-values from Fisher exact test.*

DISCUSSION

The present prospective observational study demonstrated a significant association between baseline serum 25(OH)D concentration and fracture-healing outcomes following surgical fixation of diaphyseal long bone fractures. Patients who developed non-union had substantially lower vitamin D levels, with deficiency present in more than 94% of cases. Vitamin D deficiency emerged as the strongest independent predictor of impaired healing, conferring an almost fivefold increase in risk after adjustment for confounders. The significant inverse correlation between serum 25(OH)D and time to radiological union, together with a ROC-derived threshold of approximately 20 ng/mL, highlights the prognostic importance of vitamin D status.

These findings are consistent with those of Brinker et al., who reported vitamin D deficiency in 68% of patients with unexplained non-union and demonstrated that correction of metabolic abnormalities could facilitate fracture healing in selected cases.[6] Similarly, Pourfeizi et al. found vitamin D deficiency in 60% of patients with tibial non-union compared with 30% of patients with uncomplicated healing.[7] The stronger association observed in the present study may reflect the high background prevalence of hypovitaminosis D in India.[2] Furthermore, the incorporation of metabolic factors, including vitamin D deficiency, within the Calori Non-Union Scoring System underscores its recognized role in fracture-healing outcomes.[11]

The prevalence of vitamin D deficiency and insufficiency in our cohort (79.2%) closely mirrors the 70% prevalence reported in the systematic review by Sprague et al.[8] Experimental and clinical evidence also supports a biological role for vitamin D in fracture repair through regulation of osteoblast activity, mineralization, and callus maturation.[5] Doetsch et al. demonstrated increased callus bone mineral density in osteoporotic women receiving vitamin D_3 and calcium supplementation after proximal humerus fractures, further supporting this mechanism.[10]

However, interventional studies have produced inconsistent results. Haines et al. reported no significant improvement in fracture union following a single high-dose vitamin D supplementation regimen in adults with long bone fractures.[9] Similarly, retrospective and randomized studies have shown only modest or non-significant improvements in healing outcomes despite correction of vitamin D levels.[12] [13] These discrepancies may be explained by small sample sizes, low non-union rates, heterogeneous supplementation protocols, and variations in baseline vitamin D status. Current evidence suggests that supplementation may be most beneficial in patients with established deficiency rather than unselected fracture populations.[14] [15]

The strengths of this study include its prospective design, consecutive recruitment, blinded radiographic assessment, and comprehensive biochemical evaluation. Nevertheless, several limitations should be acknowledged. The single-centre design may limit generalizability, subgroup analyses were underpowered for individual fracture sites, and the observational nature of the study precludes causal inference. Residual confounding from factors such as dietary intake, physical activity, and sun exposure cannot be excluded.

CONCLUSION

Low baseline serum 25(OH)D concentration was significantly associated with delayed union and non-union following surgical fixation of diaphyseal fractures of the femur, tibia, and humerus. Vitamin D deficiency was present in over 94% of patients with non-union and independently increased the risk of impaired healing by nearly fivefold. A serum 25(OH)D level of approximately 20 ng/mL was identified as a clinically relevant threshold for predicting adverse healing outcomes. These findings support consideration of routine vitamin D assessment and correction in fracture patients, particularly in populations with a high prevalence of hypovitaminosis D. Further adequately powered randomized controlled trials are required to determine whether correction of deficiency improves fracture-healing outcomes.

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