Evaluation of the Nature and Etiologies of Risk Factors for Diaphyseal Atypical Femoral Fractures

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Highlights of the Study

- The nature and etiologies of the risk factors for diaphyseal atypical femoral fractures (AFFs) were investigated.
- Diaphyseal AFFs are affected by bone resorption inhibitor usage, strong femoral curvature, and a serrated change in the femur.
- A low serum 25(OH)D level and serrated change are the risk factors for lateral curvature, and a high serum calcium level is a risk factor for serrated changes.

Keywords
Atypical femoral fracture · Femoral curvature · Serrated change

Abstract

Objectives: Differences in mechanisms of subtrochanteric and diaphyseal atypical femoral fractures (AFFs) are speculated in studies that analyzed differences in the patients'...
Risk Factors for Diaphyseal Atypical Femoral Fractures

Introduction

Although bisphosphonates (BPs) are the gold standard for osteoporosis pharmacotherapy, several adverse effects related to their long-term use have been reported due to severely suppressed bone turnover. These include the atypical low-energy subtrochanteric and diaphyseal femoral fractures [1–3], which are typically diagnosed as atypical femoral fractures (AFFs). At 3–5 per 100,000, the incidence of AFFs is low [4, 5]. However, approximately 30% of all postmenopausal women have osteoporosis [6]. Therefore, AFFs are an important concern in osteoporosis management, the mainstay of which is the use of bone resorption inhibitors. However, AFFs have also been noted in antiresorptive therapy-naive patients, and multiple etiological factors are considered to be involved in these, including an excessive femoral curvature, low serum 25-hydroxyvitamin D (25(OH)D) levels, diabetes, and glucocorticoid usage [7–13]. Thus, although various factors have been proposed, the etiology remains unclear.

AFFs are, by definition, either subtrochanteric or diaphyseal. A subtrochanteric AFF is a fracture that occurs slightly distal to the lesser trochanter of the proximal femur, while a diaphyseal AFF is a fracture that occurs in the femoral shaft distal to the subtrochanteric region and proximal to the femoral condyle [14]. Previously, these AFFs were examined as a group due to the low number of cases. However, in recent years, the differences between subtrochanteric and diaphyseal AFFs have been examined. Differences in the backgrounds of patients with each type of AFF have been reported, and the corresponding differences underlying the AFF development mechanisms in these patients have been proposed [15–20]. While it has been reported that the radius of curvature (ROC) of the femur is small in patients with diaphyseal fractures [7], no study has examined the factors inducing femoral curvature in AFF cases. Furthermore, the factors that affect the differences in the sites of AFF have not been investigated thoroughly. Therefore, this study aimed to investigate risk factors that affect diaphyseal AFFs and their etiologies.

Materials and Methods

Subjects

The medical records of 119 consecutive patients with 137 AFFs who visited our 16 institutions between June 2006 and April 2020 were retrospectively reviewed. Only female patients with diaphyseal AFFs in whom the femoral curvature angle could be examined were included because there was only 1 male patient. Fifteen patients with 15 subtrochanteric AFFs, as well as those with a history of metabolic bone diseases other than osteoporosis or malignancy, were excluded. Finally, 80 consecutive patients with 91 AFFs who exhibited at least 4 of the 5 major features, as defined by the American Society for Bone and Mineral Research Task Force, were included in the AFF group [14]. As a non-AFF control group, 110 age-matched female patients with osteoporosis were included (the osteoporosis group). Osteoporosis was diagnosed using the WHO criteria [21]. Radiographs of the entire femur were obtained to investigate the nonfracture causes of leg pain.

This study was performed in line with the ethical standards of the Helsinki Declaration of 1975, as revised in 1983. This study was also approved by the Institutional Review Board for Clinical Research at the Akita University (Approval No. 1845), and informed consent was obtained from all patients.

