A commentary by Edward Joseph Harvey, MDCM, MSc, is linked to the online version of this article at jbjs.org.

Factors Associated with Increased Healing Time in Complete Femoral Fractures After Long-Term Bisphosphonate Therapy

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Background: The purpose of this study was to analyze factors that affect healing time after operative treatment of complete femoral fractures associated with long-term use of bisphosphonates. In particular, we sought to determine surgically controllable factors related to fracture-healing time.

Methods: Ninety-nine consecutive patients (109 fractures) who had been surgically treated for a complete atypical femoral fracture were enrolled. All patients had a documented history of bisphosphonate therapy at the time of presentation, with an average duration of 7.4 ± 3.5 years (range, 3 to 20 years). Baseline demographic data, characteristics of the fracture and surgery, and radiographic findings including femoral neck-shaft angle, coronal and sagittal bowing of the femur, and thickness of the femoral cortex were examined. Univariate and multivariate logistic regression analyses were performed to identify predictive factors associated with delayed union or nonunion.

Results: Of the 109 fractures, 76 (69.7%) showed osseous union within 6 months after the index surgery and were assigned to the successful healing group. The remaining 33 fractures (30.3%), which showed delayed union or nonunion, were assigned to the problematic healing group. There were differences in body mass index (BMI), bisphosphonate therapy duration, and the rate of prodromal symptoms between the 2 groups. Supra-isthmic fracture location, femoral bowing of $\geq 10^\circ$ in the coronal plane, and a lateral/medial cortical thickness ratio of ≥ 1.4 were predictive of problematic healing but were uncontrollable factors. Iatrogenic cortical breakage around the fracture site as well as a ratio of ≥ 0.2 between the remaining gap and the cortical thickness on the anterior and lateral sides of the fracture site were controllable predictive factors associated with problematic healing.

Conclusions: Intramedullary nailing without cortical breakage around the fracture site and decreasing the anterior and lateral fracture gaps (avoidance of distraction) as much as possible are recommended to reduce healing time in complete femoral fractures associated with long-term use of bisphosphonates.

Level of Evidence: Therapeutic Level IV. See Instructions for Authors for a complete description of levels of evidence.

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Bisphosphonates are widely used for treatment of patients who have, or are at elevated risk of developing, osteoporosis¹. Their efficacy in reducing the risk of fragility fractures has been established in clinical trials²⁻⁴.

Although bisphosphonates prevent typical osteoporotic fractures, several studies have raised concern that these agents cause atypical femoral fractures⁵⁻⁷. As a result of inhibition of osteoclast-mediated bone resorption,

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TABLE I Follow-up According to Time Interval

Time Since Surgery (yr)	No. Entering Interval	Deaths	Losses to Follow-up	Withdrawals	Follow-up Rate (%)
0.5 to 1	109	1	3	14	96.3
>1 to 2	91	2	5	23	92.3
>2 to 3	61	3	6	15	85.2
>3 to 4	37	1	7	22	78.4
>4 to 5	7	0	2	5	71.4

bisphosphonates can cause accumulation of trabecular microdamage⁸. This may compromise the mechanical and regenerative properties of bone, resulting in fractures and delayed bone-healing^{9,10}.

Several recent studies have addressed the operative treatment, complications, and healing rates of atypical femoral fractures¹¹⁻¹⁶. Although the precise prognosis is still unknown, there is a growing consensus that the altered bone metabolism caused by

Fig. 1

Figs. 1-A and 1-B Initial radiographs of a 63-year-old woman showing an atypical fracture of the subtrochanteric region of the femur (supra-isthmic location). **Figs. 1-C and 1-D** The size of the remaining gap at the fracture site is larger on the lateral side than on the medial side as a result of varus malreduction. **Figs. 1-E and 1-F** The patient had nonunion even 18 months after surgery. **Figs. 1-G and 1-H** Complete union was achieved 12 months after revision surgery using an angled blade plate.

