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Full Length Article

A retrospective bicenter comparative study of surgical outcomes of atypical femoral fracture: Potential effect of teriparatide on fracture healing and callus formation

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ABSTRACT

Background: The main purpose of the present study was to assess the radiologic effect of teriparatide on fracture healing, including union rate, union time, and callus formation, by quantitative measurements using serial follow-up X-ray imaging examinations in patients with complete atypical femoral fractures (AFFs) treated using closed intramedullary nailing.
Methods: From January 2010 to October 2017, 58 consecutive patients with complete AFF who were treated with intramedullary nailing at two institutions were enrolled. Patients were classified into two groups: those who received teriparatide therapy (group A) and those who did not (group B). Teriparatide (Forsteo®; Eli Lily Co., Indianapolis, IN, USA) at a once-daily 20 μg dose was prescribed as continuous treatment of osteoporosis or with the expectation of better bone healing. Surgical outcomes, including union rate, union time, modified radiologic union score (mRUS), and callus formation at 3, 6, and 12 months postoperatively, were assessed to evaluate the effect of teriparatide on fracture healing. Quantitative measurement of callus formation was performed using the region of interest (ROI) tool in the picture archiving communication system (PACS).
Results: Non-union was not observed in group A, whereas two patients had non-union in group B. Union time was 18.3 ± 4.8 (range, 12–28) weeks in group A and 23.6 ± 9.5 (range, 12–64) weeks in group B and was significantly shorter in group A than group B (p = 0.010). The average mRUSs during periods A (3–4 months postoperatively), B (6–8 months postoperatively), and C (12–14 months postoperatively) were 10.0, 13.9, and 15.9 in group A, and 8.7, 12.0, and 14.9 in group B, respectively. The average mRUSs during periods A and B were significantly different (p = 0.027 and 0.011, respectively). The medial, posterior, and total callus areas during periods A and B were also significantly greater in group A than in group B. No difference was observed in the union rate between the two groups (p = 0.492).
Conclusion: Teriparatide may improve callus formation and shorten union time in patients with complete diaphyseal AFF who underwent closed intramedullary nailing.
Level of Evidence: Level III retrospective comparative study.

1. Introduction

Internal fixation with intramedullary nails is the treatment of choice for complete atypical femoral fractures (AFFs) [1–4]. However, studies have reported that the surgical outcomes of complete AFF are worse than those of typical femoral fractures [5–8]. Bogdan et al. [8] reported that healing was slower in patients with complete AFF who were treated surgically than in those with typical femoral fractures, and there was a high rate of non-union, with 12% requiring revision surgery at an average of 11 months. Furthermore, patients with AFF were four times more likely to require reoperation than those with ordinary femoral shaft fractures because of peri-implant fragility [5].

Immediate discontinuation of antiresorptive therapy has been recommended as a prerequisite for the medical management of patients with AFF [9]. In addition, teriparatide has been frequently prescribed to accelerate fracture healing in AFF despite the diversity of local practices and regulations. A few studies attempted to demonstrate the effect of teriparatide on AFF healing [9–13]. However, the number of patients

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enrolled in these studies was relatively small, and many different methods were used to demonstrate its effects on fracture healing. In particular, there was no quantitative assessment of radiologic outcome, and there were no longitudinal data.

Here, we report our results from a retrospective review of surgical outcomes for the treatment of complete AFF using intramedullary nailing and the clinical impact of teriparatide on fracture healing via quantitative measurement of callus formation using serial follow-up X-ray imaging examinations. We hypothesized that the use of post-operative teriparatide would be associated with improved union rate and callus formation as well as shortened union time in patients with complete AFF treated with intramedullary nailing.

2. Materials and methods

2.1. Study population

This study conformed to the World Medical Association Declaration of Helsinki and KGCP guidelines, with institutional review board approval (H-1905-021-079). From January 2010 to October 2017, 84 consecutive cases (76 patients, **8 with bilateral fractures**) with complete AFF who underwent surgeries at **two institutions** were identified. Patients who had (1) previous surgery for hip arthroplasty; (2) plate osteosynthesis; (3) any femoral deformity due to previous trauma or surgery; (4) identifiable bone tumors, including metastatic tumors, enchondromatosis, and giant cell tumors; (5) metabolic bone disorders such as Paget's disease and hyperparathyroidism with the exception of osteoporosis; (6) lesions associated with high-energy fractures; and (7) follow-up < 1 year (Fig. 1) were excluded from the study. AFF was diagnosed based on radiographic evidence of transverse or short oblique fracture lines, medial spikes, focal lateral cortical thickening, and a relative lack of comminution at the fracture site [14,15]. The initial diagnosis of AFF was made by one hip trauma surgeon with > 5 years' experience, and one musculoskeletal specialized radiologist with > 10 years' experience. High-energy fracture was defined as fracture due to falling from a height higher than the standing height, motor vehicle accident, or a crush injury [16].

2.2. Surgical protocol

All patients with complete AFF who were enrolled in the present study were treated with closed intramedullary nailing. We made it a surgical principle to choose the intramedullary nail with the longest length and the largest diameter based on the geometry of each patient's femur to maximize the stability of the fracture site. Furthermore, cephalomedullary fixation was performed to avoid insufficiency fracture of the femoral neck or proximal locking screw site after fixation. Bilateral radiographs of the femur and bone scans were routinely checked for the presence of incomplete fractures of the contralateral side in all patients. When cortical buckling on the lateral cortex of the contralateral femur in plain radiographs and uptake on the same lesion in bone scan were identified, simultaneous bilateral intramedullary nailing was performed [17]. Partial-weight bearing using crutches was allowed as tolerated postoperatively. As full-weight ambulation was allowed on incomplete fracture sites, the same rehabilitation protocol was applied to patients with incomplete fractures on the contralateral side.

