Factors related to curved femur in elderly Japanese women

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ABSTRACT

Background: Multiple factors are involved in the development of atypical femoral fractures, and excessive curvature of the femur is thought to be one of them. However, the pathogenesis of femoral curvature is unknown. We evaluated the influence of factors related to bone metabolism and posture on the development of femoral curvature.

Methods: A total of 139 women participated in the present study. Curvatures were measured using antero-posterior and lateral radiography of the femur. We evaluated some bone and vitamin D metabolism markers in serum, the bone mineral density (BMD), lumbar spine alignment, and pelvic tilt.

Results: We divided the women into two groups, curved and non-curved groups, based on the average plus standard deviation as the cut-off between the groups. When univariate logistic regression analysis was performed to detect factors affecting femoral curvature, the following were identified as indices significantly affecting the curvature: age of the patients, serum concentrations of calcium, intact parathyroid hormone, pentosidine, homocysteine and 25-hydroxyvitamin D (25(OH)D), and BMD of the proximal femur (P < 0.05) both in the lateral and anterior curvatures. When we used multivariate analyses to assess these factors, only 25(OH)D and age (lateral and anterior standardized odds ratio: 0.776 and 0.385, and 2.312 and 4.472, respectively) affected the femoral curvature (P < 0.05).

Conclusion: Femoral curvature is strongly influenced by age and serum vitamin D.

Introduction

Although bisphosphonates (BPs) are the gold standard for osteoporosis pharmacotherapy, several adverse effects related to their long-term use have recently been reported, such as osteonecrosis of the jaw (ONJ) and atypical low-energy subtrochanteric and diaphyseal femoral fractures due to markedly suppressed bone turnover (SSBT) (1,2). These fractures are typically diagnosed as atypical femoral fractures (AFF). However, many patients have been reported with atypical femoral fractures (AFF) in the absence of BP therapy (3), although the fracture type was consistent with the criteria of AFF suggested by a task force of the American Society for Bone and Mineral Research (ASBMR) (4). The detailed cause of AFF has not been clarified, and multiple factors are thought to be involved in its development. Sasaki et al. were the first to report that excessive curvature of the femur may be one of the associated factors, and this was also stated in a review by a task force of ASBMR (4,5). However, the pathogenesis of femoral curvature in elderly women is unknown.

The aim of this study was to evaluate the influence of factors related to bone metabolism and posture on the development of femoral curvature in elderly women.

Material and methods

Subjects

A total of 139 women, with a mean age of 75.4 years (53 to 93), all being outpatients visiting a single institution for the treatment or examination of osteoporosis between April 2014 and March 2015, were included in this study. Of the 139 patients 64 had received osteoporosis treatment prior to evaluation: bisphosphonate, vitamin D3, selective estrogen receptor modulator, teriparatide, and denosumab were prescribed in 34, 19, 13, 2, and 2 patients, respectively. In addition, a history of fragility fracture was present in 29 patients: vertebral fracture, 15 patients; femoral neck or trochanteric fracture, 13 patients; and distal radius fracture, 4 patients. We excluded patients unable to walk by themselves.

Clinical evaluations

Curvature of the right femur was measured with antero-posterior (AP) and lateral views as the angles between two linear lines drawn along the proximal and distal portions of the femoral shaft, using a method to measure femoral curvature.
immunoassay method, 25(OH)D and 1,25(OH)2D were measured by an enzyme immunoassay method, P1NP and TRACP5b was measured using standard laboratory procedures. Multivariate logistic regression analysis was used to have associations with femoral curvature by univariate logistic regression. We divided the women into two groups, curved and non-curved, based on the average plus standard deviation as the cut-off between the groups for lateral and anterior curved groups, respectively: the lateral curvature was 6.3 degrees and anterior curvature was 12.3 degrees. Because there are many evaluation items, we extracted some factors likely to have associations with femoral curvature by univariate logistic regression. Multivariate logistic regression analysis was used to examine the factors of femoral curvature. Probability (P) values less than 0.05 were considered statistically significant.