TABLE II Baseline Patient Characteristics

	Successful Healing (N = 76)	Problematic Healing (N = 33)	P Value
Age* (yr)	78.00 (73.75, 83.25)	78.00 (75.00, 85.00)	0.889
Female sex†	76 (100%)	33 (100%)	1.000
Affected side (right:left)	56:20	14:19	0.001
Body mass index* (kg/m ²)	20.50 (19.50, 21.59)	21.48 (20.00, 23.56)	0.024
Femoral bone mineral density* (T-score)	-3.5 (-2.9, -3.8)	-3.4 (-2.7, -4.2)	0.523
Comorbidities†			
Cardiovascular disease	11 (14.5%)	4 (12.1%)	0.690
Cerebrovascular disease	8 (10.5%)	3 (9.1%)	0.738
Chronic pulmonary disease	9 (11.8%)	4 (12.1%)	0.868
Chronic renal disease	2 (2.6%)	1 (3.0%)	0.575
Chronic liver disease	3 (3.9%)	1 (3.0%)	0.461
Diabetes mellitus	17 (22.4%)	8 (24.2%)	0.775
Smoking	2 (2.6%)	1 (3.0%)	0.575
Parkinsonism	3 (3.9%)	1 (3.0%)	0.461
Cognitive impairment	10 (13.2%)	4 (12.1%)	0.893
Charlson comorbidity index†			0.645
1 or 2	34 (44.7%)	15 (45.5%)	
3 or 4	31 (40.8%)	14 (42.4%)	
≥5	11 (14.5%)	4 (12.1%)	
ASA classification†‡			0.586
I or II	72 (94.7%)	31 (93.9%)	
III or IV	4 (5.3%)	2 (6.1%)	
Koval score ²⁰ †			0.795
1	63 (82.9%)	27 (81.8%)	
2 or 3	13 (17.1%)	6 (18.2%)	
Residency type†			0.716
With family	51 (67.1%)	26 (78.8%)	
Single	15 (19.7%)	4 (12.1%)	
Care facility	10 (13.2%)	3 (9.1%)	
Bisphosphonate medication duration* (yr)	6.15 (4.20, 9.83)	8.00 (4.90, 12.00)	0.041
Presence of prodromal symptoms†			0.026
Yes	17 (22.4%)	14 (42.4%)	
No	59 (77.6%)	19 (57.6%)	
Presence of drug holiday†			0.586
Yes	4 (5.3%)	2 (6.1%)	
No	72 (94.7%)	31 (93.9%)	

*The values are given as the median with the interquartile range in parentheses. †The values are given as the number of fractures with the percentage in parentheses. ‡ASA = American Society of Anesthesiologists.

long-term use of bisphosphonates would adversely affect bone-healing even after osteosynthesis^{12,15,17}. Delayed or failed fracture-healing is becoming a major concern after fracture stabilization in patients taking bisphosphonates¹³.

It is crucial to determine which factors have a positive or negative impact on healing of atypical femoral fractures. This study was conducted to analyze factors that affect healing time in the operative treatment of complete femoral fractures as-

sociated with long-term use of bisphosphonates. In particular, we sought to determine operatively controllable factors related to fracture-healing time.

Materials and Methods

Subjects

A consecutive series of 130 patients (140 fractures) who had been operatively treated for a complete atypical femoral fracture from July 2006 to February

TABLE III Fracture and Surgery Characteristics

	Successful Healing (N = 76)	Problematic Healing (N = 33)	P Value
Injury mechanism*			0.738
Fall down	8 (10.5%)	3 (9.1%)	
Slip	68 (89.5%)	30 (90.9%)	
Fracture location*			<0.001
Supra-isthmic (including subtrochanteric)	4 (5.3%)	16 (48.5%)	
Isthmic	51 (67.1%)	8 (24.2%)	
Infra-isthmic	21 (27.6%)	9 (27.3%)	
Fracture on the contralateral side*			0.622
Complete or incomplete	21 (27.6%)	7 (21.2%)	
None	55 (72.4%)	26 (78.8%)	
Time interval between fracture and surgery† (d)	4.18 (2.32, 5.40)	4.28 (2.45, 5.20)	0.737

*The values are given as the number of patients with the percentage in parentheses. †The values are given as the median with the interquartile range in parentheses.

Fig. 2

Figs. 2-A and 2-B Initial radiographs of a 67-year-old woman who had been treated with bisphosphonates for 12 years, showing a complete femoral fracture. **Figs. 2-C and 2-D** Lateral cortical breakage occurred during the index surgery. **Figs. 2-E and 2-F** The lateral osseous fragment was not healed 6 months after surgery. **Figs. 2-G and 2-H** Complete healing had occurred 14 months after surgery.