2.3. Data collection and group classification

The following preoperative data were collected for all patients: duration of teriparatide use, age, sex, type of fracture (subtrochanteric vs. diaphyseal), level of fracture, incomplete fracture on the contralateral side, body mass index (BMI), osteoporosis, bone mineral density (BMD), levels of metabolic bone markers (osteocalcin, C-telopeptide), fracture side, smoking history, medical history of bisphosphonate or other antiresorptive drug (denosumab), medical history of vitamin D supplementation, vitamin D level, medical history of high-dose steroid use, and other underlying medical condition (diabetes mellitus, rheumatoid arthritis, and systemic lupus erythematosus). The

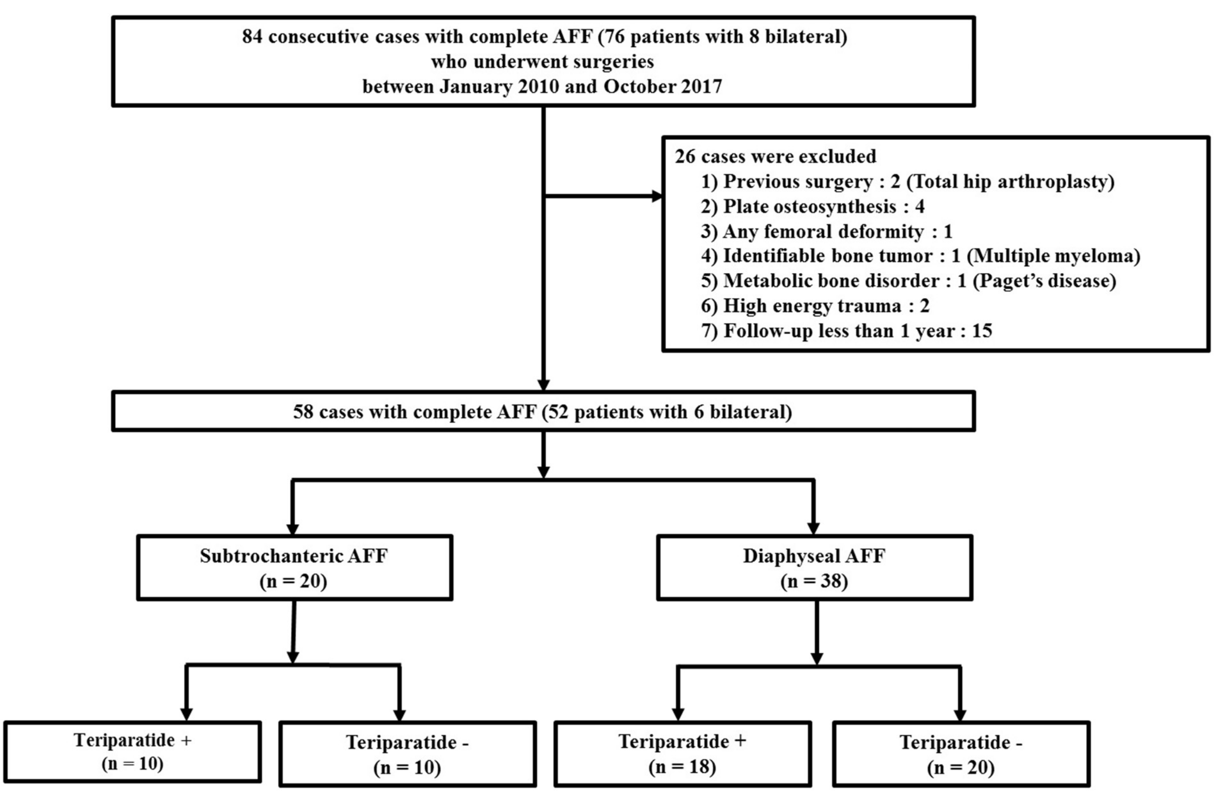

Fig. 1. Study design flowchart.

level of fracture was defined as the distance from the greater trochanter to the fracture site divided by the total length of the femur. Subtrochanteric fractures were defined as fractures that occur in the area from the lesser trochanter to 5 cm distally according to Fielding's classification. Diaphyseal fractures were defined as fractures occurring in the distal part of the subtrochanteric area [18]. For BMD, the contralateral side of the proximal femur and the lumbar area were measured using dual-energy x-ray absorptiometry (DEXA) at the time of admission; the lowest value among L1–4, femur total, and femoral neck was used for analysis. Vitamin D deficiency was defined as serum 25-hydroxyvitamin D level below 20 ng/mL.

Patients who were on long-term bisphosphonate therapy had their medication discontinued following the diagnosis of complete AFF; calcium and vitamin D supplements were continued or initiated for all those who were not previously supplemented. Between March 2015 and October 2017, teriparatide (Forsteo®; Eli Lily Co., Indianapolis, IN, USA) at a once-daily 20 μg dose was prescribed with the expectation of improving bone healing. We therefore classified patients enrolled in the study into two groups: those who received teriparatide therapy (group A) and those who did not (group B). Teriparatide was prescribed for at least 6 months in group A.

2.4. Radiologic assessment and measurement of callus formation

All patients were requested to visit for follow-up 3, 6, and 12 months after the initial surgery. Radiologic assessment was based on follow-up radiographs taken during their visit. When bone union was identified in unscheduled visits, union time was calculated accordingly. Follow-ups were divided into three periods: 3–4 months (period A), 6–8 months (period B), and 12–14 months (period C). All follow-up X-ray images were taken using the same X-ray machine at the out-patient clinic. Bone union was defined as full painless weight bearing with bridging callus across at least three cortices on anteroposterior (AP) and lateral views of the femur [19]. Nonunion was defined as a definite fracture gap after a minimum of 9 months with no visible progressive signs of healing for 3 months [20,21].

For the fracture healing assessment at each follow-up, the modified radiologic union score (mRUS) was calculated. A cortical score from 1 to 4 was given to each cortical segment of the fracture site according to the scoring system of Litrenta et al. [22]: 1, lack of callus; 2, non-bridging callus; 3, bridging callus; and 4, remodeled bridging callus. The mRUS value was calculated by adding the four cortical scores.

