The effects of biphosphonate use in the healing of hip fractures: A systematic review

Dimitrios G. Begkas

Private Orthopaedic Surgeon, 21 Saronikou Str., Ilioupolis, 16345, Athens, Greece

Abstract

Hip fractures are serious fractures in the upper quarter of the femur bone. The underlying cause of most of them is osteoporosis. Biphosphonates are the most commonly prescribed drugs used to treat osteoporosis worldwide. However, there are concerns as to whether their use can cause problems with the healing of hip fractures and if so, is the timing of their initiation and the duration of their application important? The purpose of this systematic review was to answer the above questions. A literature search was conducted, with the use of the PubMed, Google Scholar and Cochrane databases. The abstracts of all potentially relevant studies, were extensively examined. All of them referred to the biphosphonate treatment, the duration of healing and/or the non-union rates of hip fractures, were included to the study. Biphosphonates, were found to affect hip fracture healing, when applied prior to the fracture and to have no effect on healing process, when applied after the fracture event. There was no statistically significant correlation between treatment duration and union time. There is a need of additional studies to investigate the effects of biphosphonates on hip fracture healing. These studies need to be focused on healing time, non-union rates and the duration of treatment.

Keywords: Hip fracture, Biphosphonates, Union, Non-union, Fracture healing

Introduction

Hip fractures are serious fractures in the upper quarter of the femur bone. Their presence is related to the increase of age, with most cases occurring in people over 75 years old (y.o)\(^1\). Falling, poor vision, weight and height are all seen as risk factors. They are classified as intracapsular and extracapsular. In intracapsular hip fractures belong the fractures of the femoral head and those of the femoral neck (subcapital, transcervical and basicervical). In extracapsular hip fractures belong intertrochanteric and subtrochanteric fractures\(^2\). Their diagnosis is generally made by clinical examination and imaging tests\(^3\). Most of them are treated surgically by implanting anorthosis. Non-operative treatment is applied in very rare cases\(^1\). Hip fractures and hip surgery can lead to a large number of complications such as nonunion, malunion, avascular necrosis, wound infections, implant failure, deep venous thrombosis (DVT), pulmonary embolism, heart attack, stroke, chest and urinary tract infections and pressure sores on the sacrum and heels\(^4\).

Patients with hip fractures are at high risk for future fractures including hip (mainly), wrist, shoulder and spine. The underlying cause of most of these fractures is osteoporosis, thus after treatment of the acute fracture, patients must receive work up and treatment for it. Current treatment standards include the starting of a biphosphonate. Biphosphonates are a class of drugs that prevent bone mass loss. They are the most commonly prescribed drugs used to treat osteoporosis worldwide\(^5\). Evidence shows that they reduce risk of fractures in postmenopausal women with osteoporosis\(^5-7\). They are accumulated in high concentration in bone (preferentially into sites with high turnover rates) due to their binding affinity to hydroxyapatite crystals, inhibiting crystal breakdown and suppressing bone resorption\(^8\). Of the biphosphonate that is resorbed (orally or intravenously), about 50% is excreted unchanged by kidney and the remainder is absorbed onto bone surface\(^9\). Long-term treatment with biphosphonates produces anti-fracture effects. There is a need of additional studies to investigate the effects of biphosphonates on hip fracture healing. These studies need to be focused on healing time, non-union rates and the duration of treatment.
and mineral density effects that persist for 3-5 years, after an initial 3-5 years of treatment. After five years of medications by mouth or three years intravenously, among those of low risk, biphosphonate treatment can be stopped. In those at higher risk, ten years of medications orally or six years intravenously may be used.

Generally, biphosphonates are drugs that are well tolerated by the vast majority of patients, and evidence shows that are relatively safe. Adverse effects include gastritis, esophagitis, musculoskeletal pain and there are also recent studies that report them as a risk factor for atrial fibrillation in women. Other reported complications are osteonecrosis of the jaw and atypical fragility fractures of the femoral shaft (diaphyseal or subtrochanteric) and neck. However, there are concerns as to whether the use of bisphosphonates can cause problems with the healing of hip fractures and if so, is the timing of their initiation and the duration of their application important? The purpose of this systematic review was to answer the above questions.