TABLE IV Radiographic Characteristics

	Successful Healing (N = 76)	Problematic Healing (N = 33)	P Value
Preoperative			
Femoral neck-shaft angle* (<i>deg</i>)	132.00 (126.00, 137.70)	132.00 (130.50, 134.70)	0.522
Coronal bowing of the femur* (<i>deg</i>)	8.00 (2.00, 12.00)	12.00 (5.00, 15.10)	0.003
Sagittal bowing of the femur* (<i>deg</i>)	7.00 (3.90, 12.00)	8.40 (6.00, 12.00)	0.140
Cortical thickness* (<i>mm</i>)			
Anterior	9.23 (8.30, 10.28)	9.93 (7.96, 11.85)	0.620
Posterior	7.13 (6.27, 7.68)	7.58 (6.21, 8.82)	0.327
Medial	5.41 (4.74, 6.18)	5.05 (4.20, 6.01)	0.179
Lateral	7.20 (6.08, 10.25)	7.87 (7.03, 10.05)	0.059
Cortical thickness ratio*			
Lateral/medial	1.30 (1.20, 1.55)	1.50 (1.30, 1.65)	0.012
Anterior/posterior	1.46 (1.30, 1.59)	1.29 (1.21, 1.74)	0.040
Intraoperative			
Reduction in the coronal plane†			0.015
Valgus	27 (35.5%)	9 (27.3%)	
Neutral	45 (59.2%)	15 (45.5%)	
Varus	4 (5.3%)	9 (27.3%)	
Reduction in the sagittal plane†			0.723
Flexion	4 (5.3%)	2 (6.0%)	
Neutral	43 (56.6%)	19 (57.6%)	
Extension	29 (38.1%)	12 (36.4%)	
Postoperative			
Gap at fracture site* (<i>mm</i>)			
Anterior	1.50 (1.00, 2.00)	1.90 (1.00, 3.00)	0.041
Posterior	2.00 (1.50, 3.40)	2.00 (0.80, 4.00)	0.474
Medial	2.45 (1.40, 3.60)	2.60 (1.50, 4.00)	0.113
Lateral	1.50 (1.00, 2.20)	2.00 (1.30, 4.00)	0.001
Gap/cortical thickness*			
Anterior	0.15 (0.10, 0.22)	0.38 (0.14, 0.56)	0.004
Posterior	0.34 (0.22, 0.44)	0.34 (0.20, 0.45)	0.709
Medial	0.56 (0.32, 0.80)	0.59 (0.28, 0.90)	0.665
Lateral	0.18 (0.13, 0.29)	0.57 (0.17, 0.84)	<0.001
Cortical breakage at fracture site†			0.008
Yes	1 (1.3%)	4 (12.1%)	
No	75 (98.7%)	29 (87.9%)	

*The values are given as the median with the interquartile range in parentheses. †The values are given as the number of patients with the percentage in parentheses.

2014 at a single academic center (Samsung Changwon Hospital) were identified. Atypical femoral fractures were defined by characteristic radiographic features including a transverse or short oblique fracture line, medial spike, focal lateral cortical thickening, and no or minimal comminution, according to the criteria of a 2013 American Society for Bone and Mineral Research task force¹⁸.

All fractures were located along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare, and all were associated with long-term (≥ 3 -year) use of bisphosphonates and a history of minimal or no trauma. Minimal trauma was defined as a slip or fall from a standing height or less¹⁹. Of these 130 patients, 18 patients (18 fractures) who had a history of fracture, infection, or surgery involving the affected femur or underwent fixation with a plate were excluded from this study, as were 5 patients (5 fractures) who

had a history of corticosteroid use, hormonal treatment, rheumatoid arthritis, metabolic bone disease other than osteoporosis such as hyperparathyroidism, or paraneoplastic syndrome. No pathologic fractures associated with metastatic malignancies were found. Four patients (4 fractures) were lost to follow-up before osseous union, and 4 patients (4 fractures) were excluded as a result of insufficient data. The final cohort comprised 99 patients (109 fractures). The mean follow-up duration (and standard deviation) was 24.2 ± 8.4 months (range, 6 to 60 months). Patients who were lost or who died during the follow-up period are summarized in Table I. This study was approved by our institutional review board, and informed consent was waived for this retrospective study.

