Comparison of Radiographic Fracture Healing in the Distal Radius for Patients on and off Bisphosphonate Therapy

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Purpose To compare healing rates of distal radius fractures in patients on bisphosphonate therapy at the time of injury to rates in those not on bisphosphonate therapy.

Methods A total of 196 consecutive patients treated for distal radius fractures were included in this study. Patients currently on bisphosphonate therapy at the time of injury (bisphosphonate group, n = 43) were compared to the remaining patient group (control group, n = 153). Demographic information was recorded from the patients' medical records, and radiographs were reviewed to determine fracture healing. Patients were further stratified according to age, gender, fracture complexity, type of treatment, and comorbidities. Univariate and multivariate regression were used to identify factors associated with time to radiographic fracture union.

Results The mean time to union was 55 (±17) days in the bisphosphonate group versus 49 (±14) days in the control group. Bisphosphonate use and surgical treatment were associated with a longer time to radiographic union. Bisphosphonate use was associated with increased healing times when individually controlling for age, gender, fracture complexity, or comorbidities. Bisphosphonate use was also associated with longer time to healing after adjusting for age, gender, and treatment type. Surgical fracture fixation was associated with a longer time to healing after adjusting for bisphosphonate use.

Conclusions Current bisphosphonate use and surgical treatment were both associated with longer times to radiographic union of distal radius fractures. However, the small differences in healing times (<1 week) are not considered clinically relevant. Although further studies are needed to better define the effects of bisphosphonate therapy on fracture healing, our results suggest that bisphosphonate therapy can be continued after distal radius fractures without notable deleterious effects. *(J Hand Surg 2009;34A:595–602. Copyright © 2009 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Therapeutic III.

Key words Distal radius, fracture, bisphosphonate, osteoporosis, union.

Osteoporotic fractures are recognized as a major public health problem, with over 1.5 million injuries occurring each year in the United States.[1] Responsible for 250,000 injuries a year, upper extremity—and particularly distal radius—fractures are a significant source of patient morbidity.[2] Research has shown that patients with fractures of the distal radius have twice the relative risk for having a

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subsequent hip fracture.[1–3] Because wrist fractures occur in a younger age group than do hip or vertebral fractures, patients with these injuries offer a unique opportunity to initiate preventive actions.[2]

Medical treatment of women with established osteoporosis improves bone mineral density (BMD) and decreases the incidence of future fractures by up to 50%.[4] Randomized placebo-controlled trials of bisphosphonates,[4–6] selective estrogen receptor modulators,[7] calcitonin,[8] and teriparatide[9] have all demonstrated increases in BMD and decreases in fracture risk above and beyond calcium and vitamin D.[10]

Bisphosphonates are the most commonly used antiresorptive medications.[7] Their mechanism of action involves inhibition of osteoclastic bone resorption with a resulting increase in BMD.[11] Because they suppress bone remodeling, it has been hypothesized that bisphosphonates can interfere with fracture healing.[12] Animal studies have provided controversial evidence, reporting delays in fracture healing,[13,14] no effect,[15,16] or even enhanced fracture healing.[17–20]

In general, animal studies have shown that, whereas the early stages are relatively unaffected, remodeling of the bony callus may be delayed by bisphosphonate treatment.[13,14,21,22] Clinical trials of bisphosphonates have not reported any adverse events associated with fracture healing, but the heterogeneity of these studies and the lack of specific data in humans make it difficult to apply results to the clinical management of patients who are on bisphosphonates and have new fractures. The purpose of this study is to compare healing rates of distal radius fractures in patients on bisphosphonate therapy at the time of injury to rates in patients not on bisphosphonate therapy.

MATERIALS AND METHODS

We reviewed inpatient and outpatient records of 300 consecutive patients treated in our institution for fragility fractures of the distal radius between 2001 and 2006. Fragility fractures were defined as those resulting from a fall from a standing height or less. Patients were identified using ICD-9 codes through a billing database (codes 813.40, 813.41, 813.42, and 813.44). Patients younger than 50 (n = 83), those with fractures resulting from high-energy trauma (n = 29), and those with multiple traumas (n = 11) were excluded from the study. Patients with incomplete medical records (n = 5) and inadequate follow-up x-rays (n = 12) were also excluded from the analysis. One additional patient was excluded because of loss of reduction following open reduction internal fixation (ORIF), which required a second surgical procedure. The remaining 196 patients form the basis of this report.