**Literature search**

A literature search was conducted during the first week of April of 2016, with the use of the PubMed, Google Scholar and Cochrane databases. The keywords that we used were: biphosphonates and hip fracture healing, biphosphonates and hip fracture union, alendronate and hip fracture healing, alendronate and hip fracture union, risendronate and hip fracture healing, risendronate and hip fracture union. All abstracts found with the aforementioned keywords, were examined whether they were relevant to the aim of this review. From the study were excluded articles that were not written in English, when the full text was not available and those with patients suffering from bone metastases, hip tumors, multiple myeloma and metabolic diseases other than osteoporosis. The articles that were included in the study, should be referred to treatment with bisphosphonates, to the duration of fracture healing and/or to the non-union rate of the fractures. Healing was defined radiologically, as bridging at the fracture site by a callus or a cortical continuity involving at least three cortices in the hip using anteroposterior and lateral views of the femur and clinically by the ability of the patient to fully bear weight and by the lack of pain at the fracture site.

**Results**

The literature research in PubMed, Google Scholar and Cochrane databases, with the above mentioned keywords, identified 99 potentially relevant articles. After an extensive examination of their abstracts, only seven of them were found to meet the inclusion criteria of the study and were retrieved for further evaluation. The references of these articles were also investigated for other relevant articles, in order to be included in the study. However, there weren’t other that met the inclusion criteria of this review. Therefore, only the aforementioned seven articles were finally included (Figure 1).
There were four retrospective cohort studies, one randomized double blinded controlled trial, one prospective pilot study and one case series study. One of them was of evidence level 1, one of level 2, four of level 3 and one of level 4. The minimum follow-up time for all of the studies was 52 weeks (Table 1). The ethnicity of the patients was specified in two of the seven articles and their race in only one. Their number varied from 1 to 2127 and their mean number per study was 328.1. Of them, 1759 (76.6%) were females and 511 (23.4%) males. Their age varied from 44 years old (y.o.) to 91 y.o. Despite the fact that in one study the age of the patients was not specified, it was mentioned that all of them were over 50 y.o. For the rest six studies, where the data about age were available, the mean of all the average ages was 64.9 y.o (Table 2). In four of the seven articles were reported co-morbidities such as hypertension, coronary artery disease, diabetes mellitus, previous stroke, osteoarthritis, depression, asthma, Adamantiadis-Behcet’s disease, renal transplantation, tobacco and alcohol use.

The types of biphosphonates used and details about their dosage, were specified in four of the seven studies. In five studies the drug was applied before the hip fracture, for a mean time period of 5.8 years (range 3.0 - 8.8 years). In the remaining two studies the biphosphonate was taken after the fracture. In one of these two, the mean duration of application was 3 years and in the other, the drug was applied for more than 1 year, in three different groups of patients according to the timing of its commencement. The types of hip fractures were specified in six studies (Table 3).

All of the fractures were treated surgically, using different operative techniques. Of the five articles, wherein the bisphosphonates had been applied prior to the fracture, only

<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>STUDY TYPE</th>
<th>LEVEL OF EVIDENCE</th>
<th>FOLLOW-UP TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al.</td>
<td>Prospective randomized case study</td>
<td>II</td>
<td>&gt; 12 months</td>
</tr>
<tr>
<td>Lyles et al.</td>
<td>Randomized double blinded controlled trial</td>
<td>I</td>
<td>Median 1.9 years</td>
</tr>
<tr>
<td>Odvina et al.</td>
<td>Case series</td>
<td>IV</td>
<td>Up to 2 years</td>
</tr>
<tr>
<td>Das De et al.</td>
<td>Retrospective cohort study</td>
<td>III</td>
<td>Up to 60 months</td>
</tr>
<tr>
<td>Teo et al.</td>
<td>Retrospective cohort study</td>
<td>III</td>
<td>Mean 21.7 months (range 0-53)</td>
</tr>
<tr>
<td>Prasam et al.</td>
<td>Retrospective case control study</td>
<td>III</td>
<td>Mean 29 months (range 5-60)</td>
</tr>
<tr>
<td>Egol et al.</td>
<td>Retrospective cohort study/case study</td>
<td>III</td>
<td>Mean 33 months (range 6-85)</td>
</tr>
</tbody>
</table>

Table 1. Types of the studies included in the review.

