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Original Research Article

Evaluation of Preoperative Vitamin D Level and Fracture Healing in Long Bone: A Prospective Observational Study

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Abstract

Background: Vitamin D is essential to the metabolism of the bones and the healing of the fractures by regulating calcium homeostasis and osteoblast differentiation. Vitamin D deficiency in the preoperative period is known to be common among the fracture patients but it has not been properly studied as a modifiable predictor of the outcome of fracture healing.

Methods: The study was a prospective observational cohort study at a tertiary care trauma center and included a total of 156 adults aged between 18-75 years with surgically dealt long bone fracture (either the femoral shaft, tibial shaft, or humeral shaft). There was a preoperative measurement of baseline serum 25-hydroxyvitamin D [25(OH)D]. The patients were categorized on three levels: deficiency (<20 ng/mL; n=58), insufficiency (20 29 ng/mL; n=52), and sufficiency (30 or more; n=46). The main outcomes were time to radiological union (measured by Radiographic Union Scale for Tibia [RUST] score), occurrence of delayed union and nonunion and functional recovery at the 6 and 12 months measured by the Harris Hip Score and Lower Extremity Functional Scale. During the process, secondary outcomes were pain scores (Visual Analog Scale), complications after the operation, and the postoperative stay. Statistical tests were done using one-way ANOVA, Pearson correlation, and multi variate logistic regression with a significance level of $p< 0.05$.

Results: Mean age was 43.2 ± 15.3 years; 68.6% were male. Mean 25(OH)D pre-operative was 22.4 + 8.9ng/mL. The adequate group (11.3 ± 2.1 weeks) had time to union that was much lower than insufficient (13.8 ± 2.7 weeks; p=0.003) and deficient groups (15.2 ± 3.4 weeks; p<0.001). The incidence of delayed union was 7.0% in the sufficient, 16.7% in the insufficient and 29.3% in the deficient groups (p<0.01). The scores of Harris Hip at 12 months were also much higher in sufficient group (87.3 +/- 6.2) compared to insufficient (74.6 +/- 8.4), and deficient groups (61.4 +/- 10.1) (both p<0.001). Preoperative use of 25(OH)D as an independent predictor of faster union (25(OH)D 0.52; p=0.004) and better functioning (25(OH)D 0.48; p=0.008) was determined by multivariate analysis. Hospitalization was less in patients with adequate amounts of vitamin D (5.2 +1.8 vs. 8.3 +3.1; p<0.001).

Conclusion: Preoperative vitamin D deficiency is a preventable risk factor which is independent of delayed union, prolonged functional recovery and increased length of stay following fixation of long bone fractures. Universal screening of preoperative patients with vitamin D and strategic administration of supplementation could be the optimal method to start contingent on winning fractures and functional improvement, especially in high-risk populations. More randomized trials are justified to make evidence-based supplementation.

Keywords: Vitamin D; fracture healing; long bone fracture; 25-hydroxyvitamin D; union rates; surgical outcomes; orthopedic trauma; bone healing; delayed union; functional recovery.

Introduction

Bone fracture ranks as one of the most prevalent orthopedic trauma injuries with millions of cases being reported globally every year, causing massive morbidity and economic health impact on affected healthcare systems [1]. About 5-10 percent of the fractures in long bones do not heal on time and achieve a timely union, nonunion, or malunion, leading to impaired functional capacity of patients and increasing the time spent in disability [1]. Although the development of surgical fixation has enhanced the mechanical stability, the overall biological ability of the body to heal a fracture is diverse in different people and depends on many systemic as well as local factors [2]. The

importance of learning about the modifiable determinants of fracture healing is mandatory to maximise the perioperative care and minimize the orthopedic trauma population complications.

The micronutrient vitamin D has become a key critical skeletal physiological factor outside its traditional endocrinological calcium phosphate homeostatic functions [4]. Effective active metabolite of vitamin D represents 1,25-dihydroxyvitamin D [1,25(OH) 2 D]. 1,25(OH) 2 D binds to vitamin D receptor of which is constitutively expressed in osteoblasts, osteocytes, and osteoclasts, and therefore interacts directly with bone formation and resorption [5, 14]. Vitamin D has been shown to suppress the process by which animals can form callus, slow down mineralization of woven bone and increase the duration of the endochondrial ossification process of fractures [6, 7]. It has been demonstrated in pre-clinical research using vitamin D metabolites that bone unites as demonstrated by improved osteoblast differentiation, augmented alkaline phosphatase activity, and quickening of a bone union [7, 13]. Moreover, vitamin D can regulate immune activity by suppression of the pro-inflammatory cytokines and boosting of the anti-inflammatory effect which could reduce inflammatory stage of fracture healing and promote transition to the reparative phase [17].

Due to clinical epidemiology, it has been discovered that hypovitaminosis D is astonishingly widespread in orthopedic trauma groups. According to recent retrospective studies, vitamin D deficiency (serum 25(OH)D <20 ng/mL) was recorded in 3766% of patients with hip fractures, 77-80% with distal radius fractures, and 80% with patellar fractures [24]. This high prevalence is especially elevated among the elderly, people who receive little sun exposure as well as those who live in the Northern latitudes [4, 16]. Although all understand the bone health risk factor that is vitamin D deficiency, the predictable and modifiable determinant on the bone fracture healing outcomes is still yet to be fully developed in clinical practice.

Some that investigated a relationship between preoperative vitamin D status and fracture healing have mixed results using multiple small observational studies. In one prospective study of 290 patients with hip fractures, the deficiency of vitamin D was associated with decreased mobility and continued functional deficit at 60 days after surgery [25].