**Results**

For lateral curvature, the curved group included 25 patients with a mean age of 82.7 years, and the non-curved group included 114 patients with a mean age of 73.8 years. For anterior curvature, the curved group included 19 patients with a mean age of 84.9 years, and the non-curved included 120 patients with a mean age of 73.9 years. The number of patients who were non-curved based on both definitions was 107, the number of patients who were curved based on the lateral but not anterior curvature definition was 13, the number of patients who were curved based on the anterior but not lateral curvature definition was 7, and the number of patients who were curved based on both lateral and anterior curvature definitions was 12.

When univariate logistic regression analysis was performed to identify factors affecting femoral curvature we found that the age of the patients, serum concentrations of Ca, intact PTH, pentosidine, and 25(OH)D, and BMD of the proximal femur, both with regard to lateral (Table 2) and anterior curvatures (Table 3), differed between women belonging to the non-curved and curved groups. Homocysteine, however, only did so with regard to the lateral curvature (Table 2). We used multivariate logistic regression analysis to exclude a mutual influence of different factors, and then only 25(OH)D and age affected the femoral curvature (Tables 4 and 5).

**Discussion**

We evaluated some factors that may affect the development of femoral curvature, such as the bone turnover, bone quality, vitamin D metabolism, BMD, and posture, and only 25(OH)D and the age were selected as indices significantly affecting the curvature. Osteomalacia is a condition causing the deposition failure of calcium and phosphorus in osteoids after epiphyseal line closure. The causes are broadly divided into failure of vitamin D action and hypophosphatemia; failure of vitamin D action includes the deficiency of vitamin D, abnormal vitamin D metabolism, and abnormalities of the vitamin D receptor (7). Published data indicate that the presence of vitamin D deficiency should be suspected when serum 25(OH)D is lower than 20 ng/mL (8,9). In this study, curved group patients with both lateral and anterior curvature showed low serum 25(OH)D, at about 16 ng/mL. Although there is a report that vitamin D becomes lower as age increases (10), the serum 25(OH)D concentrations showed significant correlations with femoral curvature both anteriorly and laterally in the present study, even when we eliminated the effect of age. It might be anticipated that vitamin D deficiency, namely osteomalacia, strongly affects the curvature of the femur.

The ASBMR Task Force 2013 Revised Case Definition of AFF is as follows: 1) the fracture is associated with minimal or no trauma, as in a fall from a standing height or lower; 2) the fracture line originates at the lateral cortex and is

| Table 1. Characteristics of study patients. |
|------------------------------------------|
| Total number                             | 139 |
| Age (years)                              | 75.4 ± 10.0 |
| AP curvature (degrees)                   | 2.98 ± 3.32 |
| Lateral curvature (degrees)              | 9.79 ± 2.48 |
| Laboratory examinations                  |     |
| ALP (IU/L)                               | 270 ± 198 |
| Ca (mg/dL)                               | 9.15 ± 0.33 |
| IP (mg/dL)                               | 3.50 ± 0.43 |
| P1NP (µg/L)                              | 53.5 ± 33.5 |
| TRACP5b (mU/dL)                          | 280 ± 125 |
| Pentoosidine (µg/mL)                     | 0.054 ± 0.030 |
| Homocysteine (nmol/L)                    | 10.0 ± 5.9 |
| Intact PTH (pg/mL)                       | 44.0 ± 20.2 |
| 25(OH)D (ng/mL)                          | 22.6 ± 8.3 |
| 1,25(OH)D, D (pg/mL)                     | 51.1 ± 18.6 |
| BMD (g/cm^2)                             |     |
| Lumbar spine                             | 0.722 ± 0.146 |
| Proximal femur                           | 0.486 ± 0.114 |
| Lumbar lordosis angle (degrees)          | 23.1 ± 18.6 |
| Lumbo-sacral angle (degrees)             | 25.6 ± 10.0 |
| Steroid usage: number                    | 5/139 |
| Average                                  | 4.4 ± 3.4 |
| Vitamin D usage: number                  | 19/139 |

Values are expressed as number of patients, or mean ± SD with ranges. 1,25(OH)D, 1,25-hydroxyvitamin D3; 25(OH)D; 25-hydroxyvitamin D3; ALP: alkaline phosphatase; AP: antero-posterior; BMD: bone mineral density; Ca: calcium; IP: inorganic phosphorus; P1NP: intact procollagen I N-terminal propeptide; PTH: parathyroid hormone; TRACP5b: tartrate-resistant acid phosphatase 5b.
### Table 2. Univariate logistic regression analysis of lateral curvature.