<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>NUMBER OF PATIENTS</th>
<th>AGE (Years)</th>
<th>SEX (Male/Female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al.</td>
<td>Group A: 26</td>
<td>Group A: 75.0 (SD 10.2)</td>
<td>Group A: 7/19</td>
</tr>
<tr>
<td></td>
<td>Group B: 26</td>
<td>Group B: 75.3 (SD 9.9)</td>
<td>Group B: 10/16</td>
</tr>
<tr>
<td></td>
<td>Group C: 25</td>
<td>Group C: 78.1 (SD 9.5)</td>
<td>Group C: 10/15</td>
</tr>
<tr>
<td>Lyles et al.</td>
<td>Total: 2127</td>
<td>Cases: 74.4 ± 9.48</td>
<td>Total: 508/1619</td>
</tr>
<tr>
<td></td>
<td>Cases: 1065</td>
<td>Controls: 74.6 ± 9.86</td>
<td>Cases: 248/817</td>
</tr>
<tr>
<td></td>
<td>Controls: 1062</td>
<td></td>
<td>Controls: 260/802</td>
</tr>
<tr>
<td>Odvina et al.</td>
<td>1</td>
<td>49.0</td>
<td>0/1</td>
</tr>
<tr>
<td>Das De et al.</td>
<td>Total: 20</td>
<td>63.1 (range 44-88)</td>
<td>1/19</td>
</tr>
<tr>
<td></td>
<td>Cases: 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Controls: 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teo et al.</td>
<td>33</td>
<td>67.5 (range 47-91)</td>
<td>0/33</td>
</tr>
<tr>
<td>Prasam et al.</td>
<td>Total: 20</td>
<td>&gt; 50</td>
<td>Cases: 0/12</td>
</tr>
<tr>
<td></td>
<td>Cases: 12</td>
<td></td>
<td>Controls: 0/8</td>
</tr>
<tr>
<td></td>
<td>Controls: 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egol et al.</td>
<td>19*</td>
<td>59.3 (range 46-75)</td>
<td>2/17**</td>
</tr>
</tbody>
</table>

*19 patients with a total number of 25 subtrochanteric fractures. **5 of 17 female patients had bilateral fractures

Table 2. Demographics of the patients.
<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>BIPHOSPHONATE TYPE</th>
<th>DURATION OF BIPHOSPHONATE</th>
<th>FRACTURE TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al.</td>
<td>Risedronate 35 mg/week</td>
<td>Group A: 1 week postoperatively (p.o) *</td>
<td>Intertrochanteric</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group B: 4 weeks p.o*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Group C: 12 weeks p.o*</td>
<td></td>
</tr>
<tr>
<td>Lyles et al.</td>
<td>Zoledronic Acid i.v. within 90 days p.o. and every 12 months after</td>
<td>3 years p.o</td>
<td>Not specified</td>
</tr>
<tr>
<td>Odvina et al.</td>
<td>Alendronate 70 mg/week</td>
<td>3 years pre op.</td>
<td>Subtrochanteric</td>
</tr>
<tr>
<td>Das De et al.</td>
<td>Alendronate (12/20 patients), 70 mg/week</td>
<td>4.6 years pre op.</td>
<td>Subtrochanteric</td>
</tr>
<tr>
<td>Teo et al.</td>
<td>Not specified</td>
<td>4.9 years pre op.</td>
<td>Subtrochanteric</td>
</tr>
<tr>
<td>Prasam et al.</td>
<td>Not specified</td>
<td>Mean 7.6 years (SD: 3.4, range 1-12), preoperatively (pre op.)</td>
<td>Subtrochanteric</td>
</tr>
<tr>
<td>Egol et al.</td>
<td>Not specified</td>
<td>Mean 8.8 years (range 5-20), pre op.</td>
<td>Subtrochanteric</td>
</tr>
</tbody>
</table>

* Continued for ≥1 year after.

Table 3. Biphosphonates and types of fractures.