Quantitative measurement of callus formation was performed using the region of interest (ROI) tool in the picture archiving communication system (PACS). When the ROI drawn along the margin of the callus around the fracture site was selected, information for the selected image, including the minimum, maximum, mean, standard deviation of gray values, and area were displayed (Fig. 2). The areas of the anterior and posterior callus were measured in the lateral view of the femur, while the areas of the medial and lateral callus were measured in the AP view of the femur. Total callus formation was defined as the sum of the anterior, posterior, medial, and lateral callus. Radiologic outcomes, including bone union, mRUS, and callus formation were independently assessed by two orthopaedic surgeons who were blinded to all clinical information, and the average value of two measurements of the mRUS and callus formation was used for analysis. The inter-observer reproducibility of all the measurements for callus formation was evaluated using the intra-rater correlation coefficient (ICC). The results were interpreted as follows: > 0.8 = almost perfect agreement, 0.7–0.8 = strong, 0.5–0.6 = moderate, 0.3–0.4 = fair, and 0–0.2 = poor.

2.5. Statistical analysis

Student's *t*-test was used to compare preoperative details including age, level of fracture, BMI, BMD, metabolic bone markers, duration of bisphosphonate use, vitamin D level, and surgical outcomes, including union time, mRUS, and area of callus formation between the two groups. Fisher's exact test or the chi-square test was used to compare variables between the two groups: the chi-square test was used for sex, type of fracture, incomplete fracture on the contralateral side, osteoporosis, fracture side, medical history of bisphosphonate use or other antiresorptive drug, and medical history of vitamin D supplementation, whereas Fisher's exact test was used for medical history of high-dose steroid use, other underlying medical condition, bone union, and reoperation. The SPSS software (version 21.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. $P < 0.05$ indicated statistical significance.

3. Results

A total of 58 complete AFFs (52 patients with 6 bilateral fractures) were included in the present study. The average age was 74.3 years (range, 47–86), and all were women (100%). A comparison of the preoperative demographics between groups A and B is presented in Table 1. Twenty eight patients (48.3%) were included in group A and the average duration of teriparatide use was 6.9 months. The number of patients with subtrochanteric AFF was 10 (35.7%) in group A and 10 (33.3%) in group B. The number of patients with diaphyseal AFF was 18 (64.3%) in group A and 20 (66.7%) in group B. The number of patients with osteoporosis at the time of admission was 19 (67.9%) group A and 19 (63.3%) in group B. The numbers of patients who were on bisphosphonate before surgery were 18 (64.3%) in group A and 22 (73.3%) in group B. There were no significant differences between the two groups in terms of age, sex, type of fracture, level of fracture, incomplete fracture on the contralateral side, BMI, osteoporosis, BMD, levels of metabolic bone markers, fracture side, medical history of bisphosphonate use or other antiresorptive drug, medical history of vitamin D supplementation, vitamin D level, medical history of high-dose steroid use, and other underlying medical condition.

A comparison of surgical outcomes and measurement of callus formation between groups A and B is presented in Table 2. Non-union was not observed in group A, whereas two patients (6.7%) had non-union in group B. There was no significant difference in the union rate between the two groups. Union time was significantly shorter in group A (18.3 weeks) than in group B (23.6 weeks) ($p = 0.010$). Two patients (7.1%) required reoperation in group A (1 case of insufficiency fracture at proximal locking screw and 1 case of distal locking screw loosening), while 5 patients (16.7%) required reoperation in group B (2 cases of nonunion, 1 case of fracture at proximal locking screw, 1 case of femoral neck insufficiency fracture, and 1 case of deep infection). All causes of reoperation were identified after union except two cases of non-union. There was no significant difference in the reoperation rate between the two groups.

The average mRUSs during periods A, B, and C were 10.0, 13.9, and 15.9 in group A, and 8.7, 12.0, and 14.9 in group B, respectively; the average mRUSs during period A and B were significantly different ($p = 0.027$ and 0.011, respectively). The posterior callus areas during periods A and B were 298.9 mm^2 and 255.4 mm^2 in group A, and 118.9 mm^2 and 128.3 mm^2 in group B, respectively; these were significantly different ($p = 0.002$ and 0.014, respectively). The medial callus areas during periods A and B were 482.8 mm^2 and 395.8 mm^2 in group A, and 202.7 mm^2 and 189.0 mm^2 in group B, respectively; these differences were also significant ($p = 0.009$ and 0.012, respectively). The total callus formation during periods A and B was 1182.1 mm^2 and 985.2 mm^2 in group A, and 568.8 mm^2 and 573.8 mm^2 in group B, respectively; these differences were also significant ($p = 0.026$ and 0.048, respectively). There were no significant differences in terms of anterior and lateral callus areas during periods A, B, and C between the two groups. There were also no significant differences in the posterior, medial, and total callus areas during period C between the two groups (Fig. 3). ICCs for the measurement of callus formation ranged from