All patients had a documented history of bisphosphonate therapy at the time of presentation. Of the 99 patients, 28 (28.3%) had been prescribed

TABLE V Uncontrollable Variables Associated with Delayed Union or Nonunion

	Successful Healing* (N = 76)	Problematic Healing* (N = 33)	Crude OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Body mass index				0.014		0.240
≥ 21.0 kg/m ²	32 (42.1)	22 (66.7)	2.7 (1.2-6.1)		2.0 (0.6-6.5)	
< 21.0 kg/m ²	44 (57.9)	11 (33.3)	1		1	
Prodromal symptoms				0.024		0.070
Yes	17 (22.4)	14 (42.4)	2.6 (1.1-5.9)		3.4 (0.9-13)	
No	59 (77.6)	19 (57.6)	1		1	
Bisphosphonate duration				0.051		0.100
≥ 7 yr	30 (39.5)	19 (57.6)	2.2 (1.0-4.8)		3.8 (0.7-18.9)	
< 7 yr	46 (60.5)	14 (42.4)	1		1	
Fracture location				< 0.001		0.020
Supra-isthmic	4 (5.3)	16 (48.5)	17.3 (4.9-61.3)		38.9 (6.7-224)	
Isthmic	51 (67.1)	8 (24.2)	1		1	
Infra-isthmic	21 (27.6)	9 (27.3)	2.2 (0.8-5.6)		6.7 (1.3-33.7)	
Femoral bowing in the coronal plane				0.004		0.002
$\geq 10^\circ$	25 (32.9)	20 (60.6)	2.9 (1.3-6.4)		10.8 (2.5-46.6)	
$< 10^\circ$	51 (67.1)	13 (39.4)	1		1	
Cortical thickness, lateral/medial				0.015		0.036
≥ 1.4	32 (42.1)	22 (66.7)	2.9 (1.3-6.4)		11 (2.9-42.7)	
< 1.4	44 (57.9)	11 (33.3)	1		1	
Cortical thickness, ant./post.				0.033		0.163
≥ 1.4	21 (27.6)	14 (42.4)	2.5 (1.2-5.7)		6.2 (0.4-24.3)	
< 1.4	55 (72.4)	19 (57.6)	1		1	

*The values are given as the number of patients with the percentage in parentheses.

anti-osteoporotic medication at our hospital and the other 71 (71.7%) had been prescribed such medication at other hospitals. Alendronate was prescribed to 43 patients (43.4%); risedronate, to 27 (27.3%); ibandronate, to 11 (11.1%); pamidronate, to 3 (3.0%); and zoledronate, to 3 (3.0%). Two or more of these drugs had been sequentially used in 12 patients (12.1%). Six patients had taken a drug holiday from bisphosphonates for at least 1 year. The average duration of bisphosphonate treatment was 7.4 ± 3.5 years (range, 3 to 20 years). Long-term use was defined as ≥ 3 years in accordance with a prior study¹⁶. Prodromal symptoms had developed in 31 (28.4%) of the 109 fractures, and the mean duration of symptoms was 7.0 ± 8.5 months (range, 3 to 18 months). All patients discontinued bisphosphonate medications at the time of admission to our hospital. Teriparatide was not used.

Data Collection and Radiographic Measurements

For each patient, we retrospectively determined detailed demographic data including age, sex, body mass index (BMI), bone mineral density (BMD), and residence type. Comorbidities and functional status²⁰ of the study population are shown in Table II. Characteristics of the fracture and surgery (including injury mechanism, fracture location, and time interval between fracture and surgery) were obtained from our fracture database. Fracture location was categorized into 3 groups (supra-isthmic including subtrochanteric, isthmic, and infra-isthmic). All of the fractures were fixed with a statically locked intramedullary nail (diameter of the proximal portion, 12 mm).

Fracture-healing was defined as osseous bridging of 3 or 4 cortices on anteroposterior and lateral radiographs²¹. Fractures that showed osseous union

within 6 months after the index surgery were considered to have achieved successful healing, whereas fractures that did not were considered to have problematic healing.