Detailed demographic data were collected from the medical records, including gender, age at the time of injury, side involved, type of treatment (surgical vs nonsurgical), and medication use, as well as the presence of comorbidities that could affect fracture healing (diabetes, tobacco use, steroid use, and immunosuppressant therapy). The presence of fracture-related complications requiring additional treatment was also tabulated. In some instances, primary care providers or patients themselves were contacted for key data not recorded in the medical records.

On presentation to the orthopaedic clinic, nondisplaced fractures were treated with casting until union. Comminuted fractures and those that had manipulation in the emergency department were followed up with weekly radiographs for 3 weeks after injury. During this time, patients were kept in a sugar-tong splint. Those fractures in which reduction was maintained were then transitioned to a short arm cast until clinical and radiographic union occurred. Displaced fractures—defined as those with greater than 20° of dorsal angulation on the lateral view, greater than 100% loss of apposition, greater than 5 mm of shortening by ulnar variance on the posteroanterior radiograph, and greater than 2 mm of articular incongruity—were offered surgical treatment. Several patients declined surgical intervention and healed with an ensuing malunion (n = 30). For patients having surgery, 67 were treated with internal fixation (volar plate, n = 30; dorsal plate, n = 29; volar and dorsal plate, n = 8), 16 were treated with external fixation or percutaneous pinning, or both, and 4 were treated with both ORIF and external fixation. The average time to surgery was 10 (SD±10) days after the initial injury.

We reviewed each patient's initial radiographs and classified fractures according to the AO fracture classification.[23] Follow-up radiographs were reviewed to determine time to radiographic union, defined as external bridging of callus across fracture lines in at least 2 cortices.[24,25] The date of the first radiograph that met the radiographic criteria of union was recorded as the date of radiographic healing. Time to healing was defined as the difference between the date of fracture (for closed, nonsurgical treatment) or the date of surgery (for fractures having surgical treatment) and the date of union. Radiographs were reviewed by a fellowship-trained orthopaedic hand surgeon (T.R.) without knowledge of the patient's medical history.

Current use of bisphosphonates (at least 1 month in duration) was recorded and used to separate patients into either the BP group or the control group. The duration and type of bisphosphonate used were also recorded. The 2 patient groups were compared for homogeneity in gender, side of fracture, method of treatment, fracture severity, and the presence of other factors affecting fracture healing (diabetes, smoking, and immunosuppression).

All patients in the BP group were prescribed these medications for low BMD on a dual energy x-ray absorptiometry scan. There were 9 patients with osteopenia and 5 patients with osteoporosis in this group, and 3 patients had had a prior fragility fracture. Eight patients in the BP group were also being treated with hormone replacement therapy (n = 7) or corticosteroids (n = 2). In the control group, 37 of 151 patients had had a BMD test before their injury. Of these 37 patients, 18 had osteopenia, 9 had osteoporosis, and 10 had normal bone density. Five of the patients in this group had had a prior fragility fracture. After their wrist fracture, 26 additional patients in the control group had a dual energy x-ray absorptiometry scan and were diagnosed with osteoporosis (n = 8), osteopenia (n = 14), or normal bone density (n = 4).

Times to union were calculated for several subgroups. Specifically, patients' age was tabulated, and patients were stratified by type of treatment (nonsurgical vs surgical) and fracture severity (simple vs complex). Complex fractures were defined as AO types A3, B2, B3, C2, and C3, and simple fractures were defined as AO types A2, B1, and C1. Times to union were also determined separately for patients with 1 or more comorbidities that could affect fracture healing and for patients with malunions (n = 11 BP, n = 19 control).

Statistical analyses were performed using chi-square analysis for nonparametric data and independent *t*-tests for parametric data, as well as linear regression with a level of significance of 0.05 (JMP statistics program, SAS Corporation, Cary, NC). Regression models were used to determine the association between bisphosphonate use and days to healing, adjusting for age, gender, fracture complexity, treatment, and comorbidities. Data are presented as mean ± standard deviation, unless otherwise noted.

The study was approved by our institution's institutional review board.

RESULTS

Baseline demographics of the 2 study groups are shown in Table 1. The BP group consisted of 43 patients (women = 42, men = 1), whereas the control group had 153 patients (women = 113, men = 40). The average age of the patients in the BP and control groups was similar (70 ± 11 [range: 54 to 102] and 68 ± 13 [range: 50 to 100], respectively). There was a higher percentage of women in the BP group than in the control group (98% vs 74%, $p < .01$). Otherwise, no differences were detected among the 2 groups with regard to age, treatment type, fracture complexity, or the presence of comorbid conditions that could affect bone healing (Table 1).

