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Role of Vitamin D Deficiency in Fracture Healing

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ABSTRACT

Vitamin D deficiency is prevalent throughout the world and has been long suspected to play a role in fracture healing. The goals of this study were to evaluate rates of union, time to union and vitamin D treatment patterns in adult fracture patients. A retrospective review was performed by evaluating charts and radiographs of patients who underwent fracture fixation. Vitamin D levels were recorded postoperatively and correlated with fracture union rate and time to union. The rate of vitamin D supplementation was also reviewed. Results showed an 11% decrease in fracture union rate in patients with 25(OH) vitamin D levels <20 mg/ml compared with levels >20 mg/ml; 81% and 92%, respectively (p=0.07). Vitamin D levels also did not significantly impact time to union. Despite low vitamin D in 58% of included patients, only 13% were discharged with a vitamin D prescription. These results suggest there is room for improvement with regards to assessing and treating deficiency in fracture patients. While an 11% decrease was noted in fracture union with Vitamin D deficiency, our report does not provide statistically significant data to make overarching conclusions about the role of vitamin D in fracture healing or time to union following fixation. However, it was noted that Vitamin D supplementation following fracture fixation may be inappropriately deficient. Further studies are needed to define the best cutoff for treatment and to establish the mechanisms by which vitamin D influences bony healing.

Keywords: Fracture, Non-union, Union, Vitamin D, Hypovitaminosis D

INTRODUCTION

Fracture healing is influenced by both catabolic and anabolic factors. Typical fracture healing proceeds in four stages; inflammation, soft callus formation, hard callus formation and remodeling [1]. Throughout this process, osteoblasts provide the structural framework for calcium and phosphate deposition, which then allows for hydroxyapatite formation and bone mineralization to ensue [2-4]. The influence of vitamin D on calcium homeostasis and bony mineralization has been well established [3,5]. It allows for intestinal absorption of calcium, activates osteoclasts via osteoblast-induced production of receptor activator of nuclear factor kappa-B ligand (RANKL) resulting in calcium release from bone, increases renal reabsorption and modulates parathyroid hormone homeostasis [2,3,6,7]. More recently, the cellular impacts of vitamin D have been described, demonstrating increased production of endothelial growth factors that stimulate osteoblast production [8,9]. This complex interplay affects fracture healing, most notably in the hard callus and remodeling stages of healing [10]. While the general importance of vitamin D is understood, its role as it pertains to fracture healing is not well established. Past studies have investigated the influence of vitamin D levels and its effect on calcium and bony mineralization [11]. Moreover, the mechanisms by which Vitamin D influences fracture healing remain largely unknown. Understanding the role of vitamin D on fracture healing may help to direct therapeutic treatment to minimize the incidence of fracture non-union. Several studies have demonstrated that patients with fractures often have vitamin D levels below the recommended serum values; in fact, the prevalence of

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vitamin D deficiency in fracture patients has been described to be as high as 37% [12-15]. Nevertheless, the laboratory values that should guide treatment remain controversial. Some studies have recommended a cutoff level of >20 ng/mL 25(OH) vitamin D [16,17]. Conversely, as studies have demonstrated delayed union and non-union in vitamin D deficient patients [18,19], others argue for a level >50 ng/ml to encourage bony healing [3]. With such controversy, a study evaluating the prevalence of fracture non-union, delayed union, and time to union with the minimum recommended level of 25(OH) vitamin D is needed. The objective of this study was to retrospectively evaluate rates of union, time to union and vitamin D treatment patterns in patients with a 25(OH) vitamin D level < or >20 ng/mL.

MATERIALS AND METHODS

A retrospective chart review of our institution's repository for orthopedic trauma patients treated for fracture by the senior surgeon author between June 2012 and December 2014 was performed. Institutional Review Board approval was granted prior to initiation of this study.

Inclusion criteria were patients >18 years of age who underwent operative internal fracture fixation. Exclusion criteria included lack of documented 25(OH) vitamin D levels during initial hospitalization, those lost to follow up before fracture union, amputation of fractured limb, cancerous bony lesions and those taking medications pre-injury that would affect bone metabolism such as bisphosphonates and teriparatide. Polytrauma patients were not excluded and each fracture was recorded and reviewed separately for union. Fracture type and patient demographics were extracted from the patient's medical record, while operative reports were reviewed to determine the fixation method utilized. Fracture union was compared to initial postoperative films **(Figure 1)** and defined as the lack of visible fracture lines or presence of abundant callus/bone bridging the fracture site at three cortices or more on orthogonal postoperative radiographs **(Figure 2)**. Union was confirmed by two separate physician reviewers. Time to union was recorded based on time from fixation to fracture union. Review of electronic medical records was performed to determine hospital length of stay, postoperative calcium and vitamin D levels, and postoperative bisphosphonate or teriparatide supplementation. Statistical analysis was performed, with means; ranges and confidence intervals calculated for continuous variables and compared using Student's t-tests. Fisher's exact test was employed for increased accuracy in small proportion analysis. A significance level of $P<0.05$ was set as significant.