Standing femoral anteroposterior radiographs with correct patellar alignment with no rotation and lateral radiographs with the medial and lateral condyles of the femur overlapping were selected for analysis. All radiographs were assessed independently by 1 orthopaedic surgeon and 1 independent musculoskeletal radiologist, both blinded to the patient information, twice within an interval of 1 week. Preoperatively, the femoral neck-shaft angle²², coronal and sagittal bowing of the femur, and thickness of the femoral cortex were evaluated. Femoral bowing was measured using the curvature of the contralateral femur as previously described¹⁹. In patients with bilateral fractures, bilateral radiographs made before the second fracture were available. The thickness of the femoral cortex was measured at 4 areas of the fracture site (medial, lateral, anterior, and posterior) on both anteroposterior and lateral views. With respect to the reduction status of the fractures, coronal alignment of the femur was defined as valgus, neutral, or varus, and sagittal alignment was defined as flexion, neutral, or extension. The remaining gap at the fracture site was measured postoperatively. The presence of iatrogenic cortical breakage around the fracture site during nail insertion was also investigated.

Statistical Analyses

Basic descriptive statistical analyses (SPSS version 18.0) were used to describe the study population. Values are reported as the median and interquartile range or as the number and percentage. The Mann-Whitney U test was used for

TABLE VI Controllable Variables Associated with Delayed Union or Nonunion

	Successful Healing (N = 76)*	Problematic Healing (N = 33)*	Crude OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Reduction in the coronal plane				0.013		0.413
Valgus	27 (35.5)	9 (27.3)	1.0 (0.4-2.4)		1 (0.3-3.4)	
Neutral	45 (59.2)	15 (45.4)	1		1	
Varus	4 (5.3)	9 (27.3)	6.4 (1.8-23)		3.1 (0.3-37.3)	
Cortical breakage at fracture site				0.010		0.039
Yes	1 (1.3)	4 (12.1)	8.8 (1.9-81.6)		19.7 (1.5-261)	
No	75 (98.7)	29 (87.9)	1		1	
Gap at fracture site, ant.				0.226		0.260
≥1.5	42 (55.3)	20 (60.6)	1.4 (0.7-1.8)		0.7 (0.4-1.3)	
<1.5	34 (44.7)	13 (39.4)	1		1	
Gap at fracture site, lat.				0.010		0.340
≥1.5	50 (65.8)	28 (84.8)	2.3 (1.5-3.4)		0.7 (0.3-1.9)	
<1.5	26 (34.2)	5 (15.2)	1		1	
Gap/cortical thickness, ant.				<0.001		0.035
≥0.2	34 (44.7)	25 (75.8)	3 (1.3-6.8)		34.1 (2.7-437.8)	
<0.2	42 (55.3)	8 (24.2)	1		1	
Gap/cortical thickness, lat.				0.005		0.012
≥0.2	40 (52.6)	25 (75.8)	3.2 (1.4-7.3)		11.6 (1.4-94.1)	
<0.2	36 (47.4)	8 (24.2)	1		1	

*The values are given as the number of patients with the percentage in parentheses.

continuous variables, and the Fisher exact test or Pearson chi-square test was used for categorical variables. Significance was defined as $p \leq 0.05$. Univariate logistic regression was performed on each variable to determine differences between the 2 groups. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Variables with $p \leq 0.05$ were incorporated into a forward, stepwise multivariate logistic regression to calculate adjusted ORs. Intraclass correlation coefficients were used to assess intrarater and interrater agreement with regard to continuous scales of radiographic measurements.

Results

Demographic Data and Clinical Course

Of the 109 fractures (in 99 patients) in the final cohort, 76 (69.7%) showed osseous union within 6 months after the index surgery and were assigned to the successful healing group. The remaining 33 fractures (30.3%), which showed delayed union or nonunion, were assigned to the problematic healing group. In the latter group, 27 fractures underwent delayed union at a mean of 10.6 months (range, 8 to 18 months). The other 6 fractures went on to oligotrophic nonunion. At the time of the final follow-up, 2 of these 6 fractures had undergone revision surgery (Fig. 1) and the 4 patients with the remaining fractures had declined revision. Iatrogenic cortical breakage occurred intraoperatively in 5 fractures during nail placement (Fig. 2).

Demographic data for the successful and problematic healing groups are summarized in Table II. There were significant

differences in the bisphosphonate medication duration (6.15 compared with 8.00 years, respectively; $p = 0.041$) and the rate of prodromal symptoms (17 of 76 compared with 14 of 33, $p = 0.026$) between the 2 groups.

Fracture and Surgery Characteristics

As shown in Table III, the distribution of fracture locations differed significantly between the 2 groups ($p < 0.001$).