<table>
<thead>
<tr>
<th>ARTICLE</th>
<th>SURGICAL REPAIR</th>
<th>UNION TIME</th>
<th>DELAYED UNION</th>
<th>NON-UNIONS</th>
<th>IMPLANT FAILURES</th>
<th>REVISION SURGERIES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al.</td>
<td>IMN*/CHS†</td>
<td>Group A: mean 10.7 weeks (SD 4.4)</td>
<td>-</td>
<td>-</td>
<td>6</td>
<td>6 (Bipolar Hemiarthroplasty)</td>
</tr>
<tr>
<td></td>
<td>Group B: mean 12.9 weeks (SD 6.2)</td>
<td>Group C: mean 12.3 weeks (SD 7.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyles et al.</td>
<td>Not specified</td>
<td>Not specified</td>
<td>Incidence</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cases: 34 (3.2%)</td>
<td></td>
<td>Controls: 29 (2.7%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(risk ratio for Zoledronic Acid group: 1.17; 95 CI: 0.72 to 1.90; P=0.61)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Odvina et al.</td>
<td>Plate fixation &amp; Bone graft</td>
<td>-</td>
<td>1 (2 years)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Das De et al.</td>
<td>IMN/EM‡</td>
<td>Not specified</td>
<td>-</td>
<td></td>
<td>Total: 3 Cases: 2 Controls: 1</td>
<td>1 (Cases)</td>
</tr>
<tr>
<td></td>
<td>Cases: 6/6</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Controls: 0/6</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teo et al.</td>
<td>DCS§: 10</td>
<td>10 months</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>DHS§: 8</td>
<td>(2.2 to 27.5); ICC of 0.9; (95 CI: 0.91 to 0.98)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasam et al.</td>
<td>IMN &amp; Plate fixation</td>
<td>Cases: mean 26 weeks</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Controls: mean 19 weeks</td>
<td></td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egol et al.</td>
<td>IMN</td>
<td>Mean 8.3 months (2-18)</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>


Table 4. Surgical repair, union time, delayed union, non-unions, implant failures, revision surgeries.
three presented the mean time of fracture union. In one of them, there were four cases of delayed fracture healing. Four of the five articles, reported the number of the non-unions and two, the cases that the implants failed. One of the two articles, wherein the bisphosphonates were taken after the fracture event, was mentioned in the time of fracture union. The second one, reported only the incidence of delayed fracture healing (Table 4).

**Discussion**

Hip fractures are associated with increased morbidity, functional decline, and death in older adults, as well as increased use of health care services. Mortality is increased in the year after the hip fracture, with reported rates of 15 to 25% and an estimated 9 excess deaths per 100 patients among women 70 years of age or older. Falling from standing height is the most common risk factor (approximately 90% of hip fractures). A hip fracture following a fall is likely to be a pathological fracture. The most common causes of bone fragility are: osteoporosis, other metabolic bone diseases (Paget’s disease, osteogenesis imperfecta, osteomalacia, osteoporosis), primary bone tumors (benign or malignant), metastases, smoking, glucocorticoids, etc. However, data suggest that few patients with hip fractures actually receive pharmacologic therapy for osteoporosis. Bisphosphonates are inhibitors of bone resorption by acting on osteoclastic activity. They are the most commonly used medicaments in osteoporosis treatment. There are two types of bisphosphonates: nitrogen containing and non-nitrogen containing. Both of them inhibit apoptosis of osteocytes and osteoblasts. They are ingested by osteoclasts and they induce them to undergo apoptosis by two different methods. Nitrogen containing bisphosphonates inhibit osteoclast farenysl pyrophosphate synthetase enzyme, required in mevalonate and in that way they inhibit GTPase formation. On the other hand, non-nitrogen containing bisphosphonates form a toxic adenosine triphosphate (ATP) analogue, leading osteoclasts to premature death. Although they are generally safe and effective, they carry the potential risk of over-suppressing bone turnover that can potentially impair some of the biochemical properties of bone. Treatment of patients with osteoporosis using bisphosphonates during fracture healing is controversial because their conflicting anti-osteoclastic action. Osteoclasts are important for remodeling the callus into cortical bone, but bisphosphonates inhibit osteoclast-mediated bone resorption in order to prevent bone loss and improve bone strength. Several articles have addressed the effects of bisphosphonates on animal fracture healing. In experimental animals, they have been shown to inhibit normal repair of micro-damage arising from marked suppression of bone turnover, which, in turn, results in accumulation of micro-damage and inhibiting fracture healing. On the other hand, it has been shown that dogs treated with alendronate during the healing period had delayed callus remodeling, but that there was no adverse effect on the fracture healing.

A lot of studies have raised concerns about the action of bisphosphonates on fracture healing in humans. Rozental et al, compared 43 patients with a fracture of the distal radius, who were taking bisphosphonate, with 153 controls and reported that time to union in the bisphosphonate group was 55 days compared with 49 days in the control group. Solomon et al, found increased relative risk of non-union of humerus fractures associated with bisphosphonate use following the fracture. However, despite the fact that a large number of patients who are receiving bisphosphonates undergo hip fractures, relatively few studies have reported the effects of bisphosphonate use on hip fracture healing.

