OTA Highlight Paper

Surgical Treatment Improves Clinical and Functional Outcomes for Patients who Sustain Incomplete Bisphosphonate-Related Femur Fractures

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Abstract:

Objective: To describe the outcomes for patients treated at a single institution, who sustained incomplete bisphosphonate-induced femoral fractures.

Design: Retrospective Review

Setting: University based academic medical center

Patients/Participants: Thirty-one patients with 43 incomplete fractures met inclusion criteria.

Intervention: Non-operative management or surgical intervention for fractures with refractory symptoms or progression of fracture lucency on radiographs.

Main Outcome Measurements: Radiographic assessments and the Short Musculoskeletal Functional Assessment to gauge functional status.

Results: The cohort was all women with an average age of 69.2 (range: 46 to 92 years) and had been treated with bisphosphonate therapy for an average of 9.1 years (range: 5 to 20 years). The average healing time for all incomplete fractures was 9.4 months (range: 1.5 to 36 months). Forty-nine percent of fractures (21/43 fractures) were ultimately treated with surgery for impending complete fracture or failure of nonsurgical management. Of the incomplete fractures treated with surgery, 81% became pain free and 100% were radiographically healed at a mean 7.1 months (range: 1.5-12 months). In contrast, of the non-operatively treated incomplete fractures, only 64% were pain free at latest follow-up with only 18% of fractures demonstrating radiographic evidence of healing at an average of 11 months (range: 6 to 24 months). Standardized dysfunction index from the SMFA was better (19.7) in the surgical group than in the non-surgical group (19.7 Vs. 25.7, p=0.0017).
Conclusions: A higher percentage of patients treated surgically became asymptomatic and demonstrated radiographic evidence of healing earlier than those treated non-surgically. Surgical intervention is effective for relief of symptoms when treating incomplete bisphosphonate-related femur fractures, and patients should be counseled to the potential benefits of prophylactic surgery.

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

Introduction

Osteoporosis is a major health problem, causing nearly 50% of women and 25% of men older than 50 years of age to sustain an osteoporosis-related fracture.\(^1\)\(^2\) Alendronate therapy was first approved for the prevention of osteoporotic fractures by the USA Food and Drug Administration in 1995.\(^3\) Alendronate is a second-generation bisphosphonate that interferes with protein prenylation and inhibits the mevalonate pathway of cholesterol synthesis to induce osteoclast apoptosis, thus inhibiting osteoclast function.\(^1\)\(^4\) As such, it decreases biomechanical markers of bone resorption and increases bone mineralization, with a consistent increase in BMD of 5% to 8% in the lumbar spine and upper femur over 3 years.\(^1\)\(^4\) Bisphosphonates have become a treatment of choice, with decreased fracture rates and prevention of postmenopausal bone loss.\(^4\)

There have been several reports in recent literature suggesting a correlation between long-term bisphosphonate therapy and the development of atypical subtrochanteric and diaphyseal femoral fractures.\(^5\)\(^6\) This may be explained by chronic bone turnover suppression which produces hypermineralized bone that is brittle and susceptible to fracture following low-energy trauma.\(^1\) The association is now well recognized but since only a small subset of patients is affected, bisphosphonates continue to be the mainstay of treatment in the management of
osteoporosis.\textsuperscript{7,8} When a patient presents with a complete, bisphosphonate related femur fracture, the treatment is surgical, most commonly with an intramedullary nail (IMN). Treatment of incomplete bisphosphonate-related femur fractures is underreported in the literature and there is currently no standard protocol for treatment. The purpose of this study is to describe the ultimate outcomes for patients treated at a single institution, for incomplete bisphosphonate induced femoral fractures.

**Patients and Methods:**

This study was approved by the Institutional Review Board and informed consent was waived for this retrospective HIPAA-compliant study. Between 2004 and 2011, 68 patients with 101 femur fractures were identified as having radiographic findings consistent with complete or incomplete bisphosphonate-related femur fractures and were enrolled in our database. Inclusion criteria for this study were the following: 1. Incomplete bisphosphonate related femur fracture, as defined on radiographs, 2. Initial non-operative treatment for the incomplete fracture and 3. Clinical follow up for at least one year after initial diagnosis of incomplete femur fracture.