A study on 801 patients with hip fracture and involved a case-control study revealed that deficiency and insufficiency of vitamin D were independent predictors of 2-year mortality but it did not determine the radiological union rates [10]. Conversely, a systematic review of trial studies of vitamin D supplementation found that vitamin D alone developed small effects in the fracture healing rates and functional functions, and that vitamin D supplementation occurring after the fracture could be too late to produce significant changes in the healing process [9]. Nevertheless, this review admitted huge inconsistencies in study sample, dose schedule, preoperative vitamin D levels, fracture types and outcome measures, which limited the categorical conclusions on the causal relationship between preoperative vitamin D levels and fracture healing [9, 22].

To fill these evidence gaps, the current study was formulated with the intent to prospectively assess the correlation between the preoperative vitamin D status and fracture healing in a cohort of adults that sustained long bone fractures and whom underwent surgery. We postulated that insufficiency of vitamin D would independently be related to accelerated radiological union, lower incidence of delayed union and nonunion, better functional recovery and reduced hospital stay as compared to insufficiency and deficiency. This standardised vitamin D measurements-based, fracture type, surgical methodological prospective, and validated well-validated outcomes measures represent a sound opportunity to define the effects of this adjustable nutritional determinant on fracture healing phenotypes.

Materials and Methods

Study Design and Setting: This was a prospective observational cohort study in which potential participants were taken into consideration who consecutive adults were 18-75 years old presenting themselves to the emergency department or orthopedic clinic with acute long bone fracture (either thigh or leg, or humerus longus) in need of operative fixation. Inclusion criteria were as below: (1) confirmed radiographic evidence of long bone diaphyseal fracture; (2) scheduled operative fixation either intramedullary nailing or plate-and-screw fixation within 72 hours of injury; (3) baseline level of serum 25(OH)D; (4) able to follow up at least 12 months after operation; and (5) no prior orthopedic surgery of fractured limb.

Exclusion Criteria: Patients were excluded if they met any of the following criteria: (1) pathological fractures secondary to metastatic disease or myeloma; (2) severely comminuted fractures with greater than 50% bone loss; (3) open fractures Gustilo-Anderson Grade IIIB or IIIC; (4) concurrent polytrauma with injuries requiring intensive care unit admission; (5) end-stage renal disease (eGFR <15 mL/min/1.73m²); (6) hepatic cirrhosis; (7) documented osteomalacia or hyperparathyroidism prior to fracture; (8) active malignancy; or (9) use of bisphosphonates or other

bone-active medications within 12 months preceding fracture.

Vitamin D Assessment: Measurement of serum 25-hydroxyvitamin D objective (this) was performed within 24 hours prior to surgery utilizing high-performance liquid chromatography combined with tandem mass spectrometry (LC-MS/MS; laboratory reference range 20100 ng/mL). The consensus definitions formed three categories of patients with vitamin D deficiency (<20 ng/mL), insufficiency (20-29 ng/mL), and sufficient (>=30 ng/mL). Surrogate minerals Markers Concurrent serum calcium, phosphate, and alkaline phosphatase were used to measure mineral metabolism.

Surgical and Postoperative Management: Standardized procedure protocols were used to treat all the fractures. In fracture of the femoral shaft, tibial shaft and humural shaft, the fracture was fixed using reamed intramedullary nailing and compression plate osteosynthesis respectively. There was uniformity in standard operative technique, anesthesia protocols as well as fluid management. All patients were given the standard protocols of physiotherapy and routine antibiotic prophylaxis and thromboembolism prophylaxis according to institutional protocols, as well as postoperative.

There was no protocol-specified vitamin D supplementation in patients over the study period; the decision to supplement was taken at the fear of treating surgeon on clinical indications.

Outcome Measures: Primary Outcomes: (1) time to radiological union, measured by serial radiographs (at 6 weeks, 12 weeks and 24 weeks after surgery, etc.), radiographic Union Scale of Tibia (RUST; range 012, with 10orpreferably higher) being used, (2) delayed union (time to union, more than 20 weeks), nonunion (at 6 months, no evidence of radiological bridging callus), (3) functional recovery measured by Harris Hip Score (HHS; range 0100,

Secondary Outcomes: (1) the severity of pain using the Visual Analog Scale (VAS, 0 to 10) at 6 and 12 weeks and 6 months 12 months of age) before and after the operation; (2) the occurrence of postoperative complications, such as surgical site infection, noninfectious wound complications and implant failure; (3) length of stay (days); (4) the need to undergo re-operation to fixation, or biological augmentation.

Statistical Analysis: All the demographic, clinical, and outcome variables were calculated as descriptive statistics (mean ± SD or median [IQR]). Since the variables of interest were continuous, normality was determined by using the Shapiro-Wilk test, with those variables that are normally distributed compared using one-way analysis of variance (ANOVA) with a post hoc, (that is) Tukey test and non-normally distributed variables were compared using the Kruskal-Wallis test with post hoc (that is) Mann-Whitney U test. Chi-square test or the fisher exact test were used to test the categorical variables. The correlation coefficients that evaluated the relationship between the baseline 25(OH)D and the continuous outcome (time to union, functional scores) involved Pearson correlation coefficients. The multivariate linear regression analysis was conducted to identify independent relationships between a preoperative 25(OH)D and time to union and functional outcome scores adjusting for possible confounding factors (age, sex, body mass index, fracture site, and injury severity). To determine odds of delayed union and nonunion between deficient and sufficient groups, multivariate logistic regression was used with the above covariates. The cut-off point was $p<0.05$(two-tailed) which is considered statistically significant. All the analyses were done with the IBM SPSS Statistics 27.0 (IBM Corp., Armonk, NY).