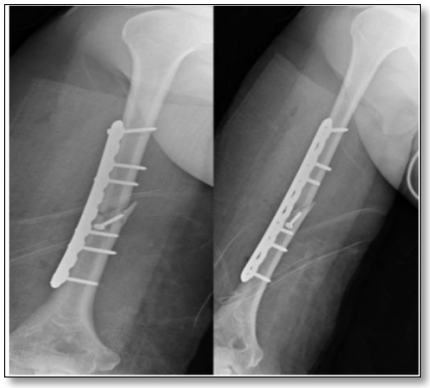

Figure 1. Anteroposterior and lateral radiographs demonstrating initial postoperative open reduction and internal fixation of humeral shaft fracture.

Figure 2. Anteroposterior and lateral radiographs demonstrating union of humeral shaft fracture pictured in **Figure 1** at 6 months postoperatively.

RESULTS

Initial screening revealed 259 patients that met inclusion criteria, however, a total of 56 patients were lost to follow up before fracture union was noted and 1 was excluded due to amputation. Patient demographics in this population did not differ significantly from the overall study group. The average age was 53 years (range, 18-101 years). There were 147 male and 112 female patients. Prevalence of fracture location is outlined in **Table 1**.

Table 1. Prevalence of fracture type.

Fracture Types	Number	Percentage
Total	280	-
Ankle	56	20%
Tibia	49	17.5%
Humerus	31	11.1%
Femur	29	10.4%
Radius	29	10.4%
Ribs	15	5.4%
Foot	14	5.0%
Ulna	12	4.3%
Clavicle	10	3.6%
Pelvis	10	3.6%
Hip	6	2.1%
Talus	5	1.8%
Patella	4	1.4%
Calcaneus	3	1.1%
Acetabulum	2	0.7%
Olecranon	1	0.4%

The final cohort consisted of 202 patients with 118 suffering multiple fractures which were individually evaluated. The average vitamin D level was 20 mg/ml (range, 4-78 mg/ml). Vitamin D and calcium levels are reported in **Table 2**. A total of 84 patients had vitamin D levels >20 ng/ml with an average of 28 ng/ml, (range, 21-78 ng/ml). Serum calcium averaged 8.7 and 8.6 in the vitamin D ≤ 20 ng/ml and >20 ng/ml groups, respectively. Rate of union for vitamin D levels >20 ng/ml was 92%, while only 81% in the group with vitamin D<20 ng/ml (p=0.07). Time to union was 7.3 months with vitamin D<20 ng/ml and 8.5 months with vitamin D>20 ng/ml (p=0.07) **(Table 3)**. Despite a postoperative vitamin D level ≤ 20 ng/ml in 118 patients, only 15 (13%) patients were discharged with vitamin D supplementation. Among the 202 patients, bisphosphonates were not used in any patient and teriperatide was given in 2 (1%) patients postoperatively.

Table 2. Demographic Information, vitamin D and calcium levels.

		Overall	Vit D ≤ 20 ng/ml	Vit D >20 ng/ml
N		202	118	84
Gender	Male	112	63	49
	Female	90	55	35
Age (years)	Mean ± SD	51.8 ± 18.2	50.4 ± 18.4	53.6 ± 17.8
	Range	18-101	19-101	18-92
Polytrauma (# pts)	Multiple Fractures	118	75	43
	Single Fracture	84	43	41
Vitamin D Level (ng/ml)	Mean ± SD	19.8 ± 9.80	13.7 ± 4.61	28.3 ± 8.69
	Range	4-78	4-20	21-78
Calcium Level (mg/dl)	Mean ± SD	8.66 ± 0.61	8.68 ± 0.64	8.64 ± 0.55
	Range	7-10.9	7.0-10.9	7.4-9.7

Table 3. Outcomes.

		Vit D ≤ 20 ng/ml	Vit D >20 ng/ml	P value
Fracture Union	Yes	95	77	0.074
	No	23	7	
Time to Union (mos)	N	95	77	0.070
	Mean ± SD	7.28 ± 6.55	8.49 ± 6.43	
	Range	1-27	2-38	
Vitamin D Prescribed	Yes	15	19	
	No	103	65	
Bisphosphonate Use	Yes	0	0	
	No	118	84	
Teriperatide Use	Yes	0	2	
	No	118	82	