Incomplete fractures were defined by a pattern of focal lateral cortical thickening on radiographs, with or without, obvious incomplete fracture line (Figure 1). Initial non-operative treatment if chosen, included discontinuation of bisphosphonate therapy at time of presentation, protected weightbearing, and, if indicated, use of an external bone stimulator. Patients who experienced refractory pain during non-operative treatment and did not wish to pursue surgical intervention were indicated for bone stimulators, at the surgeon’s discretion. Some patients were also treated with Teriparatide (Eli Lilly, Indianapolis In) based upon referral to an endocrinologist. A subset of incomplete fractures were identified in patients who presented with a contralateral complete, displaced fracture and underwent IM nailing of the incomplete fracture, despite presence or
absence of symptoms, because they were felt to be at high risk for subsequent displacement. There was no protocol or algorithm used to determine a specific time frame to demonstrate response to nonoperative treatment. The trial of nonoperative care was determined at surgeons’ discretion and by the amount and duration of pain symptoms that the patient reported. Subsequent surgical treatment with intramedullary nailing was indicated for patients with refractory features such as persistent thigh pain or progression of fracture lucency on follow up radiographs, despite nonsurgical treatment. Persistent thigh pain was documented in patients who consistently reported pain or aches in the thigh at follow up visits. When indicated, the surgery was performed, based on a mutual decision between the orthopaedic surgeon and the patient, following a thorough conversation regarding the risks and benefits of surgery versus continued nonoperative care. Patients with asymptomatic incomplete femur fractures, patients with any improvement in thigh pain and those who did not wish to consider surgical intervention continued to be followed with conservative non-operative management.

A cephalomedullary IMN was utilized in all patients who underwent surgery, with the exception of one patient with one fracture who was treated with a plate and screws due to the presence of a femoral prosthesis from a previous total hip replacement. Surgeries were performed on a radiolucent flat or fracture table. The nails were inserted closed and locked with a large lag screw placed into the femoral head and neck. Distal locking screws were utilized at surgeon discretion. All patients were allowed to be weightbearing as tolerated. The treating surgeons followed all patients at standard follow up intervals for fracture healing of 6 weeks, 3 months, 6 months, and one year.

Radiographic healing was documented as loss of fracture lucency (if previously present) on standard AP and lateral femoral radiographs taken at standard follow up intervals, while
clinical healing was documented as absence of pain (in those who presented without fracture lucency) and or loss of fracture lucency on radiographs. Patient demographics, initial radiographic diagnosis, treatment modality, and time to healing were extracted from the medical records. Patients’ self-reported functional status was retrospectively documented at a mean 26.9 months post presentation with the Short Musculoskeletal Functional Assessment (SMFA).

Patients with surgically treated fractures that had not yet reached the one-year follow up interval were excluded from functional analysis. Functional status and clinical data were analyzed by Student’s T-test and Fisher’s exact test.

Source of Funding:

There was no external funding source for this investigation.

Results:

Of the 68 patients identified as having a bisphosphonate related atypical femur fracture, 42 patients with 54 incomplete fractures were identified. (Figure 2) Radiographs of all 54 fractures demonstrated presence of focal cortical thickening, with or without an incomplete fracture line, consistent with our definition of incomplete fractures. Twenty-nine patients were radiographed bilaterally, and 28 patients presented with contralateral femoral pain or fracture.

Of these 42 patients with 54 fractures, a subset of eight patients with eight fractures went on to complete fractures during nonoperative care phase. Three of these patients had sustained a complete bisphosphonate-related femur fracture on the contralateral side prior to completing their fractures. All three went on to complete fractures within the first 6 months of non-operative treatment. Of the remaining five patients in this subset, 2 fractured within the first 6 months of
non-operative treatment, while 3 fractured after more than one year. This subset of 8 patients was
excluded from further analysis to eliminate the contribution of displaced fractures to the outcome
measures. Of the remaining 34 patients with 46 fractures, 3 patients with 3 fractures did not meet
the inclusion criteria because they had not yet reached the one year follow up and were also
excluded from further analysis.

Our final patient cohort included 31 patients with 43 incomplete fractures (12 were
bilateral). (Figure 2) All 31 patients were women with an average age of 69.2 years (range: 46 to
92) and had been on bisphosphonate therapy for an average of 9.1 years (range: 5 to 20 years).
Thirteen of these patients presented with a complete bisphosphonate-related femur fracture on
the contralateral side that underwent repair. Of these 13 patients, 3 underwent immediate surgery
for the incomplete side based upon patient and surgeon preference due to the presence of a
contralateral completed fracture. All of the remaining 28 patients with 40 fractures were given a
trial of non-operative management prior to making a decision for surgery or continuing non-
operative management.