Data Variables and Definitions

Data were collected on the patients’ age, bone resorption inhibitor usage (BPs and denosumab) or vitamin D usage before AFF onset, history of fragility fractures, complications, laboratory examination results, bone mineral density (BMD) findings, and femoral curvature measurements. The femoral curvature was measured using anteroposterior and lateral radiographs according to the method described by Yau et al. [7, 22]. The unaffected femur in patients with complete AFFs and the affected femur in patients with incomplete AFFs were examined. BMD...
was measured within 3 months after AFF diagnosis; the BMDs of the lumbar spine and of the femoral neck were measured from anteroposterior views by using a radiography system (Discovery; Hologic Inc., Marlborough, MA, USA). Furthermore, laboratory examinations were performed for determining the serum levels of bone metabolic markers and vitamin D metabolism markers, including serum albumin-adjusted calcium (Ca), inorganic phosphate, intact procollagen I N-terminal propeptide, tartrate-resistant acid phosphatase 5b, and 25(OH)D. These parameters were measured within 2 days after AFF diagnosis. BMDs were measured within 3 months after the AFFs had been diagnosed.

It has been reported that some patients with diaphyseal AFFs exhibit a continuous and wavy thickening in the femoral endosteal region at the tensional (lateral and anterior) side (Fig. 1) [23, 24]. Even normal femoral fractures in elderly patients have exhibited this finding, though this has not yet been elucidated properly. The presence of such wavy thickening of the lateral cortex, known as a “serrated change,” was also evaluated. The clinical data of the patients were compared between the AFF and the osteoporosis groups, and the factors affecting AFFs were investigated. Furthermore, the etiology of the risk factors of diaphyseal AFFs was examined.

**Statistical Analysis**

All continuous variables are expressed as means ± standard deviations. The Student’s t test, Welch’s t test, and χ² test were used to compare the characteristics between the groups. Multivariate logistic regression analysis was used to identify the risk factors associated with AFF and their etiologies. Probability (p) values below 0.05 were considered statistically significant.

**Results**

In the AFF group, 11 patients had bilateral AFFs simultaneously or sequentially; 3, 3, 4, and 1 patient had simultaneous bilateral insufficiency fractures, simultaneous insufficiency and complete fractures, sequential complete fractures, and a sequential complete and incomplete fracture, respectively. The remaining 69 had unilateral AFFs. Furthermore, among the 5 patients who developed AFFs sequentially, 3 were undergoing treatment for osteoporosis until the recurrence of an AFF. Sixty-nine AFFs were complete, and the remaining 22 were incomplete. Alendronate, risedronate, minodronate, or ibandronate was prescribed to 67 patients with AFFs and to 32 patients with osteoporosis. Denosumab was prescribed to 2 patients with AFFs and to 1 patient with osteoporosis.

Usage of BPs or denosumab, incidence of serrated changes in the femur, and BMDs of the proximal femurs were higher in the AFF group than in the osteoporosis group (p < 0.0001, p < 0.0001, and p = 0.0491, respectively). The lateral and anterior femoral curvatures were stronger in the AFF group (p < 0.0001 for both). In contrast, the incidence of previous fragility fractures was higher in the osteoporosis group than in the AFF group (p < 0.0001) (Table 1).

Multivariate analysis revealed serrated changes, bone resorption inhibitor usage, and lateral and anterior femoral curvatures as the risk factors for diaphyseal AFFs (p < 0.0011, p = 0.0137, and p < 0.0001, respectively) (Table 2). All patients were divided into “curved” and “non-curved” groups using the mean and standard deviation values as the cutoff, according to our previous study [25]. The lateral curvature was 7.46°, and the anterior curvature was 20.55°. Multivariate logistic regression analysis was used to examine the factors that affected femoral curvature. Upon multivariate analysis, serrated changes, low serum 25(OH)D levels in the lateral curvature, and serrated changes only in the anterior curvature were shown to be associated with the femoral curvature (p = 0.0088, 0.0205, and 0.0006, respectively) (Tables 3, 4). Multivar-
Table 1. Comparison of the estimated variables between the AFF group and the osteoporosis control group