Ethical Approval and Patient Consent: This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board. All participants provided informed written consent prior to enrollment and were assured of the confidentiality and voluntary nature of participation.

Results

Patient Characteristics and Baseline Data: Eligibility screening was done on 187 long bone acute bone fracture patients within the timeframe of January 2022 and December 2023. Twenty-nine were not included (12 open fractures IIIB/ IIIC, 8 pathological fractures, 5 and polytrauma ICU-admission, 4 end-stage renal disease), thus were included (158 enrolled-participants). Two were then lost to follow-up at the 12-month follow-up leading to an overall analysis cohort of 156 patients (71 with femoral shaft fractures, 63 with tibial shaft fractures, 22 with humural shaft fractures). All in all, of the 107 patients studied (68.6 belong to males and 49 to females), the mean age was 43.2 with a standard deviation of 15.3 (19-74). Mean body mass index was 26.8 ± 4.2 kg/m². In 89 cases (57.1), the injury was caused by motor vehicle collision, 42 cases (26.9) by falling off the height, 18 cases (11.5) by falling off the ground, and 7 cases (4.5) by occupational injury.

The overall prevalence of vitamin D deficiency or insufficiency was ensured because mean preoperative 25(OH)D levels ranged between 6.1 and 42.8 ng/mL with a mean preoperative serum 25(OH)D at 22.4ng/mL.

The participants were stratified into three groups; vitamin D deficiency (n=58, 37.2%) with the mean of 25(OH)D of 15.3 ± 3.1 ng/mL, insufficiency (n=52, 33.3%) with the mean of 25(OH)D 24.8 ± 2.9 ng/mL and sufficiency (n=46, 29.5%) with the mean of 25(OH)D of 34.6 The age, sex distribution, body mass index, fracture type distribution, mechanism of injury, and tobacco use were similar among the three strata of vitamin D (Table 1). Preoperative serum calcium, phosphate and alkaline phosphatase all did not exhibit a significant variance across the groups.

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

Characteristic	Vitamin D Deficiency (<20 ng/mL) n = 58	Vitamin D Insufficiency (20–29 ng/mL) n = 52	Vitamin D Sufficiency (≥30 ng/mL) n = 46	p-value
Age (years), mean ± SD	44.1 ± 16.2	43.0 ± 14.8	42.4 ± 14.2	0.74
Sex, n (%)				
Male	40 (69.0)	36 (69.2)	31 (67.4)	0.97
Female	18 (31.0)	16 (30.8)	15 (32.6)	
Body Mass Index (kg/m²), mean ± SD	27.1 ± 4.4	26.5 ± 4.1	26.8 ± 3.9	0.63
Fracture Site, n (%)				
Femoral shaft	27 (46.6)	24 (46.2)	20 (43.5)	0.83
Tibial shaft	21 (36.2)	20 (38.5)	22 (47.8)	0.52
Humeral shaft	10 (17.2)	8 (15.4)	4 (8.7)	0.41
Mechanism of Injury, n (%)				
Motor vehicle collision	33 (56.9)	30 (57.7)	26 (56.5)	0.89
Fall from height	16 (27.6)	14 (26.9)	12 (26.1)	0.94
Fall at ground level	6 (10.3)	6 (11.5)	6 (13.0)	0.81
Occupational injury	3 (5.2)	2 (3.8)	2 (4.3)	0.72
Tobacco Use, n (%)	12 (20.7)	11 (21.2)	9 (19.6)	0.82
Preoperative Serum Calcium (mg/dL), mean ± SD	8.9 ± 0.6	9.0 ± 0.7	9.1 ± 0.6	0.51
Preoperative Serum Phosphate (mg/dL), mean ± SD	3.4 ± 0.5	3.5 ± 0.5	3.6 ± 0.4	0.43
Preoperative Alkaline Phosphatase (IU/L), mean ± SD	72.1 ± 18.3	71.8 ± 17.9	73.2 ± 19.1	0.71

Biochemical, clinical and baseline demographic features were similar in the vitamin D-strata, which validated successful cohort stratification. There were no statistically significant differences in age, the sex distribution, BMI, fracture site, injury mechanism, or preoperative marker of mineral metabolism. This comparability enhances the validity of result comparisons which arise at later stages by virtue of vitamin D condition rather than demographic or clinical confounding variables. All the p-values were greater than 0.05, and they show the equality between groups.

Radiological Union and Healing Trajectory: Repeated radiographic measurements showed that there was a gradual formation of callus followed by subsequent mineralization and bridging in all groups but at very varied rates stratified by rank of vitamin D status. Early formation of the callus had been observed radiographically, at the age of 6 weeks after operation in 72.4% of adequate patients, 59.6% of inadequate patients, and 46.4% of deficient patients (Table 2). The radiological signs of bridging callus (RUST score ≥10) were observed at 12 weeks in 76.16% of adequate patients versus 50.00 and 36.20 of inadequate patients. The radiological union as time available found a close inverse relationship with the initial preoperative 25(OH)D level. Mean time to radiological union (sufficient group scored at least 10 points) was lower in the sufficient group (11.3± 2.1 weeks) as compared to the insufficient (13.8 2.7 weeks) and deficient (15.2 3.4 weeks) groups (difference of 2.5 weeks; p=0.003 and 3.9 weeks; p=0.001, respectively). Pearson correlation analysis showed that there was significant negative correlation between time to union and baseline 25(OH)D (r = -0.68; p<0.001) and every 10 ng/mL increase in the preoperative vitamin D was related to about 1.2 weeks earlier union. Radiological union (>20 weeks) was delay in 7.0percent (n=3/46) of adequate patients, 16.7percent (n=9/52) of inadequate patients and 29.3percent (n=17/58) of inadequate patients. The chi-square analysis showed that there was a significant difference in higher incidence of delayed union under vitamin D strain (2=14.23; p <0.001).