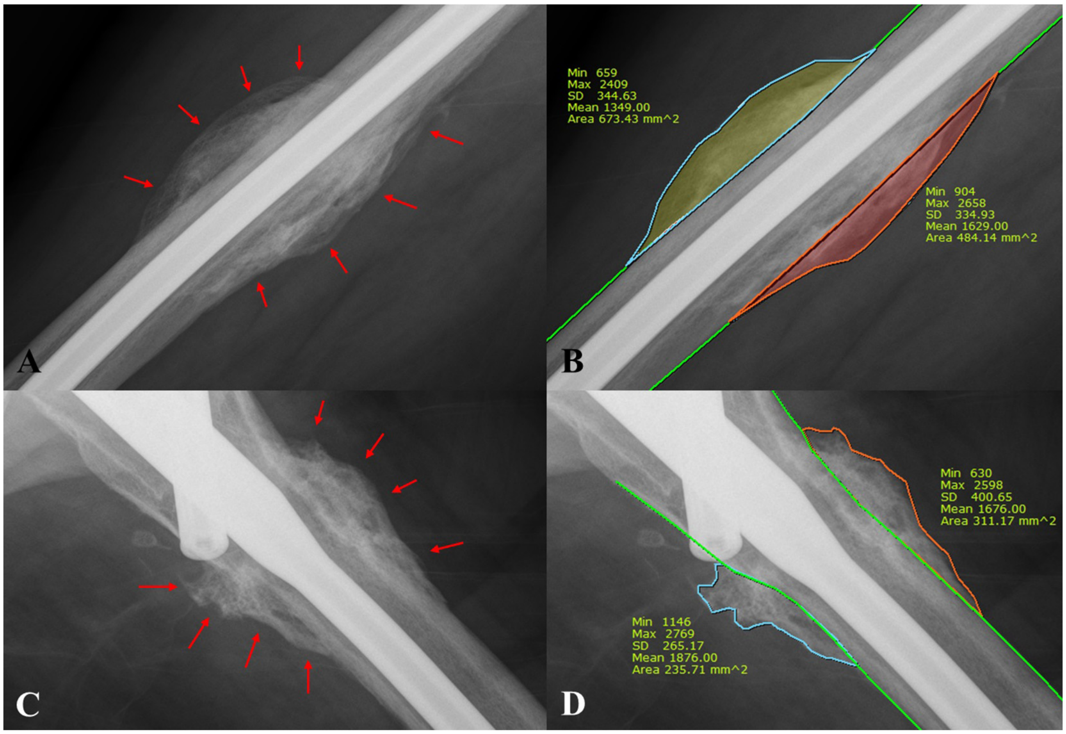

Fig. 2. (A) Ovoid pattern of callus formation with clear margin at the 6-month follow-up in patients with diaphyseal atypical femoral fracture (femur AP view). (B) Quantitative measurement of medial and lateral callus using the ROI tool of PACS. (C) Callus formation with clear margin at the 6-month follow-up in patients with subtrochanteric atypical femoral fracture (femur lateral view). (D) Quantitative measurement of anterior and posterior callus using the ROI tool of PACS.

Table 1
Comparison of preoperative demographics between teriparatide group and no teriparatide group.

Variables	Group A	Group B	*p*-Value
Number (n, %)	28 (48.3)	30 (51.7)	–
Duration of teriparatide use (months)	6.9 ± 2.0 (6–12)	–	–
Age (years)	74.8 ± 9.8 (47–84)	73.8 ± 7.4 (55–86)	0.666
Female (n, %)	28 (100.0)	30 (100.0)	–
Type of fracture (n, %)			
Subtrochanteric	10 (35.7)	10 (33.3)	1.000
Diaphyseal	18 (64.3)	22 (73.3)	
Level of fracture (%)	39.8 ± 14.6 (21.6–63.6)	38.7 ± 13.3 (17.5–67.5)	0.753
Incomplete fracture in contralateral side (n, %)	4 (14.3)	2 (6.7)	0.415
Body mass index (kg/m2)	22.4 ± 2.9 (17.1–28.3)	24.3 ± 4.2 (15.1–36.5)	0.053
Osteoporosis (n, %)	19 (67.9)	19 (63.3)	0.717
Bone mineral density (T-score)	−2.4 ± 1.0 (−3.9 to −0.1)	−2.0 ± 0.8 (−3.7 to −0.5)	0.091
Metabolic bone marker			
Osteocalcin (ng/ml, normal range 0.7–6.5)	1.58 ± 1.10 (0.28–4.12)	1.64 ± 1.13 (0.36–3.65)	0.858
C-telopeptide (ng/ml, normal range 0.050–0.450)	0.35 ± 0.22 (0.11–0.56)	0.32 ± 0.21 (0.08–0.68)	0.650
Right side (n, %)	15 (45.5)	18 (54.5)	0.791
Smoking (n, %)	2 (7.1)	1 (3.3)	0.605
Medical history of bisphosphonate (n, %)	18 (64.3)	22 (73.3)	0.457
Alendronate	11 (39.3)	9 (50.0)	0.457
Risedronate	4 (14.3)	4 (13.3)	0.916
Ibandronate	3 (10.7)	3 (10.0)	0.929
Zoledronic acid	4 (14.3)	2 (6.6)	0.341
Duration of bisphosphonate use (years)	3.2 ± 2.3 (0 − 10)	2.8 ± 2.0 (0–8)	0.471
Medical history of other antiresorptive drug (Denosumab)	0 (0.0)	0 (0.0)	–
Medical history of vitamin D supplement (n, %)	17 (60.7)	18 (60.0)	0.956
25-OH vitamin D3	31.9 ± 19.3 (4.4–70.4)	25.7 ± 20.4 (1.40–73.4)	0.242
Vitamin D deficiency (n, %)	11 (39.3)	15 (57.7)	0.412
Medical history of high dose steroid use	0 (0.0)	0 (0.0)	–
Other underlying medical condition			
DM	5 (17.9)	7 (2.3)	0.607
RA	1 (3.6)	0 (0.0)	0.483
SLE	0 (0.0)	0 (0.0)	–

Values are presented as mean ± standard deviation (range), or number (%).
VEGF; vascular endothelial growth factor, DM; diabetes mellitus, RA; rheumatoid arthritis, SLE; systemic lupus erythematosus.

Table 2
Comparison of surgical outcomes and measurements of callus formation area around the fracture site between the teriparatide group and no teriparatide group.

