Delayed/non-union of upper limb fractures with bisphosphonates: systematic review and recommendations

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Key words
alendronate, diphosphonate, fracture healing, fracture, bone, review.

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Abstract

Background: Bisphosphonates (BPs) are widely used for the treatment of osteoporosis. Oversuppression of bone turnover with BPs may paradoxically limit the reserve capacity of bone to heal. The aim of this review was to study the predisposition of some patients to delayed/non-union of upper limb fractures associated with BPs and give recommendations on how they should be treated.

Methods: A systematic search of two electronic databases was conducted to identify relevant studies for inclusion. All relevant studies found were included and assessed through methodology criteria predetermined by two independent reviewers.

Results: Six papers comprising of three case reports, one nested case control study, one retrospective review and one randomized clinical trial were used. In comparative studies of pre-fracture BP use, a 6-day delay in average healing times was reported among BP users. There was no elevation in risk of non-union. Post-fracture BP use was associated with an approximate doubling of the risk of non-union. Timing of BP therapy initiation following a fracture was not associated with a difference in healing times. An atypical ulna fracture treated conservatively resulted in non-union, there was no effect of type of surgical treatment on distal radius fracture healing and there was insufficient evidence to comment on humeral fracture treatment.

Conclusions: Differences in union time between BP users and non-users are not significant enough to change current practice patterns and do not outweigh the benefits of BP therapy. There is no evidence to encourage early surgical management of BP-related upper limb fractures.

Background

Since its induction in the mid-1990s, bisphosphonate (BP) therapy has become the most widely used method for the treatment of osteoporosis.1–4 Approved for the US market in 1995, more than 150 million prescriptions for oral alendronate, risedronate and ibandronate were dispensed in an outpatient setting from 2005 to 2009 in the United States alone.5–7

BPs decrease the rate of bone resorption, thus increasing bone mineral density and stabilizing osteolytic lesions.5 There are concerns that the use of BPs may impair the ability of bone to heal.2,4 The proposed mechanism involves oversuppression of bone turnover that limits the reserve capacity of bone to repair microdamage.2,3 Animal studies have reported mixed results, with some articles reporting no effect,8,9 delays in fracture healing,10,11 or even enhanced fracture healing.12–16 Most animal studies to date have concluded that while preliminary stages of bone healing may be unaffected, further bone remodelling and callus formation may be interrupted with long-term BP use.17

While much of the literature has focused on delayed healing of the femur, evidence on this phenomenon is limited with regard to bones in the upper limb. Hip fractures account for only one third of total osteoporotic fractures in the elderly. An equal percentage of fractures in this population occur at the proximal humerus and distal radius – fractures for which BP therapy is also prescribed for.18,19 Moreover, the relative risk of sustaining a hip fracture is doubled in the year after a distal radius or proximal humerus fracture.20 These observations highlight the importance of upper limb fractures within the wider context of osteoporosis and BP management.

Few studies have raised the question of a potential predisposition of some patients to delayed and/or non-union of upper limb fractures
associated with BP therapy. To answer this question, we conducted a systematic literature review of reported cases of delayed and/or non-union in the upper limb associated with BP treatment with the aim of giving recommendations on how they should be treated.

**Methods**

**Search strategy**

Our search strategy was based on PRISMA (Preferred Reporting Items for Systematic reviews and Meta-analyses) standards (Fig. 1). The following databases were searched: PubMed (1950–present) and Embase (1947–present). Initial search citation terminology was as follows: ‘Fractures, Bone OR Fracture Healing OR Osteoporotic Fractures AND Diphosphonates OR Alendronate OR Pamidronate’ and ‘fracture OR non-union OR delayed union OR bone healing OR bone union AND bisphosphate OR bisphosphate acid derivative’ for PubMed and Embase, respectively. Search citation terminology was based on a MeSH terms database search provided by each database. ‘Bisphosphonates’ was not an available MeSH search term on PubMed and hence, the most relevant alternatives (‘Diphosphonates’, ‘Alendronate’ and ‘Pamidronate’) were selected. The search was performed on 18 September 2013.