Sixteen patients with eighteen fractures were eventually treated with surgery for pain
refractory to nonsurgical management. Including the 3 patients with 3 fractures who underwent
immediate surgery, forty-nine percent of fractures (21/43) were ultimately treated with surgery.
All fractures were treated with an intramedullary implant, with the exception of one that was
treated with a plate and screws due to presence of a femoral prosthesis from a previous total hip
replacement (Figure 3). Of the 19 patients with 21 surgically treated fractures, 15 patients with
17 fractures (81%; 17/21 fractures) became pain free. One hundred percent of surgically treated
fractures (21/21 fractures) were radiographically united at a mean 7.1 months (range: 1.5-12
months). One fracture in one patient failed to unite following surgery and remained symptomatic
but united seven months status-post exchange nailing with bone graft. One patient developed a trochanteric bursitis that was successfully treated with a cortisone injection. There were no other reported complications.

Eighteen patients with 22 fractures were definitively treated non-operatively. In contrast, only 12 patients with 14 fractures (64%; 14/22 fractures) were pain free at latest follow up with only 18% of fractures (4/22) showing radiographic evidence of healing at an average of 11 months (range: 6 to 24 months).

The average healing time for all incomplete fractures was 9.4 months (range: 1.5 to 36 months). Patients were assessed at a mean 26.9 months using the Short Musculoskeletal Functional Assessment to gauge baseline as well as post-intervention functional status. Standardized dysfunction index from the SMFA was 19.7 in the surgical group and 25.7 in the non-surgical group (p=0.0017).

Discussion:

Osteoporosis affects 13% to 18% of women in the United States and is a major health concern in the elderly population. Available treatment options include bisphosphonates, estrogen, estrogen receptor modulators, Teriparatide and Denosumab (Amgen, Thousand Oaks Ca). Bisphosphonate therapy has been widely used as a treatment for osteoporotic patients because of its effectiveness in reducing the risk of fractures. Bisphosphonates are unique in their pharmacological properties, which include prolonged suppression of bone turnover and suppression of osteoclastic activity. Long-term bisphosphonate therapy potentially impairs
the ability of the bone to remodel, causing an accumulation of microdamage and compromised bone strength.\textsuperscript{14-15}

Recent articles and case reports in the literature have detailed several additional negative effects, such as osteonecrosis of the jaw and low-energy non-vertebral fractures.\textsuperscript{16} The latter has become heavily focused on, as the incidence of bisphosphonate-related femur fractures continues to increase. This association is interesting, as subtrochanteric or femoral shaft fractures are relatively uncommon and only represent 10\% to 30\% of all hip and femur fractures\textsuperscript{16}.

Furthermore, although increased risk of fractures is commonly associated with osteoporosis, the atypical femoral fractures sustained by osteoporotic patients who have been treated with bisphosphonates occur spontaneously or with minimal trauma.\textsuperscript{17}

In a study of non-operative versus prophylactic treatment of bisphosphonate-associated femoral stress fractures, Banffy et al. emphasized the importance of orthopaedic surgeons recognizing incomplete bisphosphonate-related femur fractures.\textsuperscript{18} Incomplete fractures often resemble stress or insufficiency fractures and may be missed clinically and radiographically.\textsuperscript{9}

Radiographs of patients who have been treated with bisphosphonates for five years or longer and have sustained low-energy subtrochanteric and diaphyseal femoral fractures show characteristic imaging features such as focal lateral cortical thickening or transverse orientation of the proximal femoral fracture line. If displaced, a medial cortical spike or beak, superior displacement of the distal fragment, and varus angulation at the fracture site are seen.\textsuperscript{9}

Wang et al reported a study of 8 patients that suggested that prodromal thigh pain may serve as an indicator of impending fracture. We found that prodromal thigh pain is a characteristic symptom of most patients with incomplete bisphosphonate-related femur fractures.
and may be helpful in identifying these fractures in osteoporotic patients who have been on long-term bisphosphonate therapy