The purpose of this study was to determine whether the use of bisphosphonates can cause problems in the healing of hip fractures, as well as the importance of the timing of their initiation and of the duration of their application. As mentioned before, the studies that were included in this review can be divided into two groups. The first group contains the studies where the patients were receiving bisphosphonates prior to the hip fracture and the second one the studies where the patients received bisphosphonates after the fracture event. Their results about the effects of bisphosphonates in hip fracture healing differ. In the first group, all of the authors seem to agree that the use of bisphosphonates can affect the healing process. Prasern et al, compared their findings with the findings of similar hip fractures in patients that were not receiving bisphosphonate therapy and they found that hip fractures associated with bisphosphonate intake appeared delayed healing as well as a case of non-union. Ego et al, reported high rates of radiographic healing (98%), but a delay in healing time of hip fractures between patients who were receiving bisphosphonates and those who were not. Das De et al, found a slightly higher incidence of non-union, in patients who sustained subtrochanteric fractures and were using alendronate. Teo et al, observed that when using bisphosphonates, hip fracture healing was slow and patients were subjected to a prolonged period of immobility. Finally, Odvina et al, concluded that alendronate can result in poor healing in that kind of fractures. The findings of this review, for the first group of studies, agree with the results of other studies in the literature, about fracture healing in other body locations, where the bisphosphonates were applied prior to the fracture. However, a case-control study of femur fractures, conducted by Lin et al, showed a difference in the overall weighted mean union time, but difference was not statistically significant. The above disagreement may be explained due to different types of fractures, and the different techniques and implants that were used. In our opinion, this discrepancy underlines the need for further research.

On the other hand, in the second group of studies, authors consider that the application of bisphosphonates after a hip fracture, does not affect the healing process. Kim et al, found that the timing of bisphosphonate therapy after an intertrochanteric fracture, didn’t affect fracture healing or...
the incidence of complications. Lyles et al\textsuperscript{52} did not observe a significant difference in delayed union of fractured bone, between a bisphosphonate treatment group and a control study group. The above results are in agreement with the results of other similar studies, that investigated the effects of bisphosphonate use after the fracture, in the healing of other fracture types\textsuperscript{53-54}.

In both groups of studies, there was no statistically significant correlation between duration of bisphosphonate treatment and union time of hip fractures. This is in contrast with previous studies, for other kinds of fractures, who investigated the association between union and the duration of bisphosphonate therapy. Armamento-Villareal et al\textsuperscript{55}, in their retrospective cohort study looking at low-energy cortical fractures, demonstrated significantly suppressed bone turnover on histological analyses in 15 patients who had consumed bisphosphonates for a mean of 5.7 years (range 2.0-10.0 years). Fourteen patients were exposed to alendronate, and one patient had taken risedronate. Fracture locations included shaft of the femur, rib, metatarsal, pelvis, fibula and ankle. The investigators found that in bone biopsies from patients with suppressed turnover (10 patients, 67%), the mean bisphosphonate use was 6.5 years, whereas in bone biopsies from patients with normal bone turnover (five patients, 33%), the mean bisphosphonate consumption was 3.9 years (p=0.02). The histology of the patients with suppressed bone turnover showed no osteoid lining of the trabeculae, no osteoblasts and no single or double tetracycline labels. Furthermore, the authors found that there were no significant differences in age, body mass index (BMI), bone mineral density (BMD), calcium and vitamin D intake, serum calcium, parathyroid hormone and 25hydroxyvitamin D between patients with normal and suppressed bone turnover. We think that, in the view of the aforementioned study, the correlation between duration of bisphosphonate application and union time of hip fractures is an area that needs to be further explored.

This review has limitations because relatively few studies have been published looking at the effects of bisphosphonates on hip fracture healing. As the majority of the patients were women, some or all of the conclusions of this study may not apply to men. The use of different operative techniques and implants between studies, as well as the presence of comorbidities in some of the patients and the use of other drugs to treat them, perhaps influenced in some way our findings.

In conclusion, in the review of the published literature, it was found that the application of bisphosphonates prior to a hip fracture, can have negative effects on its healing process, but this is not happening if they are applied after the fracture event. It was also found that there is no correlation between duration of bisphosphonate treatment and union time of hip fractures. There is a need of additional studies to investigate the effects of bisphosphonates on hip fracture healing. These studies need to be focused on healing time, non-union rates and the duration of treatment.

References
17. Jacobsen SJ, Goldberg J, Miles TP, Brody JA, Stiers W, Rimm AA. Hip surgery...


52. Prasad ML, Jain N, Hellet DL, Lane JM, Lorch DG. Bisphosphonates and hip fracture healing