**Eligibility criteria**

We limited our search to studies carried out in humans and of English language only. All print journals, e-published journals, and meeting and/or conference abstracts were eligible for inclusion. Review articles were not eligible for inclusion. We reviewed all case series and case reports of patients with (i) fractures of the upper limb, (ii) a history of BP use and (iii) incidence of delayed/non-union. All reports that described at least one patient with these three components were included regardless of the completeness of reported data.

**Quality of data**

The quality of the reports was assessed by methodology criteria proposed by two of the authors (AN and BY) based on a previous methodology score by Coleman et al.21 Studies were scored independently by AN and BT based on the criteria listed in Appendix I. The risk factors for delayed bony healing included in the methodology score were in accordance with those identified in the current literature.22–25

**Results**

The literature search involving upper limb fractures and BPs identified 10 163 publications. 9831 of these were excluded based on the abstract as they were not related to our proposed research question. 31 manuscripts were excluded because they were not in English language, 14 because they were duplicate papers, 15 review articles were excluded; and 266 because they were trials focusing on non-upper limb fractures. The remaining six publications investigating 1140 participants were used.12,17,26–29 The six papers comprised of three case reports,17,27,28 one nested case control study,26 one retrospective review12 and one randomized clinical trial.29

**Study characteristics**

There was variability in the duration of BP therapy prescribed for upper limb fractures, ranging from 0.5 to 84 months.17,28,29 The time period investigated during which BP therapy was prescribed also...
differed. In four of the six studies, BP therapy was prescribed in a pre-fracture setting, in the study by Gong et al., BP therapy was prescribed in the post-fracture period, and in the study by Solomon et al., the timing of BP prescription was mixed (Table 1). Alendronate, risedronate and intravenous zoledronic acid were the main types of BPs used in the six studies. Timing of radiographic follow-up also demonstrated variability, with follow-up to 3, 6 and 8 months at various intervals. Three of the studies included patients who had ulna fractures, two involved distal radius fractures, and one with fractures of the proximal humerus (Table 1).

**Pertinent outcomes**

**Pre-fracture BP use**

In studies investigating pre-fracture BP use, case report fractures were reported to heal uneventfully and at 4 months post-open reduction internal fixation. An additional case report showed evidence of non-union at 2 months in the study by Tang et al. In studies with controls, pre-fracture BP use in patients with complex distal radial fractures, no co-morbidities and of female gender were listed as factors for longer healing times in the paper by Rozental et al. A 6-day difference in average healing times between BP users versus non-BP users was reported (Table 2). Average pre-fracture BP use was reported as 25 months, with radiographic follow-up to 3 months post-fracture. The paper recorded a high methodological score of 47 (Table 1). There was no elevation in the risk of non-union associated with pre-fracture BP use (RR = 0.84, 95% CI 0.19–3.74) in the study by Solomon et al.

**Post-fracture BP use**

BP use in the post-fracture period was associated with an approximate doubling of the risk of non-union (OR 2.37, 95% CI 1.13–4.96) with proximal humerus fractures (Table 2). This nested case control study involving 891 patients who presented with humeral non-union 91–365 days post-fracture received a high methodological score of 41 (Table 1). Mean BP exposure time was 26 days in this study. Timing of radiographic follow-up was not reported. Post-fracture BP use was not a risk factor for longer healing times in the study by Gong et al. This randomized clinical trial investigating distal radial fractures studied healing time differences between patients started on BP therapy at 2 weeks compared with 3 months post-fracture. A relatively high methodological score of 33 was also recorded for this trial, with timing of radiographic follow-up to 6 months (Table 1).

**Discussion**

Current literature pertaining to the incidence of delayed/non-union in upper limb fractures associated with BP treatment remains limited. Meta-analysis of the data was not possible because of low number of subjects, lack of randomization in the selected studies and heterogeneity in data presentation. With the available literature, we sought to review the evidence and give recommendations on the following three questions:
Table 2 Pertinent outcomes