Among patients treated surgically, no differences were detected between the groups in terms of surgical approach or type of implant (ORIF with a volar plate, BP 16% vs control 15%, p =.82; ORIF with a dorsal plate, BP 12% vs p = .52; ORIF with volar and dorsal plates, p = .82; closed reduction and percutaneous pinning, p = .74; external fixation p = .33).

Among current BP users, 37 (86%) were taking alendronate (Fosamax, Merck and Co., Whitehouse Station, NJ), and 6 (14%) were taking risedronate (Actonel, Procter & Gamble, Cincinnati, OH). All patients were started on bisphosphonate therapy at least 1 month before their fracture (average 25 ± 21 months, range 1 month to 10 years). Thirty-three patients were on bisphosphonates for more than a year preceding the fracture. Among the remaining 10 patients, 7 had been treated for 6 to 12 months, 2 patients were treated for 3 months, and 1 patient was started on bisphosphonates 1 month before injury.

Timing of radiographic follow-up

To ensure that groups were comparable with regard to timing of radiographic follow-up, the mean dates that follow-up radiographs were obtained were compared. On average, the first radiographs were obtained at 26 ± 15 days in the BP group vs 22 ± 13 days in the control group (p = .07). The second radiographs were obtained at an average of 53 ± 30 days in the BP group and 50 ± 24 days in controls (p = .58), and the third radiograph was obtained at an average of 80 ± 36 days in the BP group and 94 ± 90 days in controls (p = .5).

Average times to union

Fracture union was achieved in all patients in both treatment groups. There was no difference in the average time to union according to bisphosphonate treatment (alendronate, 56 ± 26 days vs risedronate, 68 ± 24 days, p = .32); therefore, the 2 treatments were considered together for all analyses. The mean time to union for the BP group was 58 ± 26 days. One patient in the BP group exhibited delayed healing, with radiographic union defined at 186 days. The patient was a 57-year-old woman with a type C3 fracture and no other comorbidities. She was treated surgically with a

TABLE 1. Demographic Characteristics of the BP and Control Groups

	Bisphosphonate Users (n = 43)	Controls (n = 153)	p Value
Gender			
Female	42 (98%)	113 (74%)	<.01
Male	1 (2%)	40 (26%)	
Side			
Left	22 (51%)	83 (54%)	.426
Right	21 (49%)	70 (46%)	
Average age at fracture (y, mean ± SD)	70.7 ± 11 (54–102)	68.5 ± 13 (50–100)	.54
Fracture treatment			
Cast	25 (58%)	84 (55%)	.36
Surgery	18 (42%)	69 (45%)	
ORIF dorsal	5 (12%)	24 (16%)	.52
ORIF volar	7 (16%)	23 (15%)	.82
ORIF dorsal and volar	2 (5%)	6 (4%)	.82
Closed reduction and percutaneous pinning	1 (2%)	13 (8%)	.16
External fixation	1 (2%)	1 (0.6%)	.33
ORIF and external fixation	2 (5%)	2 (1%)	.16
Fracture severity			
Complex	12 (28%)	49 (32%)	.371
Simple	31 (72%)	104 (68%)	
Diabetes			
Present	4 (9%)	12 (8%)	.497
Absent	39 (91%)	141 (92%)	
Smoking			
Present	3 (7%)	2 (1%)	.063
Absent	40 (93%)	151 (99%)	
Immunosuppression			
Present	0 (0%)	4 (3%)	.340
Absent	43 (100%)	149 (97%)	

volar plate, and an anatomic reduction was achieved. Despite the lag in radiographic healing, the patient had no pain at the fracture site at 8 weeks after surgery and returned to her preinjury activity level at 3 months. Excluding this outlier from the analysis yielded an average time to healing of 55 ± 17 days in the BP group vs 49 ± 14 days in controls ($p = .03$). All remaining calculations were performed excluding this patient.

Linear regression revealed that bisphosphonate use ($p = .03$) and surgical treatment ($p = .03$) were associated with a longer time to healing. Age ($p = .38$), gender ($p = .13$), fracture complexity ($p = .09$), and comorbid conditions ($p = .42$) were not associated with increased time to healing.

Multivariable regression revealed that bisphosphonate use was associated with an increased time to healing when controlling for age, gender, treatment type, fracture complexity, and the presence of comorbidities ($p = .04$). There was no correlation found between duration of BP use and days to union (Spearman correlation = −0.11, $p = 0.49$).