Variables	Group A (n = 28)	Group B (n = 30)	p-Value
Union (n, %)	28 (100.0)	28 (93.3)	0.492
Union time (weeks)	18.3 ± 4.8 (12–28)	23.6 ± 9.5 (12–64)	0.010
Reoperation (n, %)	2 (7.1)	5 (16.7)	0.425
mRUS			
Period A	10.0 ± 1.7 (4–12)	8.7 ± 2.7 (4–12)	0.027
Period B	13.9 ± 1.5 (12–16)	12.0 ± 3.6 (4–16)	0.011
Period C	15.9 ± 0.2 (15–16)	14.9 ± 1.7 (4–16)	0.083
Callus formation during period A (mm^2)			
Anterior	283.9 ± 411.4 (0.0–1658.0)	141.7 ± 161.5 (0.0–527.0)	0.085
Posterior	298.9 ± 272.3 (0.0–1040.0)	118.9 ± 131.8 (0.0–502.4)	0.002
Lateral	208.1 ± 275.8 (0.0–1124.0)	101.1 ± 142.6 (0.0–732.0)	0.066
Medial	482.8 ± 492.0 (51.0–1639.0)	202.7 ± 267.8 (0.0–857.0)	0.009
Total	1182.1 ± 1293.9 (120.0–5461.0)	568.8 ± 666.4 (0.0–2218.0)	0.026
Callus formation during period B (mm^2)			
Anterior	181.4 ± 259.8 (0.0–1000.0)	138.7 ± 141.6 (0.0–531.0)	0.436
Posterior	255.4 ± 234.5 (0.0–903.0)	128.3 ± 139.1 (0.0–559.0)	0.014
Lateral	153.4 ± 155.7 (0.0–600.0)	95.8 ± 148.9 (0.0–791.0)	0.155
Medial	395.8 ± 370.3 (43.0–1400.0)	189.0 ± 224.1 (0.0–1007.0)	0.012
Total	985.2 ± 941.0 (70.0–3800.0)	573.8 ± 581.9 (0.0–2281.9)	0.048
Callus formation during period C (mm^2)			
Anterior	166.5 ± 307.0 (0.0–1200.0)	110.7 ± 117.1 (0.0–446.0)	0.358
Posterior	168.1 ± 154.8 (0.0–651.0)	110.7 ± 119.6 (0.0–492.6)	0.118
Lateral	86.0 ± 112.5 (0.0–411.0)	81.4 ± 125.9 (0.0–672.0)	0.883
Medial	329.2 ± 389.3 (8.0–1368.0)	164.4 ± 230.8 (0.0–1004.6)	0.053
Total	672.8 ± 678.6 (60.0–2525.0)	467.2 ± 480.6 (0.0–1913.2)	0.186

Values are presented as mean ± standard deviation (range) or number (%).
mRUS; modified radiologic union score.
Period A; 3–4 months after surgery, Period B; 6–8 months after surgery, Period C; 12–14 months after surgery.

0.951 to 0.998, which is interpreted as almost perfect agreement.

Fracture type-specific comparisons of time to union, mRUS, and the area of callus formation between the two groups are presented in Table 3. In diaphyseal complete AFF, the average time to union was significantly shorter in the teriparatide group (17.3 weeks) than in the no teriparatide group (25.0 weeks) (p = 0.047). The average mRUSs during periods A and B in diaphyseal complete AFF were also higher in the teriparatide group (10.3 and 14.0, respectively) than in the no teriparatide group (8.8 and 11.6, respectively) (p = 0.042 and 0.021, respectively). In diaphyseal complete AFF, the areas of posterior callus and total callus formation during periods A and B as well as the area of medial callus during periods A, B, and C in the teriparatide group were significantly greater than those of the no teriparatide group. However, there were no differences in terms of time to union, mRUSs and the area of all callus formation between the two groups in subtrochanteric complete AFF.

4. Discussion

Previous reports mentioned the benefits of teriparatide for the treatment of patients with AFF [9–13]. Miller et al. [12] studied 15 patients with bisphosphonate-associated AFF who were treated with intramedullary rods and performed quantitative bone histomorphometry both before and after 12 months of teriparatide therapy (20 μg SC/day). The authors suggested that teriparatide may improve bone formation by demonstrating that administration of teriparatide was associated with an increase in all three dynamic histomorphometric parameters. However, they found a poor correlation between baseline histomorphometry and bone turnover markers, and heterogeneity in the bone turnover in patients with bisphosphonate-associated AFF, constituting a limitation of their study. Furthermore, their study did not include any radiologic evaluation for fracture healing. Chiang et al. [10] reported that administration of 20 μg of teriparatide subcutaneously daily for 6 months to 5 of the 14 patients with AFF was associated with a 2–3 fold increase in bone remodeling markers and fracture healing. However, this study not only included 8 incomplete fractures but also did not provide any radiologic evidence for healing at fracture sites. Furthermore, the number of subjects enrolled in that study was too small to draw a conclusion with regard to the effect of teriparatide.

Our data in the present study could not demonstrate that teriparatide significantly increased bone union in complete AFF treated with intramedullary nailing, however, the data showed that it might have a positive impact on fracture healing. In patients with diaphyseal complete AFF, the average time to union was significantly shorter and the average mRUSs during periods A and B were significantly greater in the teriparatide group than in the no teriparatide group. The mRUS scoring system was designed by Litrenta et al. [22] and was validated by Perlepe et al. [23]. It reflects the overall process of fracture healing, making it possible to quantify the healing process. The average callus formation by quantitative measurement using PACS in patients with diaphyseal complete AFF was also significantly greater in the teriparatide group than in the no teriparatide group. Despite the fact that quantitative measurement of callus formation using PACS has never been validated, judging the amount of callus formation on follow-up radiographs is widely-used by orthopaedic surgeons worldwide, and the latest PACS system offers useful annotation tools with high accuracy and reproducibility. Furthermore, complete AFF tends to show unique fracture configurations, including short transverse and short oblique fracture line with medial spike, and a consistent pattern of ovoid callus formation with clear margins during the healing period. The ICC for quantitative evaluation of callus formation in the present study demonstrated high agreement between the two observers, suggesting that measurement of the area of callus formation by adjusting the size of the ROI is simple and efficient.