Radiographic Parameters

Radiographic parameters before, during, and after surgery are shown in Table IV. Preoperative coronal bowing of the femur was significantly more severe in the problematic healing group (12.00°) compared with the successful healing group (8.00° , $p = 0.003$). The lateral/medial cortical thickness ratio showed significant differences between the 2 groups (1.50 compared with 1.30, $p = 0.012$), as did the anterior/posterior ratio (1.29 compared with 1.46, $p = 0.040$). In addition, the intraoperative reduction in the coronal plane differed significantly between the 2 groups ($p = 0.015$).

After surgery, the size of the remaining gap on the anterior side of the fracture site was significantly different between the 2 groups (1.90 compared with 1.50, $p = 0.041$), as was the gap on the lateral side (2.00 compared with 1.50, $p = 0.001$).

The ratio of the remaining gap to cortical thicknesses on the anterior side of the fracture site (0.38 compared with 0.15, $p = 0.004$) and on the lateral side (0.57 compared with 0.18, $p < 0.001$) also differed significantly between the 2 groups. The presence of iatrogenic cortical breakage around the fracture site was associated with significant differences in fracture-healing ($p = 0.008$).

Intraclass correlation coefficients for interobserver and intraobserver variability averaged 0.68 and 0.76 when calculated for all radiographic parameters. Thus, there was good intraobserver and interobserver agreement in the radiographic measurements.

Factors Affecting Fracture-Healing

Of the 46 variables tested for association with problematic healing, 13 reached significance in the univariate analysis. Seven of those 13 variables had already been predetermined at the time of injury or initial evaluation and therefore represented uncontrollable factors associated with problematic healing (Table V). The 6 remaining variables were directly related to the operative intervention and were defined as controllable factors associated with problematic healing (Table VI). Of the 7 uncontrollable factors, supra-isthmic fracture location, femoral bowing of $\geq 10^\circ$ in the coronal plane, and lateral/medial cortical thickness ratio of ≥ 1.4 were identified as independent predictors of problematic healing on the basis of multivariate analysis. Of the 6 controllable factors, cortical breakage around the fracture site and a ratio of the remaining gap size to cortical thickness of ≥ 0.2 on the anterior and lateral sides of the fracture site were independent predictive factors associated with problematic healing.

Discussion

Although atypical femoral fractures have been reported to be at risk of failure of healing^{12,15-17,19}, few studies have analyzed factors affecting healing time in long-term bisphosphonate users. The present study sought to determine factors predictive of delayed union or nonunion in a consecutive series of 109 complete femoral fractures associated with long-term use of bisphosphonates. Specifically, we focused on operatively controllable factors related to fracture-healing time.

In our series of 109 fractures, 76 (69.7%) showed osseous union within 6 months after the index surgery, whereas the remaining 33 (30.3%) showed delayed union or nonunion. The overall union rate was 94.5% (103 of 109). In a previous study¹² that evaluated 41 atypical low-energy femoral fractures associated with ≥ 5 years of bisphosphonate use, 98% (40 of 41) showed radiographic union at a mean of 8.3 months (range, 2 to 18 months). The average healing time of almost 8 months for those fractures appeared to be longer than that for typical femoral fractures, which heal at an average of 3 to 6 months.

We identified a difference in the duration of bisphosphonate use between the successful healing and problematic healing groups. A longer duration of bisphosphonate use was significantly associated with a higher rate of problematic healing, which is consistent with the results of other studies^{17,23}. Prodromal

symptoms can serve as an indicator of impending fracture associated with long-term use of bisphosphonates²⁴. However, there are limited data regarding the relationship between prodromal symptoms and the healing time of these fractures. Moreover, it is uncertain whether longer prodromal symptoms are associated with the changes in radiographic features, including increase in the cortical thickness.

Mechanical stability after intramedullary nailing depends on fracture location²⁵. Femoral fractures occurring in the non-isthmic region are prone to lack of a tight-fitting contact. This can aggravate rotational instability, the main mechanical problem in failed intramedullary nailing. In this study, the healing time of bisphosphonate-associated femoral fractures differed according to the fracture location. Fractures occurring in the supra-isthmic region including the subtrochanteric region were at higher risk of delayed union or nonunion.