Among current BP users, complex fractures had longer average healing times than simple fractures (65 ± 18 vs 51 ± 15 days, $p = .023$), whereas there was no effect of age ($p = .34$), gender ($p = .6$), type of treatment ($p = .21$), or presence of comorbidities ($p = .78$) on time to radiographic union. There was no difference detected in healing times in the BP group between patients with osteoporosis and osteopenia (59 ± 15 vs 61 ± 23 days, $p = 0.83$) or in patients treated concomitantly with corticosteroids or hormone replacement therapy (53 ± 16 vs 56 ± 18 days, $p = .65$). Healing times in patients with mal-

TABLE 2. Summary of Average Times to Union in Current Bisphosphonate Users and Controls (Means and Standard Deviations)

	Bisphosphonate Users (n = 42)		Controls (n = 153)		
	Days to Union	No. of Fractures	Days to Union	No. of Fractures	p Value
All fractures	55 ± 17	42	49 ± 14	153	**.03**
Treatment category					
Nonsurgical	52 ± 16	25 (60%)	47 ± 14	82 (54%)	.14
Surgical	59 ± 18	17 (40%)	52 ± 14	71 (46%)	.06
Fracture complexity					
Complex	65 ± 19	11 (26%)	51 ± 11	49 (32%)	**.03**
Simple	51 ± 15	31 (74%)	49 ± 15	104 (68%)	.37
Comorbidities					
Present	54 ± 15	8 (19%)	52 ± 15	21 (14%)	.84
Absent	55 ± 18	34 (81%)	49 ± 14	132 (86%)	**.02**
Sex					
Female	55 ± 17	41 (98%)	48 ± 13	113 (74%)	**.01**
Male	46 ± 0	1 (2%)	54 ± 17	40 (26%)	.64

Statistically significant values are shown in bold.

unions were similar to those of patients with adequate reductions (56 ±18 vs 54 ± 16 days, p = .74). No difference was detected in surgically treated patients between those receiving external fixation or percutaneous pinning and those treated with ORIF (53 ± 16 vs 60 ± 19 days, p = .22).

In controls, average healing times were longer in those treated surgically versus nonsurgically (52 ± 14 vs 47 ± 14 days, p = .06) and in men versus women (54 ± 17 vs 48 ± 13 days, p = .04), but times did not differ according to age (p = .49), fracture complexity (p = .35), or the presence of comorbidities (p = .31). Healing times in patients with malunions were similar to those of patients with anatomic reductions (52 ± 18 vs 49 ± 13 days, p = .37). In surgically treated patients, patients treated with external fixation or percutaneous pinning had faster healing times than those treated with ORIF (47 ± 13 vs 53 ± 14 days, p = .009).

In subgroup analyses, bisphosphonate use was associated with longer healing time among those with complex fractures (BP, 65 ± 19 days vs control, 51 ± 11 days, p = .03), among those with no comorbidities (BP, 55 ± 18 days vs control, 49 ± 14 days, p = .02) and among women (BP, 55 ± 17 days vs control, 48 ± 13 days, p = .01) (Table 2).

Comparing times to union among women only, women in the BP group averaged 55 ± 17 days to healing compared to 48 ± 13 days in the control group (p = .01). Fracture complexity (p = .03) and bisphosphonate use (p = .01) were associated with longer times to healing, and bisphosphonate use was associated with longer healing times when adjusting for fracture complexity, type of treatment, and the presence of comorbidities (p = .002). These numbers are similar to results obtained in the overall patient population.

DISCUSSION

In this study, we asked whether current bisphosphonate use affected healing of distal radius fractures, as assessed by a retrospective study of radiographic union. We found that current bisphosphonate use was associated with a slightly longer time to radiographic union (approximately 6 days) compared to patients not on bisphosphonate therapy at the time of fracture.

Bisphosphonates are common medications used for treatment of fragility fractures and can be divided into 2 groups—non–nitrogen-containing and nitrogen-containing—based on their mechanism of action. The non–nitrogen-containing group has lower potency and inhibits osteoclast function when metabolized. The nitrogen-containing group, including alendronate and risedronate, has higher potency and disrupts osteoclasts' cytoskeleton by inhibiting the enzyme farnesyl pyrophosphate synthase.[26,27] In our study, the bisphosphonate cohort was composed of patients on nitrogen-containing bisphosphonate therapy only.