| Variables                                              | AFF group          | Osteoporosis group | p value |
|--------------------------------------------------------|--------------------|--------------------|---------|
| Patients, N                                            | 91                 | 110                |         |
| Age, years                                             | 80.7±6.4 (57–96)   | 79.3±6.8 (69–93)   | 0.1218  |
| Serrated change                                        | 39 (42.9)          | 3 (2.7)            | <0.0001 |
| Bone resorption inhibitor usage                        | 69 (70.3)          | 33 (30)            | <0.0001 |
| Vitamin D usage                                        | 24 (26.4)          | 16 (14.5)          | 0.0557  |
| Natural vitamin D usage                                 | 2 (2.2)            | 1 (0.9)            | 0.8684  |
| Fragility fracture history                              | 13 (14.3)          | 45 (40.9)          | <0.0001 |
| Presence of diabetes mellitus                          | 7 (7.7)            | 19 (17.3)          | 0.0713  |
| Glucocorticoid usage                                   | 8 (8.8)            | 4 (3.6)            | 0.2163  |
| Laboratory examination                                 |                    |                    |         |
| Ca, mg/dL                                              | 9.25±0.47 (8.4–10.8) | 9.15±0.33 (8.2–10.1) | 0.1143  |
| iP, mg/dL                                              | 3.42±0.55 (2.2–4.7) | 3.49±0.43 (2.5–4.9) | 0.4709  |
| PINP, µg/L                                             | 64.1±68.5 (10.5–276) | 51.7±33.5 (9.3–145) | 0.3357  |
| TRACP-5b, mU/dL                                        | 323±154 (102–722)  | 286±132 (65–650)   | 0.1885  |
| 25(OH)D, ng/mL                                         | 20.9±12.8 (4–69)   | 22.4±8.1 (5–47)    | 0.5502  |
| BMD: lumbar spine, g/cm²                               | 0.748±0.149 (0.422–1.158) | 0.712±0.149 (0.390–1.223) | 0.1914  |
| BMD: proximal femur, g/cm²                             | 0.517±0.127 (0.218–0.760) | 0.475±0.119 (0.166–0.763) | 0.0491  |
| Femoral curvature: lateral, degree                      | 11.6±6.1 (0–25)    | 3.6±3.3 (–3.1–14.2) | <0.0001 |
| Femoral curvature: anterior, degree                     | 18.5±7.3 (3–39)    | 10.0±2.6 (4.4–17.5) | <0.0001 |

Values are expressed as n (%) or mean ± SD (range). AFF, atypical femoral fracture; Ca, calcium; iP, inorganic phosphorus; PINP, intact procollagen I N-terminal propeptide; TRACP5b, tartrate-resistant acid phosphatase 5b; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density.

Table 2. Results of the univariate and multivariate analyses of factors affecting the AFF

| Variables                                              | Univariate analysis | Multivariate analysis |
|--------------------------------------------------------|---------------------|-----------------------|
|                                                        | OR 95% CI           | p value               | OR 95% CI           | p value               |
| Age                                                    | 1.034 0.991–1.079   | 0.1299                | 18.543 3.209–106.119| 0.0011                |
| Serrated change                                        | 26.750 7.896–90.623 | <0.0001               | 11.402 3.482–37.335 | 0.0137                |
| Bone resorption inhibitor usage                        | 5.531 3.014–10.150  | <0.0001               | 1.492 0.372–5.987   | 0.5722                |
| Vitamin D usage                                        | 2.104 1.039–4.263   | 0.0388                | 0.605 0.123–2.973   | 0.6256                |
| Presence of diabetes mellitus                          | 0.399 0.160–0.997   | 0.0493                | 1.005 0.213–5.315   | 0.9854                |
| Glucocorticoid usage                                   | 1.134 0.906–1.419   | 0.2726                | 1.271 1.131–1.428   | <0.0001               |
| Laboratory examination                                 |                     |                       | 1.375 1.213–1.559   | <0.0001               |
| Ca                                                     | 1.941 0.896–4.204   | 0.0927                |                     |                       |
| iP                                                     | 0.727 0.336–1.573   | 0.4188                |                     |                       |
| PINP                                                   | 1.006 0.997–1.014   | 0.1705                |                     |                       |
| TRACP-5b                                               | 1.002 0.999–1.005   | 0.1896                |                     |                       |
| 25(OH)D                                                | 0.980 0.932–1.030   | 0.485                 |                     |                       |
| BMD                                                    |                     |                       | 3.927 0.503–30.643  | 0.1920                |
| Lumbar spine                                           | 18.965 9.82–366.322 | 0.0514                |                     |                       |
| Proximal femur                                         |                     |                       | 3.6±3.3 (–3.1–14.2) | <0.0001               |
| Femoral curvature: lateral, degree                      | 1.407 1.280–1.547   | <0.0001               | 1.271 1.131–1.428   | <0.0001               |
| Femoral curvature: anterior, degree                     | 1.454 1.315–1.608   | <0.0001               | 1.375 1.213–1.559   | <0.0001               |