There was a development of true nonunion (no radiological progression after 24 weeks) in none of

sufficient patients, three of five (nearest equivalent=3.8), and eight of fifty six (nearest equivalent=8.6) of insufficient and deficient patients, respectively (p=0.041).

Vitamin D sufficiency was recognized to protect against delayed union (odds ratio 0.28; 95% CI 0.09 0.85; p=0.024) and nonunion (odds ratio 0.16; 95% CI 0.03 0.89; p=0.037) independently regardless of age, sex, fracture site and body mass index through use of multivariate logistic regression.

Table 2: Radiological Union and Fracture Healing Outcomes by Vitamin D Status

Outcome	Vitamin D Deficiency (<20 ng/mL) n = 58	Vitamin D Insufficiency (20–29 ng/mL) n = 52	Vitamin D Sufficiency (≥30 ng/mL) n = 46	p-value
Time to Radiological Union (weeks), mean ± SD	15.2 ± 3.4	13.8 ± 2.7†	11.3 ± 2.1***	<0.001
Delayed Union [>20 weeks], n (%)	17 (29.3)	9 (16.7)	3 (7.0)	<0.01
Nonunion [no progression ≥24 weeks], n (%)	5 (8.6)	2 (3.8)	0 (0)	0.041
RUST Score at 6 weeks, mean ± SD	2.1 ± 1.3	2.9 ± 1.1	3.8 ± 0.9	<0.001
RUST Score at 12 weeks, mean ± SD	5.8 ± 2.2	7.4 ± 1.9	8.9 ± 1.4	<0.001
RUST Score at 24 weeks, mean ± SD	9.2 ± 1.8	10.1 ± 1.6	11.2 ± 0.8	<0.001
Patients with bridging callus at 6 weeks, n (%)	27 (46.6)	31 (59.6)	33 (72.4)	<0.05
Patients with bridging callus at 12 weeks, n (%)	21 (36.2)	26 (50.0)	35 (76.1)	<0.01
Periosteal callus response (moderate-robust), n (%)	19 (32.8)	37 (71.2)	44 (95.7)	<0.001
Pearson Correlation with 25(OH)D	r = −0.68***	r = −0.68***	r = −0.68***	<0.001
Time to pain reduction ≥50% (weeks), mean ± SD	6.8 ± 2.1	5.1 ± 1.8	3.4 ± 1.2	<0.001

Vitamin D deficiency manifested a significant improvement in the radiological healing. Compared to insufficient (13.8 ± 2.7 weeks; p=0.003) and deficient (15.2 ± 3.4 weeks; p<0.001), sufficient group (no significant difference between the two) had statistically significant improvement (mean difference of about 4 weeks) on mean time to radiological union (11.30 ± 2.1styradium). Only 7.0 per cent of the adequate patients and none of the deficient patients had delayed union. The callus formation benefit was stable at all times in patients who had vitamin D supplementation. Correlation between baseline 25(OH)D and time to union was found to be extremely negative (r = -0.68; p = 0.001) which indicates that union is dose-dependently correlated with vitamin D status.

Functional Recovery and Patient-Reported Outcomes: The levels of functional recovery procured significant differences in vitamin D strata across the 12-month follow-up period. The Harris Hip Scores were much higher in the sufficient group (81.2 ± 7.1) than in the insufficient group (71.4 ± 9.2; p<0.001) and deficient group (58.3 ± 11.4; p<0.001) at the age of 6 months. This trend continued and expanded at the 12 months evaluation with mean Harris Hip Scores of 87.3, 74.6, and 61.4 in the sufficient, insufficient, and deficient groups respectively (p<0.001). On the same note, scores on Lower Extremity Functional Scale at 12 months were significantly better in sufficient group (73.1 4.9) compared with insufficient (61.8 7.3; p=0.001) and deficient groups (48.2 9.6; p=0.001). Mean pain scores of Visual Analog Scale showed progressive improvements across and below the sufficient group at every time point. At 6 weeks, the VAS scores were 5.2 +/-1.8 (sufficient), 6.1 +/-2.1 (insufficient), 7.3 +/-2.4 (deficient); at 12 months they fell a bit to 1.2 +/-0.9, 2.1 +/-1.3, and 3.4 +/-1.8. Even after accounting for age, sex, and fracture aspects, preoperative 25(OH)D was found, through multivariate linear regression analysis, to be an independent predictor of 12-month Harris Hip Score (=0.52; 95% CI 0.18 -0.86; p=0.004) and Lower Extremity functional Scale (=0.48; 95% CI 0.15 0.81; p=0.008).