Although osteoclastic bone remodeling is essential in fracture healing, the effects of bisphosphonate therapy on fracture healing are not well understood. Animal studies of the effect of bisphosphonates on fracture healing in animal models have generally shown no marked adverse effects on fracture healing except for delayed callus remodeling,[13,19,28,29] yet some studies have shown that bisphosphonates delay fracture healing.[14,15]

We chose to examine distal radius fractures for several reasons. First, these are common injuries[30] in our patients, which ensures enough subjects for a meaningful statistical analysis. Second, the healing of distal radius fractures can be determined by examining plain radiograph images without need for further imaging. Because they occur in a younger patient population than fractures of the hip, distal radius fractures offer a unique opportunity to initiate treatment for underlying osteopenia or osteoporosis. This makes fractures of the distal radius an important cohort to study in the setting of anti-resorptive therapy.

Our study revealed that all fractures went on to union, although 1 patient in the bisphosphonate group had a delayed union. We found that the average time to union was slightly longer in current bisphosphonate users compared to non-bisphosphonate users (55 vs 49 days). Bisphosphonate use was associated with an increase in healing time, even after controlling for age, gender, and treatment type. We further stratified patients according to age, gender, type of treatment, fracture severity, and the presence of comorbidities known to affect fracture healing. Surgical treatment was also found to affect healing times in our overall patient population ($p = .03$). Among bisphosphonate users, fracture complexity was associated with longer healing times, whereas age, type of treatment, and comorbidities did not affect radiographic union. In addition, among bisphosphonate users, concomitant treatment with hormone replacement therapy did not adversely affect outcome.

Despite reaching statistical significance, the small difference in healing times between the 2 patient groups is not judged to be clinically relevant. Patients can be clinically "healed" (no pain to palpation or motion at the fracture) before the actual radiographic union criteria are met.[24] This was certainly the case for the patient with a delayed union. Also, animal studies have shown that bisphosphonates can inhibit callous remodeling without affecting its overall mechanical integrity.[19] This may result in a greater lag between radiographic union and clinical healing in patients on bisphosphonate therapy. Therefore, a 6-day difference in average union rates would not change our clinical management of fractures of the distal radius and, in our opinion, does not warrant cessation of bisphosphonate therapy in these patients.

There are several limitations to the study. The definition of fracture union continues to be controversial in orthopaedic practice.[31] Although other comprehensive definitions exist, we chose to focus on radiographic healing in order to achieve a more objective determination of union. In a retrospective review of patients treated by multiple physicians, we felt that clinical healing was difficult to standardize and became a potential source of bias. The timing of follow-up radiographs on the patients was also determined by each individual provider and was not performed at regular intervals. Our review of radiographs, however, revealed that radiographs were taken at similar intervals in both patient groups. Nonetheless, it is difficult to determine with precision the exact time of bony healing. We chose to record the date of radiographic healing as the date of fracture healing, but the patients' fractures might have healed several days before their follow-up visit and radiographs. An alternative approach would have been to average the time between the radiographs at fracture healing and those of the prior visit. This study includes nonsurgically treated as well as surgically treated fractures. Although we were able to determine radiographic healing in all cases, it is possible that the presence of hardware might have affected our interpretation of the radiographs. We chose to examine fracture healing in a distal radius model. Delayed unions and nonunions in patients with distal radius fractures were thought to be uncommon,[32,33] but more cases have recently been described.[34] Despite the relative rarity of nonunions in this patient population, we felt that our study group consisted of a large enough cohort that a significant difference in fracture healing could be detected. An additional limitation was that osteoporosis status was not known in all patients in the control group, whereas all subjects in the bisphosphonate group had been previously diagnosed with low BMD. This is potentially important, as several animal studies have suggested that fracture healing is impaired in osteoporotic bone.[35–38] Thus, the slower healing rate in the BP group cannot be solely attributed to treatment with bisphosphonate, as their osteoporotic status may also have contributed.

Bisphosphonate use is associated with a small increase in time to union among patients with fractures of the distal radius. Given the proven benefits of bisphosphonate therapy in patients with underlying osteoporosis, however, we do not feel that this difference is enough to change current practice patterns. Although further studies are needed to better define the effects of bisphosphonate therapy on fracture healing, our results suggest that bisphosphonates can be continued after distal radius fractures without altering the natural course of fracture healing. A prospective trial looking at both radiographic and clinical union would be essential in substantiating these results.

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