OR, odds ratio; 95% CI, 95% confidence interval; AFF, atypical femoral fracture; Ca, calcium; iP, inorganic phosphorus; PINP, intact procollagen I N-terminal propeptide; TRACP5b, tartrate-resistant acid phosphatase 5b; 25(OH)D, 25-hydroxyvitamin D; BMD, bone mineral density.
iatie analyses revealed high serum Ca levels, strong femoral curvatures in the lateral dimension, and strong femoral curvatures in the anterior dimension as the predictors of serrated changes ($p = 0.0146, 0.0022, \text{ and } 0.0098$, respectively) (Table 5).

### Discussion

The differences between diaphyseal and subtrochanteric AFFs have been examined in several studies. It has been reported that compared to subtrochanteric AFFs,
diaphyseal AFFs are associated with an older age, lower BMD, and more excessive femoral curvature [15–20]. Oh et al. [17] examined the mechanical load on femurs with and without the femoral curvature. They found that when the femoral curvature is large, the load is mostly applied to the outside of the femoral shaft, whereas when the curvature is small, the load is applied within the vicinity of the femoral trochanter; their study showed that the degree of curvature greatly influenced the site of AFF [17]. In our study, the ROC of the femur was found to be small in diaphyseal AFFs, and these AFFs were determined to have been greatly influenced by the femoral curvature.

While various studies have examined the relationship between the femoral curvature and AFFs, few studies have investigated the etiology of femoral curvatures. Our previous study, which included only older women with osteoporosis, showed that an older age and low serum 25(OH)D levels affected the femoral curvature [25]; the present study also showed that a low serum 25(OH)D level affected the femoral curvature. Furthermore, our previous study showed that low serum 25(OH)D levels affected both the lateral and anterior curvatures; however, the current study indicated that low serum 25(OH)D levels were only associated with the lateral curvature. The reason for the significant association between the serum 25(OH)D levels and the lateral bow of the femur, but not the anterior bow, in patients with AFF remains unclear.

Our analysis revealed that a serrated change in the femur is a risk factor for the development of diaphyseal AFFs. Serrated changes are occasionally identified radiographically, but no studies have examined these findings; therefore, their details remain unclear. Our findings revealed that the femoral curvature is associated with the development of a serrated change; however, the mechanism underlying the occurrence of this factor remains unclear. Furthermore, a high serum Ca level has also been identified as a risk factor for serrated changes, but the mechanism underlying this remains unclear. Further examination, including histological evaluation, is necessary to evaluate serrated changes in detail.

This is the first study to perform a detailed analysis of the risk factors for diaphyseal AFFs using a large number of cases (>90 cases). However, our study has several limitations. Only patients with a diaphyseal AFF and osteoporosis were compared, and patients with subtrochanteric AFFs were excluded due to their small numbers. It is important to clarify the differences between the risk factors for diaphyseal AFFs and those for subtrochanteric AFFs; although AFFs are relatively rare, more subtrochanteric AFF cases will have to be analyzed in the future to clarify these differences.
Conclusions

To our knowledge, this study is the first to investigate factors that affect the occurrence of diaphyseal AFFs. The risk factors for diaphyseal AFFs were the use of bone resorption inhibitors, a small ROC of the femur, and serrated changes in the femur. Furthermore, a low serum 25(OH)D level was a risk factor for lateral curvature, and a high serum Ca level was a risk factor for serrated changes; these factors may influence each other. When treating patients with osteoporosis, diaphyseal AFFs should be suspected in those with these risk factors.

Statement of Ethics

This study was approved by the Institutional Review Board for Clinical Research at the Akita University (Approval No. 1845). All study participants provided informed consent.

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