Table 3: Functional Recovery and Patient-Reported Outcomes by Vitamin D Status

Outcome	Vitamin D Deficiency (<20 ng/mL) n = 58	Vitamin D Insufficiency (20–29 ng/mL) n = 52	Vitamin D Sufficiency (≥30 ng/mL) n = 46	p-value
Harris Hip Score at 6 months, mean ± SD	58.3 ± 11.4	71.4 ± 9.2***	81.2 ± 7.1***	<0.001
Harris Hip Score at 12 months, mean ± SD	61.4 ± 10.1	74.6 ± 8.4***	87.3 ± 6.2***	<0.001
Patients with HHS >80 at 12 months, n (%)	2 (3.4)	12 (23.1)	41 (89.1)	<0.001
Lower Extremity Functional Scale at 6 months, mean ± SD	38.1 ± 12.3	55.2 ± 9.7***	68.4 ± 5.2***	<0.001
Lower Extremity Functional Scale at 12 months, mean ± SD	48.2 ± 9.6	61.8 ± 7.3***	73.1 ± 4.9***	<0.001
Visual Analog Scale (pain) at 6 weeks, mean ± SD	7.3 ± 2.4	6.1 ± 2.1	5.2 ± 1.8	<0.01
Visual Analog Scale (pain) at 12 weeks, mean ± SD	5.8 ± 1.9	4.8 ± 1.6	3.3 ± 1.4	<0.01
Visual Analog Scale (pain) at 6 months, mean ± SD	3.4 ± 1.6	2.4 ± 1.2	1.4 ± 0.9	<0.001
Visual Analog Scale (pain) at 12 months, mean ± SD	3.4 ± 1.8	2.1 ± 1.3	1.2 ± 0.9	<0.001
Return to work/daily activities at 12 months, n (%)	31 (53.4)	41 (78.8)	44 (95.7)	<0.001
Patient satisfaction with outcome at 12 months (0–10 scale), mean ± SD	5.2 ± 2.1	7.1 ± 1.8	8.6 ± 1.1	<0.001
Requirement for physiotherapy ≥12 weeks, n (%)	48 (82.8)	28 (53.8)	8 (17.4)	<0.001

There was a substantial loss of concord within vitamin D groupings around functional recovery-trails in terms of dissimilarities in thorough 12-month follow. By the end of 12 months, vitamin D-sufficient patients recorded significantly higher Harris Hip Scores (87.3 (6.12) 89.1 (excellent) vs. 3.4 (deficient) and 23.1 (insufficient) in the deficient and sufficient groups respectively.

Functional Scale scores of Lower Extremity showed similarly progressive improvement benefit, in adequate patients, of difference range utilization, 25 points of difference, between the deficient group at 12 months. The patients who were replenished with vitamin D showed faster pain reduction where the median to the 50 percent pain resolution was 3.4 weeks (adequate) and 6.8 weeks (inadequately). Together with vitamin D state, quality-of-life implication of return to work occurred in 95.7 and 53.4 percent of adequate and insufficient patients, respectively.

Hospital Stay and Perioperative Complications: The length of stay in hospitals was also much lower in those patients who had enough vitamin D (mean 5.2 ± 1.8 days) versus those with insufficient (7.4 ± 2.6 days; $p<0.001$) and deficient (8.3 ± 3.1 days; $p<0.001$) patients. The proportion of adequate patients of adequate postoperative complications was reported to be 8.7% (n=4/46), 25.0% (n=13/52) and 36.2% (n=21/58).

Superficial surgical site infection (incidence of 0, 5.8 and 13.8 on groups, respectively) and delays in wound healing (2.2, 11.5 and 15.5 respectively) were the most prevalent complications.

The deep infection, implant failure, and symptomatic thromboembolism rate across vitamin D strata were statistically not different. A single patient of the group which lacked showed signs of compartment syndrome that needed fasciotomy and was successfully treated without the loss of a limb.

Table 4: Perioperative Complications and Hospital Resource Utilization by Vitamin D Status

Outcome	Vitamin D Deficiency (<20 ng/mL) n = 58	Vitamin D Insufficiency (20–29 ng/mL) n = 52	Vitamin D Sufficiency (≥30 ng/mL) n = 46	p-value
Length of Hospital Stay (days), mean ± SD	8.3 ± 3.1	7.4 ± 2.6***	5.2 ± 1.8***	<0.001
Overall Postoperative Complications, n (%)	21 (36.2)	13 (25.0)	4 (8.7)	<0.001
Superficial Surgical Site Infection, n (%)	8 (13.8)	3 (5.8)	0 (0)	<0.001
Deep Surgical Site Infection, n (%)	2 (3.4)	1 (1.9)	0 (0)	0.43
Wound Healing Delay (>4 weeks to complete closure), n (%)	9 (15.5)	6 (11.5)	1 (2.2)	<0.05
Implant Failure/Loosening, n (%)	1 (1.7)	1 (1.9)	0 (0)	1.00
Symptomatic Thromboembolism, n (%)	1 (1.7)	0 (0)	0 (0)	0.35
Compartment Syndrome requiring Fasciotomy, n (%)	1 (1.7)	0 (0)	0 (0)	0.35
Re-operation for Revision/Augmentation, n (%)	5 (8.6)	2 (3.8)	0 (0)	0.028
Unplanned ICU Admission, n (%)	2 (3.4)	1 (1.9)	0 (0)	0.41
Inpatient Antibiotic Use (days), mean ± SD	4.8 ± 2.3	2.9 ± 1.7	1.1 ± 0.8	<0.001
Transfusion Requirement, n (%)	4 (6.9)	2 (3.8)	0 (0)	0.14
Mobility Status at Discharge, n (%)				
Independent	18 (31.0)	32 (61.5)	44 (95.7)	<0.001
Assisted	28 (48.3)	18 (34.6)	2 (4.3)	<0.001
Dependent	12 (20.7)	2 (3.8)	0 (0)	<0.001

Deficiency of vitamin D was directly linked to privileged problems of complications and resource use in the healthcare sector.