Following surgical intervention, 81% of our cohort became asymptomatic and 84% reported a return to baseline functional status. Relief of symptoms was consistent with radiographic and clinical healing. Of those treated with non-operative management, a significant proportion eventually went on to fracture completion. A lower percentage of non-operatively treated incomplete fractures ultimately became asymptomatic when compared to those treated with surgery. These findings suggest that surgical treatment, in these cases with intramedullary nailing for the most part, improves clinical and functional outcomes for patients who have sustained incomplete bisphosphonate related femur fractures. Our results corroborate those of Banffy et al. who suggest that non-operative management of bisphosphonate-associated stress fractures has a high likelihood of failure with the majority of fractures progressing to fracture completion.\(^{18}\)

There are several limitations to our study that are inherent in a retrospective case series. Despite our many attempts to obtain complete data on all of the patients included in this study, limited data was available in some patients on various clinical indices, with some information such as serum vitamin D levels and bone densitometry scores incomplete. It therefore remains unclear whether other factors may have contributed to our observed functional results. In addition, failure of non-operative management to resolve symptoms and the need for surgical intervention were not determined using a standard protocol or algorithm, but were established as a result of a thorough conversation regarding the risks and benefits of surgery as well as a mutual decision between the orthopaedic surgeon and the patient. Furthermore, the effectiveness of specific nonoperative interventions such as Teriperatide administration or bone stimulator usage
are unable to be assessed. A small number of patients were treated with Teriparatide based upon referral to an endocrinologist. With this small series of patients, it is difficult to determine the effect if any of the administration of this medication. Finally, there is a subset of patients who sustained bilateral fractures and had operative treatment on one side and operative or non-operative treatment on the other side. The SFMA is not able to distinguish the contribution of either side to the ultimate outcome. However, since these bilateral cases make up a large proportion of cases, their exclusion would potentially diminish the value of our results.

Our findings and the results of several studies reported in literature corroborate an association between long-term bisphosphonate therapy and low-energy femur fractures that is now accepted.\(^8\) We feel additional prospective large-scale trials are needed to evaluate the effects of both nonoperative modalities and surgery on patient outcomes.\(^{19-21}\) Therefore, we cannot recommend that all incomplete bisphosphonate-related femur fractures should be initially treated surgically. Non-operative treatment with partial weightbearing and cessation of bisphosphonates has proven effective in some patient cohorts, and in a proportion of our own patients who were treated.\(^{22}\) Patients who have persistent pain refractory to non-operative treatment or progressive radiographic lesions, however, should be advised to the potential benefits of prophylactic surgery as a treatment modality for incomplete bisphosphonate-related femur fractures.

In conclusion, while bisphosphonate therapy continues to be an important tool in the fight against osteoporosis, and particularly against vertebral fractures and typical hip fractures, its long-term use is not without risk in a small number of patients. We found that nearly half of the patients with incomplete bisphosphonate related femoral fractures who presented to our institution for care ultimately required surgical intervention for relief of symptoms. At an average of 26.9 months, patients who had IMN surgery reported significantly better functional
outcomes according to the SMFA, and clinical outcomes supported radiographic findings and physical signs of healing. Even with identification of this lesion and steps taken to manage the condition there was still a 15% risk of incomplete to complete progression. Considering this risk, as well as the improved clinical and functional outcomes for patients who were surgically treated for incomplete bisphosphonate related femur fractures, surgical intervention appears to be an effective treatment modality for relief of symptoms when treating incomplete bisphosphonate related femur fractures and patients should be advised to the potential benefits of prophylactic surgery.
References:


FIGURES

289 Figure 1. (a) AP radiograph of an 80-year-old woman treated with bisphosphonate therapy for 10 years. (b) Magnified view of AP radiograph showing incomplete fracture, defined by a pattern of focal lateral cortical thickening with or without an obvious fracture line.

290 Figure 2. Flowchart depicting the ultimate fate of the original patient cohort.

291 Figure 3. (a) AP radiograph at presentation, with focal lateral cortical thickening and a fracture line characteristic of incomplete bisphosphonate-related femur fractures. (b) Radiograph seven months status post intramedullary fixation shows complete disappearance of the fracture line consistent with healing.
Total
68 Patients
101 Fractures

Complete*
40 Patients
47 Fractures

Progressed to Complete
8 Patients
8 Fractures

Not yet 6 month follow up
3 Patients
3 Fractures

Incomplete
42 Patients
54 Fractures

Incomplete
34 Patients
46 Fractures

Incomplete
31 Patients (12 Bilat)
43 Fractures

Non-Operative Treatment
18 Patients
22 Fractures

Surgical Treatment
19 Patients
21 Fractures

*Some patients presented with bilateral incomplete and complete femoral fractures.