There are several limitations to this study. First was its retrospective design. Nevertheless, conducting a prospective randomized, comparative study would be difficult, because AFF is an uncommon form of femoral fracture. Therefore, we performed a multicenter study using the same surgical and medical protocol. In addition, we believe that our sample size of 58 consecutive cases of complete AFF with follow-up for > 1 year is the largest sample size to date. Thus, it might be able to

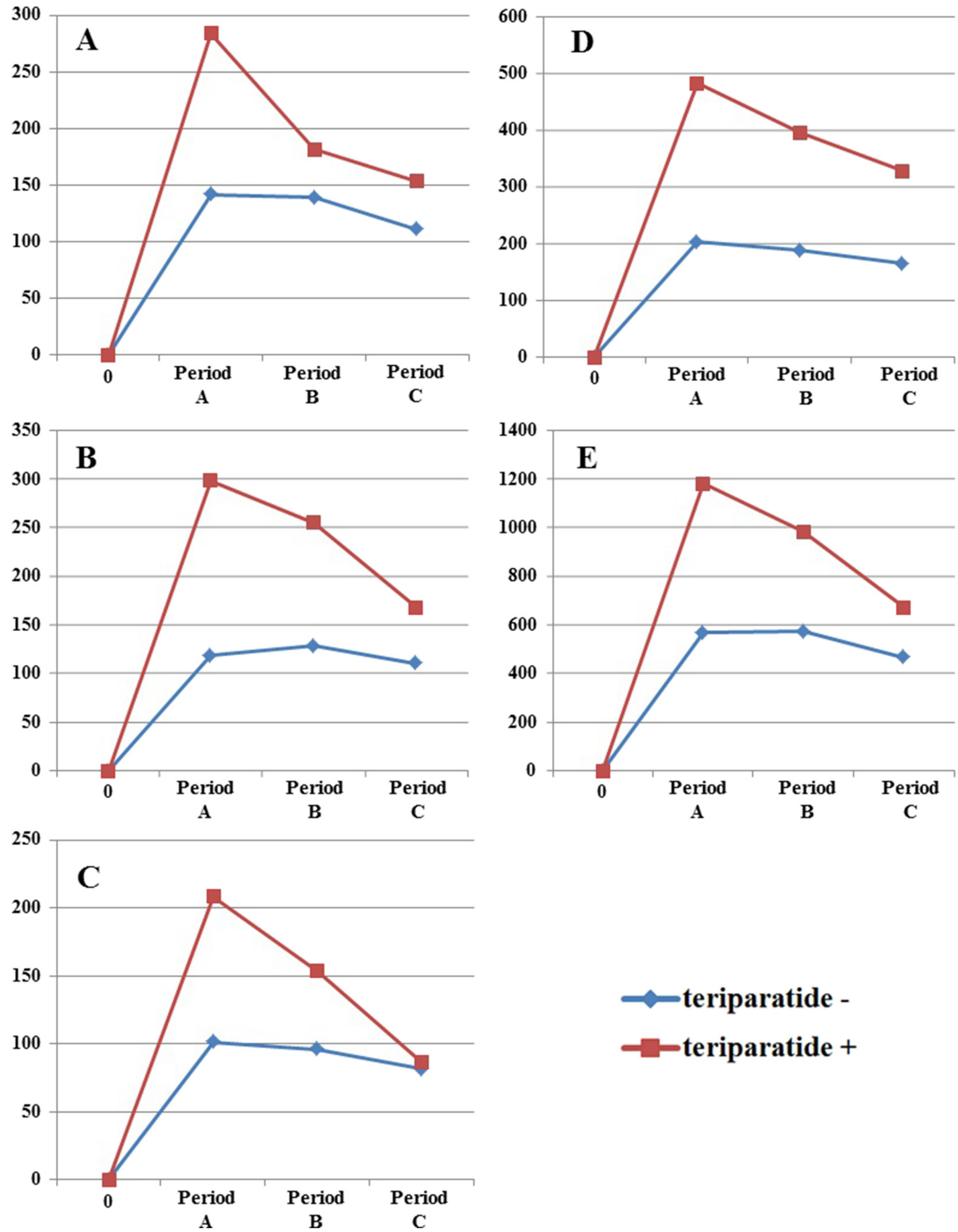

Fig. 3. The change of callus formation in all patients with complete AFF measured using the ROI tool of PACS over time. (A) Change of anterior callus formation. (B) Change of posterior callus formation. (C) Change of lateral callus. (D) Change of medial callus formation. (E) Change of total callus formation.

show the potential effects of teriparatide on fracture healing with a stronger evidence than those of previous studies. Second, we did not adjust for multiple confounding factors to demonstrate a significant association between fracture healing and postoperative teriparatide use. There was no significant difference in preoperative demographics between the teriparatide group and the no teriparatide group. However, considering this is a non-randomized retrospective comparative study without adjusting for multiple confounders, the setting in the present study might not be appropriate to draw any causative conclusions regarding the efficacy of teriparatide on fracture healing. In particular, considering the well-known correlation between AFF and long term use of bisphosphonate, there seems to be a lack of profound analysis on the effect of bisphosphonate on fracture healing. Third, the definition for union and non-union in the present study would be ambiguous when definite bridging callus cannot be observed 9 months postoperatively. We encountered two cases whose bridge callus could not be visualized at 9 months postoperatively. However, we did not diagnose them as non-union, because they had progressive signs of healing around the fracture site. Bridging callus in these patients were identified 12 and 14 months postoperatively, respectively. Finally, we could not provide consistent evidence for the association between teriparatide and bone healing in subtrochanteric complete AFF. In patients with subtrochanteric complete AFF, there was no significant difference in time to union, mRUS, and callus formation between the teriparatide group and the no teriparatide group. It is well-known that high transmitted stress is mostly concentrated on the subtrochanteric area, which is

Table 3
Fracture type specific comparison of time to union, mRUS, and callus formation area between the teriparatide group and non-teriparatide group.