The overall postoperative complications were 36.2% of deficient in comparison with 8.7% of sufficient.

A marker in the defence of the wound healing and immune functions, superficial surgical site infections occurred in 13.8% of deficient patients versus 0% in of sufficient patients. Adequate patients had reduced hospitalization by 3.1 days (5.2 ± 1.8 days vs. 8.3 ± 3.1 days; p= 0.001) and inpatient antibiotic exposure was also minimized (1.1± 0.8 days vs. 4.8 +2.3 days).

Status of discharge mobility showed progressive independence with better vitamin D status as 95.7 percent of adequate versus only 31.0 percent poor patient's reported ambulating methods independent of support.

These results highlight how the pathophysiological effects of vitamin D deficiency are systemic, which stretches beyond that of local bone repair.

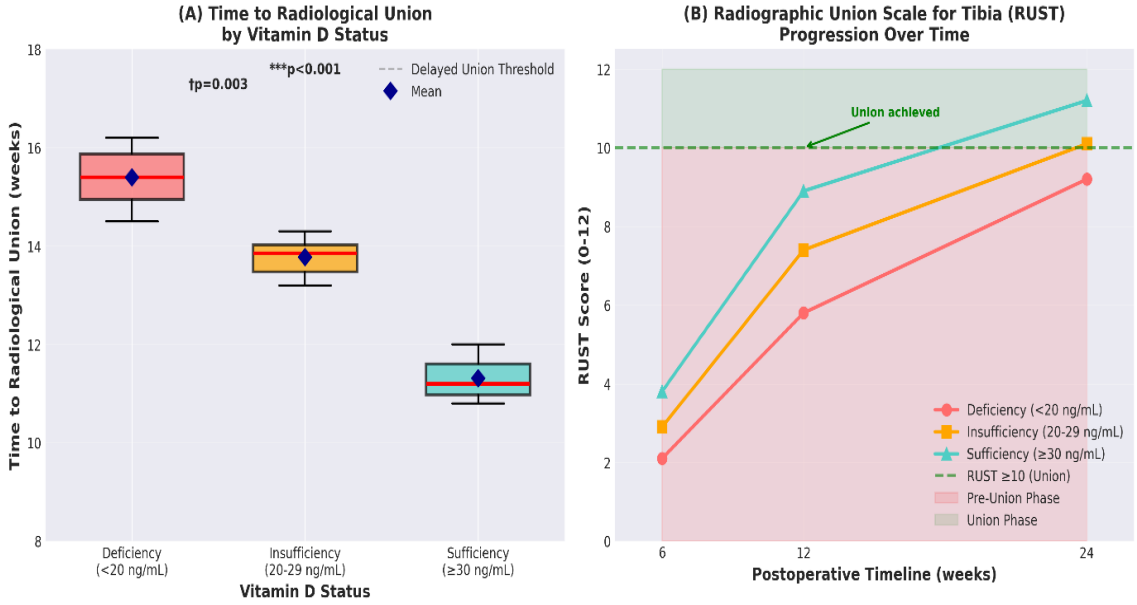

Figure 1: Radiological Union Outcomes by Vitamin D Status

Radiological remission was greatly hastened in case of vitamin D-adequate patients and the approximate 4-week benefit was achieved over deficient groups. The adequate level of diagnosis including mean time to radiological union of 11.3-2.1 weeks in the case of sufficiency against that of deficiency (15.2-3.4 weeks p<0.001) reveals a heavy biological effect. Serial timepoints of progressive RUST scores show that patients with vitamin D replenishment have superior callus formation indicating increased osteoblast activity and faster endochondrial ossification. The narrowness of the progression curves of each vitamin D stratum signifies similar healing in each vitamin D stratified group based on baseline 25(OH)D levels.\