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Pertinent outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bjogul et al. (2011)17</td>
<td>‘fracture healed uneventfully’</td>
</tr>
<tr>
<td>Rozental et al. (2009)12</td>
<td>‘average time to healing of 55 ± 17 days (case) versus 49 ± 14 days (control)’</td>
</tr>
<tr>
<td>Solomon et al. (2008)26</td>
<td>‘bisphosphonate use in the post-fracture period was associated an approximate doubling of the risk of non-union (OR 2.37, 95% CI 1.13–4.96)’</td>
</tr>
<tr>
<td>Stathopoulos et al. (2011)27</td>
<td>‘fracture healed 4 months after ORIF’</td>
</tr>
<tr>
<td>Tang et al. (2011)28</td>
<td>‘evidence of non-union at 2 months’</td>
</tr>
<tr>
<td>Gong et al. (2012)29</td>
<td>‘time to radiographic healing for group 1 (bisphosphonates started at 2 weeks post-fracture) = 6.7 ± 1.5 weeks versus group 2 (bisphosphonates started at 3 months post-fracture) = 6.8 ± 1.6 weeks’</td>
</tr>
</tbody>
</table>

(1) Does BP therapy lead to delayed or non-union?
(2) How should fractures be managed in patients on BPs?
(3) How long should patients be on BP therapy?

The evidence for each question was graded using the following system as per the National Health and Medical Research Council hierarchy system:
A. Good evidence (level I studies with consistent findings) for recommending intervention.
B. Fair evidence (level II or III studies with consistent findings) for recommending intervention.
C. Poor quality evidence (level IV or V) for recommending intervention.

1. Does BP therapy lead to delayed or non-union?

Pre-fracture BP use
In studies investigating pre-fracture BP use,12,17,27,28 case report fractures were reported normal fracture healing times.17,27 An additional case report by Tang et al. showed evidence of non-union at 2 months.28 However, this result was confounded by the patient refusing surgery for a displaced ulna fracture. Pre-fracture BP use in the study by Rozental et al.12 showed a 6-day difference in average union rates between cases and controls. The authors of this study concluded that this difference was not significant enough to change current practice patterns given the proven benefits of BP therapy in patients with underlying osteoporosis.12 Solomon et al. reported no elevation in risk of non-union associated with pre-fracture BP use.26

Summary of evidence 1.1
Pre-fracture BP use is not associated with delayed or non-union of clinical significance.
Level of evidence: III
Grade of recommendation: B

Post-fracture BP use
BP use in the post-fracture period was associated with an approximate doubling of the risk of non-union with proximal humerus fractures. The increased risk associated with BP use persisted in the subgroup of patients without a history of osteoporosis or prior fractures, albeit limited by small sample sizes.26 Despite this statistically significant difference, the authors of this study concluded that since BP use among high-risk patients is often associated with an approximate 50% reduction in fracture risk and the morbidity and mortality associated with a new fracture are often much greater than a non-union, it would appear unwise to suggest not using a BP after a fracture.26 An explanation was postulated by the authors of this study that cortical healing, such as that required in humeral fractures, is more vulnerable than metaphyseal trabecular healing.26 In the study by Gong et al. post-fracture BP use was not identified as a risk factor for longer healing times. It was also noted that the sample size in this study was too small to detect a relatively rare complication of non-union.29

Summary of evidence 1.2
(a) Post-fracture BP use is associated with non-union of proximal humerus fractures.
Level of evidence: II
Grade of recommendation: B
(b) Post-fracture BP use is not associated with delayed healing of distal radius fractures.
Level of evidence: III
Grade of recommendation: B

2. How should fractures be managed in patients on BPs?

Ulna fractures
We observed a variety of management options used for patients on BPs with upper limb fractures. Surgical treatment for patients with atypical ulna fractures prescribed with BPs in a pre-fracture setting comprised of a plate and bone graft from the ipsilateral radius17 and open reduction and internal fixation.27 These fractures healed uneventfully17 and 4 months later after ORIF,27 respectively. Non-surgical management through a long arm fiberglass cast splint was employed in a patient who declined surgery for a non-united and displaced atypical ulna fracture. Evidence of non-union was observed at 2 months post-fracture with conservative treatment.28

Summary of evidence 1.3
Atypical ulna fractures treated conservatively may be associated with non-union.
Level of evidence: V
Grade of recommendation: C