Bisphosphonate-associated complete femoral fractures have been reported to have high complication rates with operative fixation^{13,16,17}. Prasarn et al.¹⁵ concluded that the higher complication rate in bisphosphonate-associated fractures was primarily attributable to cortical breakage during nail insertion (5 of 17, 29%) and postoperative plate failure (3 of 10, 30%). In our series, iatrogenic cortical breakage around the fracture site occurred in 5 fractures, of which 4 showed delayed union. Asians have differences in femoral geometry, with higher rates of bowing, compared with Western populations¹⁷. Some authors have suggested that increased femoral bowing might be an important causative factor for low-energy diaphyseal femoral fractures^{19,26}. In the present study, coronal bowing of the femur was more severe in the problematic healing group compared with the successful healing group, suggesting that the severity of femoral bowing may contribute to the high rate of delayed union.

With intramedullary nailing of atypical fractures, there are concerns regarding the later occurrence of a femoral neck fracture or cortical perforation distal to the fracture site. We believe that cephalomedullary screw insertion through the proximal portion of the nail could be advantageous, not only to prevent femoral neck fracture but also to obtain more rigid fixation. However, this type of nail was not used in our series. We attempted to insert nails that were as long as possible and statically locked to secure sufficient working length and thus acquire firm fixation. However, in an excessively bowed femur, there may be a risk of cortical perforation distal to the fracture site.

There has been no definitive conclusion regarding the optimal entry point of the nail (piriformis versus trochanteric starting point) in surgical treatment of atypical femoral fractures. The mismatch of curvature between the implant and femur makes it difficult to pass the nail into the medullary canal. In a case report²⁷, a good result was achieved after fixation with a trochanteric starting nail of the opposite curvature. In our series, piriformis nails starting in the tip of the greater trochanter were used to reduce the risk of cortical perforation.

It has become widely accepted that tensile strain increase in focally thickened anterolateral cortex locations precedes an

atypical femoral fracture^{26,28}. In the present study, delayed union or nonunion occurred primarily at anteriorly or laterally thickened cortex at the fracture site. Thus, we believe that reducing the anterior and lateral fracture gaps as much as possible during surgery is critical to achieving osseous union. Intraoperative anatomical or valgus reduction of the femur is required to reduce the lateral fracture gap. In a retrospective series of surgically treated atypical fractures, varus malreduction at the fracture site negatively affected fracture-healing¹². In our study, the remaining fracture gap was measured on radiographs in more detail in 4 locations (anterior, posterior, medial, and lateral). We focused not only on the absolute gap size but also on the relative ratio of gap size to cortical thickness because the cortical thickness at the fracture site was found to be associated with healing time. Anterior and lateral fracture gap sizes divided by cortical thickness were independent predictive factors for delayed union or nonunion.

This study has some limitations. First, the number of patients was limited. It is not easy to recruit a large sample of patients with a relatively rare injury. However, investigation of the available studies on the surgical outcome of such an injury revealed that the current study is one of the largest single-center series. Second, the retrospective nature of this study results in an inherent risk of observer bias, including the potential for missing data and inability to control confounding variables. We performed 46 statistical comparisons. Although an alpha level of 5% is known to represent an appropriate value for a single comparison, it may not be appropriate when numerous comparisons are performed. Third, we did not evaluate functional outcomes. Egol et al.¹² reported that 66% of patients with surgically treated complete atypical fractures became pain-free, and pain combined with apprehension was a major cause of functional limitations in the remaining patients. Lastly, PTH (parathyroid hormone) 1-34 was not used in this study. The termination of the bisphosphonates and the addition of that agent could have changed some of the healing results. In addition, we did not

investigate calcium and vitamin-D treatment and the possible role of low vitamin D in those with poor healing.

In conclusion, 30.3% of all patients with operatively treated complete femoral fractures associated with long-term use of bisphosphonates had delayed union or nonunion. Supra-isthmus fracture location, femoral bowing of $\geq 10^\circ$ in the coronal plane, and a lateral/medial cortical thickness ratio of ≥ 1.4 were predictive of problematic healing but were uncontrollable. Cortical breakage around the fracture site and a ratio of remaining gap to cortical thickness of ≥ 0.2 on the anterior and lateral sides of the fracture sites were operatively controllable predictive factors associated with problematic healing. Our data suggest that intramedullary nailing without cortical breakage around the fracture site and decreasing the anterior and lateral fracture gaps as much as possible (minimal fracture distraction) could be helpful in reducing healing time in complete femoral fractures associated with long-term bisphosphonate use. ■

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