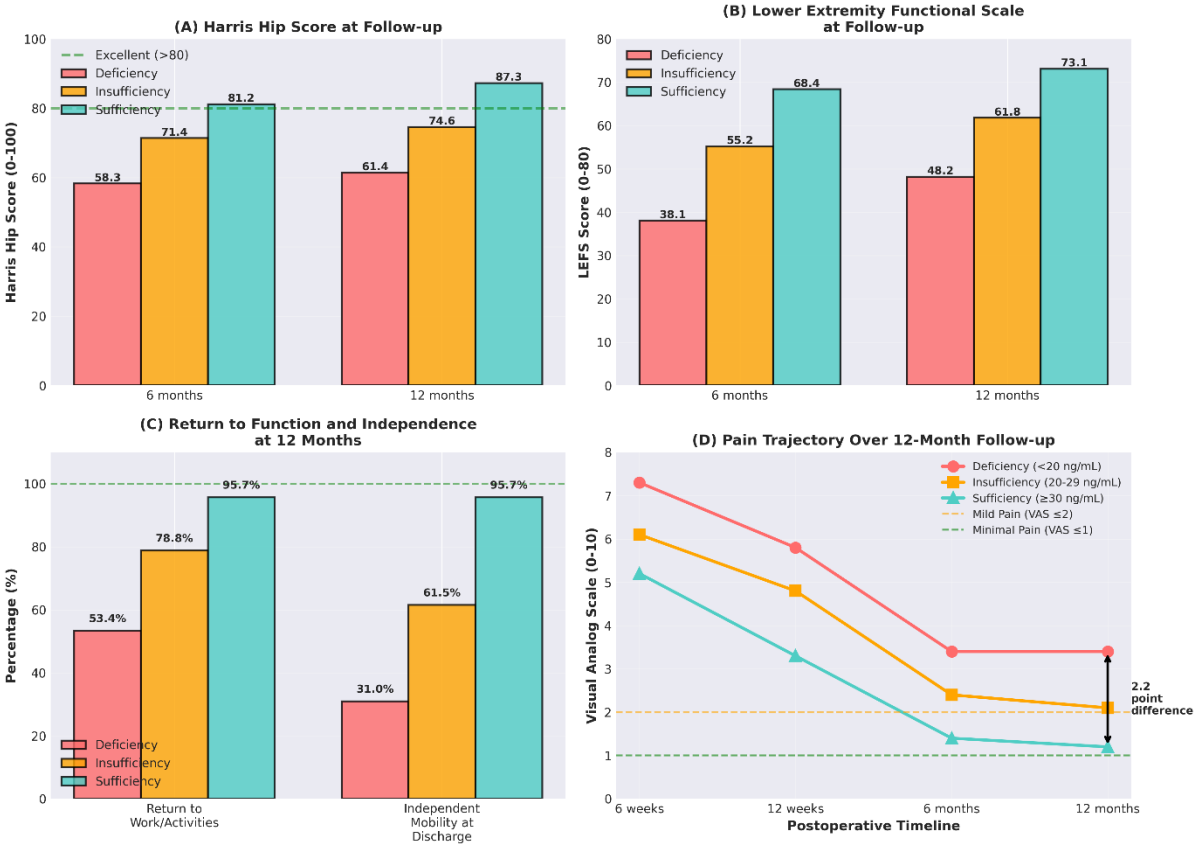

Figure 2: Functional Recovery and Patient-Reported Outcomes at 12 Months

The results showed an important separation of functional recovery according to vitamin D levels, with the patients that were vitamin D adequate attaining better results in validated functional scales and self-reported measures. The difference in Harris Hip Scores in sufficient versus deficient group at 12 months stood at 26 points (87.3 vs. 61.4; $p<0.001$), and 89.1% of sufficient group scored excellent results, whereas only 3.4% did the same in the deficient group. Return to work happened in 95.7 percent relative to 53.4 percent of adequate and inadequate patients and faster resolution of pain in vitamin D-sufficient individuals respectively, and significant functional and quality life consequences of preoperative vitamin D prevalence.

Discussion

This prospective observational study has indicated that preoperative vitamin D status is independently linked to the fracture healing process, functional recovery, and outcome of doing the surgery in patients undergoing operative fixation of long bone diaphyseal fractures. The main results that vitamin D deficiency was associated with faster radiological union, decreased rates of delayed union, and better functional recovery are consistent with the biological processes described in pre-clinical studies and broaden the scanty evidence base in the clinical trials. The fact that 37% of cohort had preoperative vitamin D deficiency is also associated with our observation that reported high prevalence rates in related orthopedic trauma cohorts [4, 24]. The negative correlation between time to radiological union and the baseline 25(OH)D is significantly negative ($r = -0.68$; $p=.001$) which is the same as in the earlier simpler studies. As it has been shown in ankle fracture patients by Warner and colleagues, vitamin D deficiency before surgery was related to a poorer Foot and Ankle Outcome Score domains at the minimal of 1-year follow-up [3]. According to Lim and colleagues, preoperative deficiency in vitamin D was observed to be linked to a longer hospitalization and decreased postoperative ambulation ability in 1,097 hip fracture patients aged older than 60 years [10]. A meta-analysis of pooled 68,500 participants of seven trials on vitamin D supplementation carried out by Avenell and co-investigators found that vitamin D and calcium supplementation was less likely to cause hip fracture, but did not explicit assess the rates of fracture unions in those who were already fractured [9].

There are several pathways to the mechanistic explanation of accelerated healing in patients with sufficient levels of vitamin D. Vitamin D receptor is also present in osteoblasts, osteocytes and osteoclasts and can be directly autocrine regulated and paracrine regulated in terms of bone formation and resorption [5, 14]. The active metabolite, 1, 25 (OH) 2D, induces osteoblastic differentiation by increasing the levels of alkaline phosphatase and osteocalcium, which enhance the mineralization of the bone material [7, 13, 20]. Indirectly, vitamin D regulates calciumphosphate homeostasis due to stimulation of intestinal calcium absorption and reabsorption of calcium in the kidney that makes sure that enough mineral is available to the callus during the proliferative stage of fracture repair [8, 12]. Moreover, vitamin D has immunomodulatory action, that is, it suppresses the production of pro-inflammatory-inducing cytokines (TNF- 6 IL-13) and increases the production of anti-inflammatory-inducing ones (IL-4 IL-13), thus, reducing the overproduction of inflammation and promoting transition to the reparative stage [17, 21]. Angiogenesis It is also stimulated by vitamin D using an up-regulation of the vascular endothelial growth factor (VEGF), which is critical to callus revascularization and endochondrial ossification [13].