Distal radius fractures
Two of the six studies12,29 demonstrated a range of options used for BP-related distal radius fractures. In the study by Rozental et al. involving pre-fracture BP use, conservative management options in the form of casting and sugar tong splints were used for non-displaced and comminuted fractures that had manipulation in the emergency department, respectively.12 Surgical treatment was offered to patients with displaced fractures. The authors of this study noted that among surgically treated BP users, there was no effect of...
the type of treatment on time to radiographic union. Volar locking plates were used in the study by Gong et al.22 A 0.1-week difference in healing times was observed between patients started on BP at 2 weeks post-fracture compared with 3 months post-fracture. An important difference in this study population was that BP use was prescribed in a post-fracture setting and hence, is not comparable to the other study on distal radius fractures.

Summary of evidence 1.4

(a) There is no effect of type of surgical treatment on healing times for patients with distal radius fractures started on BP therapy pre-fracture.
Level of evidence: III
Grade of recommendation: B

(b) Timing of BP therapy initiation following a distal radius fracture is not associated with a difference in healing times.
Level of evidence: II
Grade of recommendation: B

Humerus fractures

With regard to humerus fractures associated with BP use, the study by Solomon et al.26 presented common procedural terminology codes including ‘repair of non-union or mal-union’, ‘open treatment of humeral shaft fracture with plates/screws’ and ‘treatment of humeral shaft fracture’ for treatment of non-united humeral fractures. BPs were prescribed both in a pre- and post-fracture setting this study.26 No information on the effects of different types of treatment on fracture healing time was presented in this study.

Summary of evidence 1.5

There is insufficient evidence to comment on how BP-related humerus fractures should be managed with the present literature.

3. How long should patients be on BP therapy?

In this review, there was variability observed in the duration of BP therapy prescribed. Three case reports17,27,28 presenting atypical BP-related ulna fractures specified pre-fracture BP use of up to and over 72 months. Two studies12,29 investigating distal radius fractures associated with BP use demonstrated pre-fracture BP use of 25 ± 21 months12 and post-fracture BP use of up to 3 months.29 The nested case control investigating proximal humerus fractures by Solomon et al.26 showed BP therapy prescribed for up to 1.22 months pre-fracture and 0.85 months post-fracture.

Summary of evidence 1.6

Duration of BP therapy prescribed in both a pre- and post-fracture setting for proximal humerus, distal radius and ulna fractures remains varied.

Limitations

Two major factors contributed to the homogeneity in data presentation: (i) lack of standardized guidelines for the ideal duration of BP therapy and (ii) inconsistent definitions of delayed/non-union.

Currently, there are no clear guidelines on the ideal duration for BP therapy in a pre- and post-fracture setting. A review undertaken by the US Food and Drug Administration in 2011 investigating the efficacy and optimal duration of BP use found that there was limited fracture data on BP exposure to 10 years.7 The 10-year data collated suggested that BP therapy provides a sustained fracture benefit without any further increase in fracture benefit after 3–4 years of therapy. In patients who discontinued BP exposure after 3–5 years of treatment, fracture incidence rates were relatively consistent over time.3 Specifically, alendronate and zoledronic acid given for 3 years,30,31 and risendronate given for 5 years31 have been shown to maintain their antifracture effects for as long as 10 years.30 Another long-term study of risendronate has demonstrated that 7 years of continuous therapy in post-menopausal women significantly decreased bone turnover markers to within a premenopausal range and increased bone mineral density with no indication of loss of antifracture efficacy.32 A comparison of fracture risk between patients who remained on alendronate treatment for 10 years compared with those who discontinued treatment after 5 years was undertaken in the Fracture Intervention Trial Long-term Extension trial. No increases in the risk of suffering a vertebral or non-vertebral fracture were noted between the two groups, although osteoclast suppression continued for at least a further 5 years in the group who discontinued treatment after 5 years.30 As observed in one of the reports reviewed by this study,30 patients have been recommended for drug holidays allowing for temporary cessation of their BP therapy. The long-term effects of a drug holiday remains undetermined. In their report, the US Food and Drug Administration recommended that additional long-term data would be needed to further define an appropriate duration of drug cessation and to determine if interim monitoring is appropriate on an individual basis.7 The US National Osteoporosis Foundation has recommended a 5-year ‘drug-free holiday’ after alendronate treatment of 5 mg/day for 5 years, stating that this does not result in increased fracture risk and could be advantageous.33 Because of variability in current guidelines on the ideal duration of BP use, it is thus not surprising that from the studies in this review, three different antiresorptive agents each used to varying durations was observed.17,28,29 Nonetheless, the ideal type and duration of bisphosphonate therapy remains a pertinent question that demands further investigation.