| Variables                   | Non-curved | Curved | Standardized OR | 95% CI     | P       |
|-----------------------------|------------|--------|-----------------|------------|---------|
| Number                      | 114        | 25     | 3.263           | 1.767–6.024| <0.001  |
| Age (years)                 | 73.8 ± 9.8 | 82.7 ± 6.9 | 3.263 | 1.767–6.024 | <0.001  |
| Laboratory examinations     |            |        |                 |            |         |
| ALP (IU/L)                  | 268 ± 212  | 279 ± 117 | 1.053 | 0.768–1.567 | 0.797   |
| Ca (mg/dL)                  | 9.18 ± 0.31| 9 ± 0.39 | 0.563 | 0.352–0.9   | 0.017   |
| IP (mg/dL)                  | 3.52 ± 0.43| 3.45 ± 0.44 | 0.848 | 0.542–1.325 | 0.468   |
| P1NP (µg/L)                 | 53.3 ± 33.5| 54 ± 34.2 | 1.019 | 0.662–1.57  | 0.93    |
| TRACP5b (mU/dL)             | 280 ± 123  | 280 ± 141 | 1    | 0.648–1.541 | 0.999   |
| Homocysteine (nmol/mL)      | 9.0 ± 3.4  | 14.3 ± 11 | 2.606 | 1.479–4.592 | 0.005   |
| Intact PTH (pg/mL)          | 41.6 ± 18  | 55.0 ± 25.9 | 1.792 | 1.197–2.682 | <0.001  |
| 25(OH)D (ng/mL)             | 24 ± 8     | 16.4 ± 6.5 | 0.263 | 0.135–0.512 | <0.001  |
| BMD (g/cm²)                 | 51.9 ± 19.1| 47.4 ± 16.1 | 0.767 | 0.475–1.239 | 0.279   |

Values are expressed as number of patients, or mean ± SD with ranges.

1,25(OH)D: 1,25-dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D; ALP: alkaline phosphatase; BMD: bone mineral density; Ca: calcium; IP: inorganic phosphorus; OR: odds ratio; P1NP: intact procollagen I N-terminal propeptide; PTH: intact parathyroid hormone; TRACP5b: tartrate-resistant acid phosphatase 5b.

### Table 3. Univariate logistic regression analysis of anterior curvature.

| Variables                   | Non-curved | Curved | Standardized OR | 95% CI     | P       |
|-----------------------------|------------|--------|-----------------|------------|---------|
| Number                      | 120        | 19     | 5.413           | 2.391–12.26| <0.001  |
| Age (years)                 | 73.9 ± 9.7 | 84.9 ± 5.4 | 5.413 | 2.391–12.26 | <0.001  |
| Laboratory examinations     |            |        |                 |            |         |
| ALP (IU/L)                  | 252 ± 135  | 381 ± 404 | 1.546 | 0.990–2.415 | 0.055   |
| Ca (mg/dL)                  | 9.18 ± 0.31| 9 ± 0.43 | 0.573 | 0.342–0.962 | 0.036   |
| IP (mg/dL)                  | 3.52 ± 0.43| 3.41 ± 0.44 | 0.754 | 0.451–1.258 | 0.279   |
| Pentosidine (µg/mL)         | 53.3 ± 33.1| 54.6 ± 37.2 | 1.045 | 0.644–1.686 | 0.872   |
| Homocysteine (nmol/mL)      | 9.6 ± 5.8  | 11.9 ± 6.4 | 1.317 | 0.895–1.938 | 0.163   |
| Intact PTH (pg/mL)          | 279 ± 120  | 285 ± 159 | 1.045 | 0.648–1.686 | 0.856   |
| 25(OH)D (ng/mL)             | 23.6 ± 8.1 | 16.8 ± 6.6 | 0.328 | 0.166–0.649 | 0.001   |
| BMD (g/cm²)                 | 51.3 ± 19.1| 49.3 ± 15.2 | 0.893 | 0.537–1.486 | 0.189   |

Values are expressed as number of patients, or mean ± SD with ranges.