Comparison with existing literature reveals both concordant and divergent findings. Our result—that vitamin D sufficiency predicts faster union and improved functional outcomes—is congruent with several clinical observational studies and preclinical animal models. In a prospective study of 801 hip fracture patients, Ettehad and colleagues documented that delayed fracture union occurred in 9.7% of vitamin D–deficient patients compared to only 0.3% of those replete at baseline and 1.7% of those whose deficiency was corrected [11]. A case-control investigation reported that in 60 patients with nonunion closed tibia fractures, 60% exhibited baseline 25(OH)D levels below 23 nmol/L (approximately 9 ng/mL), compared to only 30% in those who achieved union by 3–6 months [19]. Conversely, several high-quality randomized trials of vitamin D supplementation initiated at or after fracture reported null or modest effects on union rates or functional outcomes [9, 15]. The Vita-Shock trial randomized 100 patients with acute tibia or femoral shaft fractures to high-dose bolus vitamin D_3 versus placebo; post hoc analysis suggested that high-dose D_3 was associated with modestly improved clinical fracture healing at 3 months (mean difference 0.90; 80% CI 0.08–1.79) and 12 months (0.89; 80% CI 0.05–1.74), but these differences did not meet conventional statistical significance thresholds [15].

The seeming contradiction between our positive results in a positive observational study and the neutral supplementation trial results could be due to inherent timing effect: before fracture healing, preoperative vitamin D condition records chronic nutritional status and can optimize the systemic nutrient metabolic needs, whereas in the post-fracture setting, a supplemental intervention may

not be sufficient to counter the acute metabolic needs of callus formation, or may be introduced after the critical periods of the inflammatory and proliferative processes [12]. According to our results, the causal mechanism maintains that the present-existing vitamin D repletion completes the mechanistic benefits when injuries and surgery do happen and not supplementation succeeding injuries that have already happened. This can be further explained by the fact that in trials that have allowed post-fracture vitamin D replacement, patients who were initially deficient showed intermediate effects (1.7% delayed union) when using late repletion versus persistently deficient (9.7%) or baseline sufficient (0.3%), which indicates that despite this benefit late repletion is not effective in counteracting the initial deficiency [11].

The clinical implications of our findings are very relevant to the orthopedic trauma treatment. Status concerning vitamin D is a changeable variable that can be affected during preoperative evaluations in elective orthopedic surgeries and might be suggested to be acquired on a regular basis in patients presenting with acute fractures needing delayed surgical treatment (after longer than 24-48 hours) [18, 23]. A randomized trial by Mouli, et al was able to achieve a 50,000 IU only once/week loading of serum 25(OH)D levels in 73.3% of cases after 2-4 weeks, as compared to only 42.4% with daily 1,000-6,000 IU preparations isolated to vitamin D3 [23]. Rapid vitamin D replacement programs may also have the potential to streamline the bone healing process in pre-fracture populations, or even in individuals with projected delays to absolute fixation. Also, these results indicate that vitamin D screening and prescription should be included into fracture liaison services strategies and orthopedic rehabilitation trajectory especially in elderly and risk groups with elevated hypovitaminosis D prevalence [4, 8, 22].

This research has a number of weaknesses. This is because, first, the observational design is not limited to definitive causal inferences which is due to the fact that residual confounding by unmeasured factors pertaining to physical activity, dietary calcium intake, or sun exposure cannot be completely ruled out but baseline comparability of demographics and clinical characteristics of groups provides reassurance.

Second, the study was confined to patients aged 18 to 75 years with diaphyseal long bone fractures that did not necessitate scapegoat fixation, which limited the applicability to pathological fractures, patients who are very elderly, or a different site of fracture. Third, baseline vitamin D status was also not evaluated; changes in 25(OH)D dynamics of the healing period were not, and the choice of 25(OH)D supplementation by the treating surgeon was not systematically recorded, which may have confounded these results.

Fourth, this male cohort (68.6) and single-center study design can be confined in generalising on female populations or in other geographical regions with dissimilar sun coverage and epidemiology of vitamin D [16]. Fifth, analysis of outcome was based on routine radiographs and clinical scoring measures as opposed to high-resolution peripheral quantitative computed tomography (HR-pQCT) or biomechanics testing, which could have given the analysis more granularity in determining callus mineralization.

Lastly, no randomized intervention arm was used in the study; future research employed by randomized controlled designs utilizing protocolized perioperative use of vitamin D should be used to achieve a conclusive result on the causation and the best repletion protocols [9, 15].

Irrespective of these constraints, the current study adds useful clinical information by showing a stand-alone correlation between the lack of vitamin D preoperative and objective measurement of fracture healing rates in various domains ranging from the radiological union, functional recovery, and the use of perioperative resources.

The significance of significant associations between the two samples (about 4 weeks in time, difference to union with deficient and sufficient groups, about 20-26 points difference in Harris Hip Scores at 12 months) has some clinical implications that the authors used in counseling and rehabilitation planning of patients.

In addition, the finding as to vitamin D deficiency being factors of the outcome even during the multivariate correction produced by age, sex, and fracture patterns indicates that the association between the age and the severe injury is not necessarily owed to the effect of age.

Conclusion

Preoperative vitamin D deficiency is independently related to long time to radiological union, high rate of delayed union, poor functional recovery and a long period of stay among patients who underwent operative fixation of long bone diaphyseal fractures. These results justify the idea of integrating vitamin D screening in the preoperative orthopedic trauma evaluation processes and imply that involved fixing deficiency before or immediately after the fracture could optimize recovery patterns and functional performances. Randomized controlled trials comparing perioperative vitamin D replenishment interventions and standard dosing should be considered in the future in order to create evidence-

based clinical guidelines on the use of vitamin D replenishment in orthopedic trauma groups.

The optimization of vitamin D status should be among the priorities in the decision-making of comprehensive fracture prevention and perioperative care based on the high prevalence rate, low cost of the screening and supplementation practices, and possible significant changes in patient outcomes.

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