Variables	Subtrochanteric (n = 20)		p-Value	Diaphyseal (n = 38)		p-Value
	Teriparatide + (n = 10)	Teriparatide - (n = 10)		Teriparatide + (n = 18)	Teriparatide - (n = 20)	
Time to union (weeks)	20.8 ± 5.3 (12–28)	24.8 ± 7.5 (12–42)	0.247	17.3 ± 4.3 (12–24)	25.0 ± 16.3 (12–84)	0.047
mRUS						
Period A	9.6 ± 2.4 (5–12)	8.6 ± 2.3 (5–12)	0.353	10.3 ± 1.1 (8–12)	8.8 ± 2.9 (4–12)	0.042
Period B	13.7 ± 1.8 (12–16)	12.8 ± 2.1 (10–16)	0.320	14.0 ± 1.4 (12–16)	11.6 ± 4.1 (4–16)	0.021
Period C	15.9 ± 0.3 (15–16)	15.3 ± 1.4 (14–16)	0.184	16.0 ± 0.0 (16–16)	14.8 ± 3.7 (4–16)	0.159
Period A (mm^2)						
Anterior	172.7 ± 170.7 (0.0–546.0)	188.7 ± 178.4 (0.0–415.0)	0.840	345.6 ± 492.0 (40.0–1658.0)	118.3 ± 151.5 (0.0–527.0)	0.057
Posterior	160.8 ± 110.1 (0.0–300.0)	107.3 ± 93.9 (0.0–268.0)	0.257	375.7 ± 306.4 (65.0–1040.0)	124.7 ± 149.1 (0.0–502.4)	0.002
Lateral	122.5 ± 136.9 (0.0–435.0)	78.5 ± 93.0 (0.0–212.0)	0388	255.6 ± 325.0 (31.0–1124.0)	112.3 ± 163.0 (0.0–732.0)	0.090
Medial	509.8 ± 552.3 (60.0–1507.0)	258.1 ± 331.8(0.0–856.0)	0.233	467.7 ± 471.5 (51.0–1639.0)	175.0 ± 234.4 (0.0–857.0)	0.019
Total	695.8 ± 514.1 (120.0–1497.0)	592.6 ± 671.9 (0.0–1751.0)	0.704	1452.2 ± 1517.5 (466.0–5461.0)	556.9 ± 680.8 (0.0–2218.0)	0.022
Period B (mm^2)						
Anterior	161.6 ± 188.1 (0.0–545.0)	189.9 ± 146.2 (0.0–400.0)	0.712	192.4 ± 296.8 (16.0–1000.0)	113.1 ± 135.8 (0.0–531.0)	0.289
Posterior	149.5 ± 125.3 (0.0–302.0)	81.1 ± 33.7 (0.0–120.1)	0.113	314.2 ± 262.2 (43.0–903.0)	151.9 ± 165.1 (0.0–559.0)	0.027
Lateral	125.1 ± 117.7 (0.0–327.0)	78.5 ± 85.4 (0.0–210.0)	0324	169.1 ± 174.5 (20.0–600.0)	104.4 ± 173.6 (0.0–791.0)	0260
Medial	244.9 ± 241.7 (43.0–578.0)	169.0 ± 154.6 (0.0–400.0)	0.414	479.6 ± 407.5 (52.0–1400.0)	198.9 ± 255.0 (0.0–1007.0)	0.014
Total	681.1 ± 634.4 (70.0–1552.0)	558.6 ± 426.9 (0.0–1310.0)	0.618	1154.1 ± 1052.9 (345.0–3800.0)	581.4 ± 655.9 (0.0–2281.9)	0.049
Period C (mm^2)						
Anterior	164.5 ± 121.6 (0.0–347.0)	97.4 ± 132.8 (0.0–394.0)	0.254	204.9 ± 368.8 (2.0–1200.0)	83.8 ± 107.8 (0.0–446.0)	0.169
Posterior	95.0 ± 92.8 (0.0–235.0)	64.8 ± 32.0 (0.0–108.4)	0.344	208.8 ± 169.2 (30.0–651.0)	133.6 ± 140.3 (0.0–492.6)	0.143
Lateral	78.5 ± 104.3 (0.0–327.0)	73.7 ± 81.5 (0.0–205.0)	0.910	90.2 ± 119.5 (20.0–411.0)	85.2 ± 144.9 (0.0–672.0)	0.909
Medial	181.2 ± 194.2 (0.0–510.0)	162.6 ± 160.8 (8.0–422.0)	0.818	421.8 ± 449.0 (24.0–1368.0)	156.1 ± 251.4 (0.0–1004.6)	0.029
Total	484.3 ± 374.1 (0.0–1143.0)	433.5 ± 470.6 (60.0–1237.0)	0.793	805.7 ± 749.6 (202.0–2525.0)	458.7 ± 534.7 (0.0–1913.2)	0.107

Values are presented as mean ± standard deviation (range).
mRUS; modified radiologic union score.
Period A; 3–4 months after surgery, Period B; 6–8 months after surgery, Period C; 12–14 months after surgery.

mainly constituted of thick cortical bone with poor blood supply [24]. For these reasons, once a fracture in the subtrochanteric area occurs, the process of healing tends to be relatively slower [24,25]. In addition, although we did not perform statistical analysis, our data showed that the average area of callus formation is numerically smaller in subtrochanteric complete AFF than in diaphyseal complete AFF. Based on these results, we believe that the sample size was too small to demonstrate a significant association between teriparatide use and fracture healing in subtrochanteric complete AFF and there might be a positive potential effect of teriparatide on fracture healing and callus formation in all types of AFF. Therefore, we suggest that future studies with a larger sample size should be conducted.

5. Conclusion

Although we could not demonstrate that teriparatide significantly increased the union rate, a significantly shorter union time and a greater callus formation of diaphyseal complete AFF were identified in the teriparatide group. Based on these results, we believe that teriparatide may have a positive effect on fracture healing in terms of callus formation and union time in diaphyseal complete AFF treated with closed intramedullary nailing.