### Table 4. Multivariate logistic regression analysis of lateral curvature.

| Variables                   | Standardized OR | 95% CI     | P       |
|-----------------------------|-----------------|------------|---------|
| Age (years)                 | 2.312           | 1.142–4.681| 0.02    |
| Laboratory examinations     |                 |            |         |
| Ca (mg/dL)                  | 0.649           | 0.344–1.223| 0.187   |
| IP (mg/dL)                  | 1.445           | 0.833–2.509| 0.193   |
| Homocysteine (nmol/mL)      | 1.202           | 0.749–1.928| 0.444   |
| Intact PTH (pg/mL)          | 1.209           | 0.713–2.050| 0.479   |
| 25(OH)D (ng/mL)             | 0.776           | 0.426–1.414| 0.004   |
| BMD (g/cm²)                 | 0.776           | 0.426–1.414| 0.404   |

Values are expressed as number of patients, or mean ± SD with ranges.

### Table 5. Multivariate logistic regression analysis of anterior curvature.

| Variables                   | Standardized OR | 95% CI     | P       |
|-----------------------------|-----------------|------------|---------|
| Age (years)                 | 4.472           | 1.770–11.3 | 0.002   |
| Laboratory examinations     |                 |            |         |
| Ca (mg/dL)                  | 0.65            | 0.331–1.378| 0.187   |
| Pentosidine (µg/mL)         | 1.551           | 0.926–2.596| 0.096   |
| Intact PTH (pg/mL)          | 1.145           | 0.658–1.994| 0.632   |
| 25(OH)D (ng/mL)             | 0.385           | 0.165–0.898| 0.027   |
| BMD (g/cm²)                 | 1.111           | 0.564–2.19 | 0.763   |

Values are expressed as number of patients, or mean ± SD with ranges.

1,25(OH)D: 1,25-dihydroxyvitamin D; 25(OH)D: 25-hydroxyvitamin D; ALP: alkaline phosphatase; BMD: bone mineral density; Ca: calcium; IP: inorganic phosphorus; OR: odds ratio; P1NP: intact procollagen I N-terminal propeptide; PTH: intact parathyroid hormone; TRACP5b: tartrate-resistant acid phosphatase 5b.
markedly transverse in its orientation, although it may become oblique as it progresses medially across the femur; 3) complete fracture extends through both cortices and may be associated with a medial spike, whereas incomplete fracture only involves the lateral cortex; 4) the fracture is not comminuted or is minimally comminuted; and 5) localized periosteal or endosteal thickening of the lateral cortex is comminuted or is minimally comminuted; and 5) localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site (‘beaking’ or ‘flaring’) (4). We previously reported a case of osteomalacia with marked femoral curvature being consistent with the AFF definition (11).

Although plain radiographs showed areas of endosteal thickening and horizontal lines resembling fractures over the outer cortical bones of the femoral diaphysis in this case, these constituted a Looser zone, a conventional X-ray sign of osteomalacia. Osteomalacia not only affects the femoral curvature, considered as one of the causes of AFF, but it may also have been present in previously reported AFF cases with femoral curvature.

Saita et al. reported that the fracture sites of AFF are associated with weight-bearing lower limb alignment (12), and we assumed that posture also affected it. Spino-pelvic alignment of lumbar kyphosis with posterior pelvic tilt on standing requires hip joint extension, knee joint flexion, and ankle joint dorsiflexion to maintain postural balance. Thus, the femur is positioned obliquely to the ground, not vertically, and excessive muscular force on the thigh may be required. Although we considered that an increased load on the thigh might cause a curved femur, we could not show any relation between the curved femur and posture change, such as lumbar kyphosis and pelvic tilt.

Bone quality markers, such as pentosidine and homocysteine, can be used to evaluate the deterioration of bone collagen indirectly (13). Deterioration of bone collagen causes a deterioration of bone quality, and the bone strength also declines. We suspected that bone quality affects femoral curvature, but we were unable to demonstrate such a relation. Saita et al. indicated that steroid use may be related to AFF (14), and we could also consider the influence of bone quality. Although there was no relation between the presence of curved femur and steroid usage in this study (Tables 2 and 3), we could not sufficiently evaluate this because steroid users only numbered 5 people. We have to perform further detailed studies with a larger number of patients treated with steroids.

In conclusion, to the best of our knowledge, the present study is the first to examine the influence of factors related to bone metabolism and posture on the development of femoral curvature in elderly women. Such curvatures were strongly influenced by low serum vitamin D concentrations.

Disclosure statement
The authors report no conflicts of interest.

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