DISCUSSION

Vitamin D levels significantly influence the body's calcium balance and affect bony mineralization [3]. There is growing interest in the relationship of fracture union and vitamin D levels. Despite this interest, recommendations for therapeutic intervention following fracture fixation have not been established. To our knowledge, no study has investigated fracture union and the time to union based on the generally recommended cutoff of vitamin D levels. In patients with vitamin D levels <20 ng/ml an 11% decrease was noted in union rates without reaching statistical significance. Interestingly, faster union was noted in vitamin D-deficient patients, however, again without statistical significance. Several factors have been shown to influence vitamin D level. Such reported factors include smoking, seasonal changes, and fracture [11,13,20]. Briggs et al. reported a decrease in serum 1,25(OH)2D concentrations over a 6 week period following long bone fracture. Interestingly, they noted an increase in calcium concentration without a corresponding increase in phosphate or parathyroid hormone [11]. Additionally, Brinker et al reported that 68% of patients with a fracture nonunion were found to have a previously undiagnosed vitamin D deficiency [18]; other studies have validated this conclusion [19]. Thus, many studies have now recommended vitamin D supplementation with at least 800 IU/day in fracture patients, as supplementation has little toxicity and has an association

with calcium metabolism and a link to bone healing [14,19,21]. Despite a 58% prevalence of patients with low vitamin D levels, only 13% of patients in our study were discharged home with vitamin D prescription. The role of bisphosphonate following fracture fixation remains unknown. However, its use in fracture nonunion has been reported [19]. Although over half of the patients were deemed to be vitamin D deficient, no patient was treated with bisphosphonates postoperatively. Additionally, the effect of using teriparatide, an rDNA injection, following fracture fixation in vitamin D deficient patients remains unknown. While utility has been suggested, it is impossible to draw any conclusions from this study as none of the vitamin D deficient patients who underwent fracture fixation were being treated with bisphosphonates or teriparatide. The primary objective of this investigation was post-surgical fracture union as it relates to vitamin D levels. Although not statistically significant, we demonstrate an 11% lower overall union rate amongst patients with low vitamin D levels. These results align with prior studies, which have identified a relationship between fracture healing and vitamin D levels [18,19,22,23]. We hypothesize that with a more robust sample size, this relationship may lead to statistical significance. However, studies have disputed this relationship. Despite a small sample size, Boszczyk et al. [24] compared diaphyseal non-unions to normally healing fractures in 35 patients and found no difference in the prevalence of vitamin D deficiency. Despite several publications suggesting an association between vitamin D levels and fracture union, no established guidelines exist for a reasonable and appropriate cutoff level for vitamin D therapeutic intervention. While several studies have used 20 ng/ml or less as a marker [16,17], the Institute of Medicine reported cutoffs of <30 ng/ml, arguing that at >50 ng/ml, levels are more optimal with regards to fracture patients [3]. The most sensitive and specific level has still not been identified with regards to fracture healing and merits further research. While the presence of fracture union, as it relates to vitamin D levels have been researched, the influence of such levels on time to union is unknown. In our study, vitamin D levels did not statistically influence time to union. Unexpectedly, we noted a faster time to union in vitamin D-deficient patients despite an overall lower union rate. This is in contrast to other studies, which have demonstrated a higher delayed union rate amongst vitamin D deficient patients [25]. The high incidence of polytrauma in our cohort and its effect on time to union results is unknown. It has been suggested that normalization of vitamin D levels following supplementation may reduce the incidence of delayed union [25]. Thus, it stands to reason that appropriate supplementation at the time of discharge may improve the time to union. While this was not investigated in our report, only 13% of vitamin D-deficient patients were discharged with a prescription for vitamin D. There are several limitations to this study. First, poor patient follow up may have influenced the time to union. As evident in several large trauma centers, patient follow up compliance is often challenging. Thus, the actual time to union may be falsely inflated secondary to this. This study cannot neither fully support nor oppose formerly held opinions that vitamin D is important for fracture healing and union rates given the fact that our conclusions did not reach statistical significance. Secondly, a cutoff of 20 ng/ml or less was used in this study to provide consistency with the current body of literature [16,17]. However, a different cutoff value may have influenced our findings. Further studies are needed to better establish appropriate cutoffs and subsequently examine the success of treatment methods related to inadequate vitamin D levels. Finally, the authors acknowledge that fracture healing is affected by the other variables in including fracture type, diabetes, steroid use, smoking and alcohol consumption. While these must be considered, the goal of this study was to evaluate the independent role of vitamin D in fracture healing. Subsequent studies should be performed to evaluate the effects of the aforementioned variables.

CONCLUSION

While an 11% decrease was noted in fracture union with Vitamin D deficiency, our report does not provide statistically significant data to make overarching conclusions about the influencing role of vitamin D in fracture healing or time to union following fixation. However, it was noted that Vitamin D supplementation following fracture fixation may be inappropriately deficient. Further studies establishing the appropriate cut-off value for therapeutic intervention are needed.

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