Atypical femoral shaft fractures secondary to long-term bisphosphonate therapy

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ARTICLE INFO

Article history:
Received 28 December 2016
Accepted 6 January 2017
Available online xxx

Keywords:
Atypical femoral fracture
Bisphosphonate
Femoral shaft fracture
Adverse effects
Stress reaction

ABSTRACT

Background: Bisphosphonates (BPs) are one of the most commonly used agents in the treatment of post-menopausal osteoporosis and other metabolic bone diseases.1–3 These agents are potent inhibitors of bone resorption and exert their effects by reducing the osteoclast activity and increasing apoptosis.1–3 To date, several comparative studies have shown that BPs are effective, safe and well tolerated.1,3,4

Although short-term efficacy and safety of these agents are well established, there are some concerns regarding their long-term adverse effects.5–11 It has been suggested that long-term BP therapy eventually impairs the ability of bone to remodel, leading to the accumulation of micro-damage and diminution of bone strength.7,12

Several studies on long-term BP therapy-induced spontaneous femoral fractures have been published in the recent years.5,9,11,13–15 In 2005, after the initial report on this subject by Odvina,6 several authors established the relationship between long-term alendronate treatment and atypical femoral fractures and suggested an over-suppression of bone restoration in the underlying pathogenesis.5,9,11–15 Some authors advocated that over-suppression halted the osteoclastic activity, a process for the daily repair of micro-traumas, and led to stress fractures.5,16 As aforementioned, the common characteristic is the presence of prodromal pain before the fracture formation in the thigh region without an injury with a subtrochanteric/diaphyseal transverse or short oblique complete or incomplete non-commminated fracture line with focal lateral cortical thickening and beaking of the cortex on one side, as evidenced by the imaging studies.5,6,17–20

In this study, we aimed to evaluate the clinical and radiological outcomes of atypical femoral shaft fractures secondary to long-term BP therapy in post-menopausal osteoporotic women.

1. Introduction

Bisphosphonates (BPs) are one of the most commonly used agents in the treatment of post-menopausal osteoporosis and other metabolic bone diseases.1–3 These agents are potent inhibitors of bone resorption and exert their effects by reducing the osteoclast activity and increasing apoptosis.1–3

Methods: Between 2010 and 2015, data of 22 osteoporotic women with femoral fractures due to low-energy trauma who received BPs previously were analysed.

Results: The mean duration of BP therapy was 7.6 years. The mean duration of union was 7.4 months. Five patients had non-union. Stress reaction was observed in the contralateral femur in 11 patients.

Conclusion: Radiographic studies should be performed on a regular basis to prevent atypical femoral fractures in patients on long-term BP therapy.

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Bone mineral density (BMD) values were calculated within the first week postoperatively from healthy hip images obtained by dual-energy X-ray absorptiometry (DEXA; QDR 4500 DXA System; Hologic, Bedford, USA). Femoral fractures were evaluated using imaging studies.

Stress reactions and fracture healing were assessed by an independent observer. Radiographic healing was defined as callus bridging of three of four cortices on anteroposterior and lateral radiographs, as well as painless weight bearing on the affected extremity.

The femoral shaft fractures were treated with antegrade, locked and reamed intra-medullary (IM) nailing through the piriformis fossa in all patients. Open reduction was performed in 21 femurs, while IM nailing was performed with close reduction in five femurs. The study was approved by our Institutional Review Board, and all patients provided informed consent.

3. Results

The mean age of the subjects was 73 years (range, 51–85 years). The mean duration of BP therapy was 7.6 years (range, 4–15 years). The BPs used varied, including ibandronate in eight patients and alendronate in 14 patients. All patients suffered from pain radiating to the anterior thigh and groin during walking, in particular, and relieving with the use of non-steroidal anti-inflammatory drugs 7 days to 8 months before the fracture formation. The mean (±SD) lumbar spine T-score was 3.0 ± 1.0. The mean femoral neck BMD T-score was 2.7 ± 0.9. The mean length of hospital stay was 4.5 days (range, 3–10 days).

Stress reactions of all femurs were assessed. Eleven patients (50%) with localised cortical thickening of the femoral shaft or lateral subtrochanter with lateral bowing and incomplete transverse or oblique atypical femoral fractures were recommended prophylactic IM nailing; however, only one patient with prodromal pain underwent the procedure (Figs. 2 and 3). Four of the remaining patients (18.1%) with contralateral femoral shaft fractures underwent IM nailing 18.2 months (range, 14–26 months) after the first fracture formation.

The mean duration of union was 7.4 months (range, 4–12 months). Five patients had non-union. One of them underwent a thicker reamed IM nailing with autografting, and union was achieved 8 months later. Two patients refused a repeat surgery. The remaining two patients underwent hemiarthroplasty for femoral head fracture on the same side, removing the IM nails 1 year after the femoral shaft fracture. Non-union femoral shaft fractures were treated with grafting and plate osteosynthesis. Union was achieved 16 months later in these patients.

Calcium, phosphate and creatinine levels were normal in all patients. However, alkaline phosphatase levels slightly increased in four patients, and parathyroid hormone levels slightly increased in three patients. In addition, six patients had vitamin D deficiency.

4. Discussion

Although the exact epidemiology and pathogenesis of atypical femoral fractures secondary to long-term BP therapy remain unclear, a possible imbalance between femoral bone resorption and bone formation has been suggested as an underlying mechanism. Over-suppression of the cortical bone turnover, which has already low remodelling, has been proposed to impair the removal function of the micro-damages.

Several studies have demonstrated over-suppression of bone resorption in bone biopsy specimens collected from patients with femoral fractures who were using BP therapy.

In an experimental animal model study, the mechanical strength of bones with normal bone density was shown to be reduced after receiving alendronate therapy. Another study reported that long-term BP therapy inhibited bone turnover in the majority of patients, as confirmed by bone biopsy analysis.

Although BPs have been shown to be effective in preventing osteoporotic fractures, the incidence of stress fracture formation was found to be 1:1000 among patients receiving BP
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