References

[1] K.J. Lee, B.W. Min, Surgical treatment of the atypical femoral fracture: overcoming femoral bowing, Hip Pelvis 30 (2018) 202–209.
[2] M. Githens, M.R. Garner, R. Firoozabadi, Surgical management of atypical femur fractures associated with bisphosphonate therapy, J Am Acad Orthop Surg 26 (2018) 864–871.
[3] Y.C. Park, H.K. Song, X.L. Zheng, K.H. Yang, Intramedullary nailing for atypical femoral fracture with excessive anterolateral bowing, J. Bone Joint Surg. Am. 99 (2017) 726–735.
[4] A. Koh, E. Guerado, P.V. Giannoudis, Atypical femoral fractures related to bisphosphonate treatment: issues and controversies related to their surgical management, Bone Joint J 99 (2017) 295–302.
[5] J. Schilcher, High revision rate but good healing capacity of atypical femoral fractures. A comparison with common shaft fractures, Injury 46 (2015) 2468–2473.
[6] K.A. Egol, J.H. Park, Z.S. Rosenberg, V. Peck, N.C. Tejwani, Healing delayed but generally reliable after bisphosphonate-associated complete femur fractures treated with IM nails, Clin. Orthop. Relat. Res. 472 (2014) 2728–2734.
[7] K.J. Lee, J.J. Yoo, K.J. Oh, J.H. Yoo, K.H. Rhyu, K.W. Nam, D.H. Suh, Surgical outcome of intramedullary nailing in patients with complete atypical femoral fracture: a multicenter retrospective study, Injury 48 (2017) 941–945.
[8] Y. Bogdan, P. Tornetta 3rd, T.A. Einhorn, et al., Healing time and complications in operatively treated atypical femur fractures associated with bisphosphonate use: a multicenter retrospective cohort, J. Orthop. Trauma 30 (2016) 177–181.
[9] N.B. Watts, D. Aggers, E.F. McCarthy, et al., Responses to treatment with teriparatide in patients with atypical femur fractures previously treated with bisphosphonates, J. Bone Miner. Res. 32 (2017) 1027–1033.
[10] C.Y. Chiang, R.M.D. Zebaze, A. Ghasem-Zadeh, S. Iuliano-Burns, A. Hardidge, E. Seeman, Teriparatide improves bone quality and healing of atypical femoral fractures associated with bisphosphonate therapy, Bone 52 (1) (2013) 360–365 Jan.
[11] W.L. Yeh, C.Y. Su, C.W. Chang, et al., Surgical outcome of atypical subtrochanteric and femoral fracture related to bisphosphonates use in osteoporotic patients with or without teriparatide treatment, BMC Musculoskelet. Disord. 18 (2017) 527.
[12] P.D. Miller, E.F. McCarthy, Bisphosphonate-associated atypical sub-trochanteric femur fractures: paired bone biopsy quantitative histomorphometry before and after teriparatide administration, Semin Arthritis and Rheum 44 (2015) 477–482.
[13] S.L. Greenspan, K. Vujevich, C. Britton, et al., Teriparatide for treatment of patients with bisphosphonate-associated atypical fracture of the femur, Osteoporos. Int. 29 (2018) 501–506.
[14] N. Miyakoshi, T. Aizawa, S. Sasaki, et al., Healing of bisphosphonate-associated atypical femoral fractures in patients with osteoporosis: a comparison between treatment with and without teriparatide, J. Bone Miner. Metab. 33 (2015) 553–559.
[15] E. Shane, D. Burr, B. Abrahamsen, et al., Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research, J. Bone Miner. Res. 29 (2014) 1–23.
[16] E. Shane, D. Burr, P.R. Ebeling, et al., Atypical subtrochanteric and diaphyseal femoral fractures: report of a task force of the American Society for Bone and Mineral Research, J. Bone Miner. Res. 25 (2010) 2267–2294.
[17] A.P. Diamantopoulos, G. Rohde, I. Johnsrud, I.M. Skoie, M. Hochberg, G. Haugeberg, The epidemiology of low- and high-energy distal radius fracture in middle-aged and elderly men and women in Southern Norway, PLoS One 7 (2012) e43367.
[18] B.W. Min, K.H. Koo, Y.S. Park, C.W. Oh, S.J. Lim, J.W. Kim, K.J. Lee, Y.K. Lee, Scoring system for identifying impending complete fractures in incomplete atypical femoral fractures, J. Clin. Endocrinol. Metab. 102 (2017) 545–550.
[19] R. Rizzoli, K. Akesson, M. Bouxsein, et al., Subtrochanteric fractures after long-term treatment with bisphosphonates: a European society on clinical and economic aspects of osteoporosis and osteoarthritis, and international osteoporosis foundation

working group report, Osteoporos. Int. 22 (2011) 373–390.
[20] L.A. Corrales, S. Morshed, M. Bhandari, T. Miclau 3rd, Variability in the assessment of fracture-healing in orthopaedic trauma studies, J. Bone Joint Surg. Am. 90 (2008) 1862–1868.
[21] J.H. Jang, J.M. Ahn, H.J. Lee, N.H. Moon, Surgical outcomes of biologic fixation for subtrochanteric fracture using locking compression plates, Hip Pelvis 29 (2017) 68–76.
[22] J. Litrenta, P. Tornetta 3rd, S. Mehta, Determination of radiographic healing: an assessment of consistency using RUST and modified RUST in metadiaphyseal fractures, J. Orthop. Trauma 29 (2015) 516–520.
[23] V. Perlepe, A. Cerato, D. Putineanu, C. Bugli, G. Heynen, P. Omoumi, B.V. Berg, Value of a radiographic score for the assessment of healing of nailed femoral and tibial shaft fractures: a retrospective preliminary study, Eur. J. Radiol. 98 (2018) 36–40.
[24] Z.B. Zhou, S. Chen, Y.S. Gao, Y.Q. Sun, C.Q. Zhang, Y. Jiang, Subtrochanteric femur fracture treated by intramedullary fixation, Chin. J. Traumatol. 18 (2015) 336–341.
[25] D.J. Hak, H. Wu, C. Dou, C. Mauffrey, P.F. Stahel, Challenges in subtrochanteric femur fracture management, Orthopedics 38 (2015) 498–502.