The definition of both delayed and non-union remains unclear. Several chronological, clinical and radiographic definitions have been proposed. A recent survey of 335 North American orthopaedic surgeons found that there is a lack of consensus in the definitions of delayed and non-union.25 Delayed union of a long bone has been defined as a fracture that has not gone on to full bony union after 6 months, represented by evident cessation of periostal new bone formation before union has been achieved.34 A previous survey of members of the Orthopaedic Trauma Association identified delayed unions as ranging from 1 to 8 months (average and standard deviation, 3.5 ± 1.4 months).35 Expected healing times for specific regions of bones have also been described in the literature. Most bones have a given time over which they are expected to heal: 6 weeks in the upper limb and feet, 3 months in the femur or tibia. If after twice the time there is no union, this is considered delayed union.36,37 Non-union of fractures has been defined as ‘cessation of all reparative process of healing without bone union’38. In the absence of significant bone loss, non-union is usually diagnosed between 6 and 9 months following the fracture,18,39,40 but can range from 2 up to 12...
months. In addition to the difficulty with defining healing, there was no standardized timing of follow-up. The exact time of bony healing would have been difficult to determine, as studied fractures may have healed before their follow-up radiograph.

Hence, there is no strong evidence upon which to provide recommendations regarding the role of BPs in delayed and/or non-union of upper limb fractures. As expressed by previous authors, we do not feel that differences in union time are significant enough to change current practice and do not outweigh the benefits of BP therapy. Additionally, there is no evidence to encourage early surgical management of atypical BP-related upper limb fractures. In this review, we examined mainly case reports, retrospective studies and nested case controls, which, by their nature, contain bias. Further discrepancies were noted in definitions of union, timing of radiographic follow-up and timing of BP therapy initiation. A well-designed, randomized controlled study incorporating variability in the aforementioned discrepancies is required to substantiate our recommendations.

References


Appendix I: Ng and Yue methodology score criteria

<table>
<thead>
<tr>
<th>CRITERIA</th>
<th>SCORE</th>
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<tbody>
<tr>
<td>Number of cases reported</td>
<td></td>
</tr>
<tr>
<td>1–5</td>
<td>2</td>
</tr>
<tr>
<td>5–20</td>
<td>4</td>
</tr>
<tr>
<td>20–100</td>
<td>7</td>
</tr>
<tr>
<td>&gt;100</td>
<td>10</td>
</tr>
</tbody>
</table>

Mean follow-up
- >6 months: 5
- <6 months: 0

Type of study
- Controlled: 5
- Not controlled: 0

Diagnostic certainty
- score of 1 given per variable recorded: 1
  - age
  - gender
  - race
  - duration/dose of BP use
  - type of BP use
  - bone biochemical marker (including DEXA, BMD)
  - fracture displacement
  - Vitamin D use
  - Glucocorticosteroid use
  - history of smoking
  - history of Diabetes
  - history of Rheumatoid Arthritis
  - history of kidney disease
  - history of obesity
  - history of alcoholism

Description of surgical procedure
- Adequate (technique stated and necessary details of procedure given): 2
- Fair (technique only stated without elaboration): 1
- Inadequate, not stated, unclear: 0

Outcome criteria
- Definitions of delayed and non-union
  1. elaborate (time, radiological + clinical): 4
  2. brief (one of the 3 above factors): 2
  3. none given: 0
- Absolute number for risk stated for delayed or non-union stated: 3
- not stated: 0

Procedure for assessing outcomes
- description given: 1
- description not given: 0

Description of subject selection process
- selection/exclusion criteria: 1
  score of 1 given for each criteria listed (maximum of 3)

Duration of BP therapy
- >5 years: 5
- <5 years: 0

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