Do bisphosphonates cause femoral insufficiency fractures?

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Abstract In recent years, several reports have suggested an association between the use of bisphosphonates and subtrochanteric insufficiency fractures. Research from animal studies and in some cases from histomorphometric data collected from patients provide evidence of a possible pathophysiological mechanism behind this phenomenon. Despite this, it has not yet been possible to confirm a causal relationship. The small number of cases, the lack of consistency in defining these atypical fractures, the absence of homogeneity between studies, and the fact that most data available are derived from retrospective observational studies, are some of the difficulties encountered in the evaluation of evidence. Despite the proven benefit of bisphosphonates at providing protection against osteoporotic fractures, caution should be used before continuing therapy for longer than 5 years.

Keywords Atypical · Insufficiency fracture · Subtrochanteric · Bisphosphonates

Introduction

Bisphosphonates have been widely used to treat and prevent osteoporosis, as they inhibit bone resorption. They have also been used in other medical conditions, including Paget’s disease [18] and glucocorticoid-induced osteoporosis [42]. Their supporting evidence is of high quality, with multiple randomised controlled trials confirming their efficacy [5, 6, 8, 24]. They act by inhibiting osteoclast activity and promoting osteoclast apoptosis [29], thereby increasing bone mineral density (BMD).

Recently, several reports have suggested a possible association between the use of bisphosphonates and non-osteoporotic fractures of the femur. Research was initially triggered by the pioneering animal study of Mashiba et al. [35] in 2000, who found reduced cortical remodelling and significant microdamage accumulation in beagles following alendronate and risedronate therapy, predisposing them to fractures. Five years later, Odvina et al. [39] reported a series of four patients with osteoporosis who whilst on bisphosphonates sustained atypical femoral fractures. Since then, there have been increasing numbers of case reports [2, 10, 13, 16, 17, 19, 22, 23, 25, 26, 30–32, 34, 38, 39, 43–46, 50, 51, 53, 54] in which atypical fracture patterns have occurred in the diaphysis or subtrochanteric region of femurs in patients on long-term bisphosphonates. The aim of this paper was to review evidence that has linked bisphosphonates with femoral insufficiency fractures.

Diagnosis of subtrochanteric insufficiency fractures

Subtrochanteric fractures are usually rare, with an estimated 3 % of femoral fractures occurring at the subtrochanteric region [30, 37]. Being the area of the femur subjected to maximal bending stress [40], the bone remodels accordingly, rendering low-energy fractures less likely. Subtrochanteric stress fractures were traditionally
seen in long-term cyclical loading injuries in bones unac-
customed to these actions—typically in new military
recruits [3, 15, 28]. Diagnoses of insufficiency fractures are
based on history, radiological features and bone biopsies.
The fracture is frequently preceded by a history of persis-
tent thigh pain prior to low-energy trauma. Radiographs
typically reveal a transverse fracture with a medial cortical
spike, with other features including cortical thickening or
cortical beaking [7]. This pattern had been described as an
atypical subtrochanteric fracture, and despite the lack of a
clear definition, the term has been used to describe the
presence of a subtrochanteric fracture with similar radio-
logical features as a stress fracture associated with no or
minor injury. In 2010, the American Society for Bone and
Mineral Research published guidelines regarding the defi-
nition of an atypical fracture in an attempt to provide some
homogeneity between future studies and case reports using
these fractures as primary outcomes. Indeed, according to
their report, an atypical fracture is defined by specific
major and minor features [48]. Of note is the fact that all
major features consist of specific radiological findings as
well as a history of no or minimal trauma. In view of the
lack of a clear distinction, the terms atypical/insufficiency
fractures are used interchangeably in this review.

Pathophysiology

It has been thought that during the prolonged time that bis-
phosphonates are spent in the body—half-life of 12 years—
[49], osteoclastic inhibition is sequentially followed by a
decrease in bone formation [12]. Bone remodelling is limited
to an extent that may potentially be harmful, as prevention of
this natural process eventually alters the load distribution
passing through the bone. Therefore, although BMD may be
preserved, the poorer quality bone and failure of aging col-
lagen may increase susceptibility to these insufficiency
fractures. Indeed, bone biopsies taken from fracture sites or
the iliac crest of patients on bisphosphonates confirmed low
bone turnover [38]. It has been suggested that the combina-
tion of increased bone mineralisation, together with a
marked reduction of bone turnover, promote accumulation
of microfractures, resulting in changes in bone mechanical
behaviour [14, 55].

Chapurlat et al. [11], investigated the degree of bone
turnover suppression in women who had been on long-term
bisphosphonate use (mean duration 6.5 years) by obtaining
transilial bone biopsies and found significantly reduced
turnover compared with those not on bisphosphonates. A
similar result was found by Stepan et al. [52], who per-
formed a cross-sectional analysis of postmenopausal
women on alendronate (mean duration 5.27 years) who
underwent histomorphometric biopsies.

Case reports/case series

Since the animal study by Mashiba et al. [35], there have
been increasing numbers of case reports [2, 10, 13, 16, 17, 19,
22, 23, 25, 26, 30–32, 34, 38, 39, 43–46, 50, 51, 53, 54], all of
which provide typical histories of low-energy fractures and
some in combination with classical radiological features.
Husada et al. [25] published the first report on femoral
insufficiency fractures in 2005, and although a typical history
and radiological features were provided, there was no men-
tion of the duration that the patient was on alendronate prior
to the fracture. In 2006, the National Osteoporosis Founda-
tion suggested that stopping alendronate after 5 years of
continuous therapy may be beneficial. Since then, several
case reports have clearly taken note of this and documented
longer periods of bisphosphonate use (Table 1).

Odvina et al. [39] published a case series of 4 patients
who had subtrochanteric fractures whilst on alendronate for
a mean of 6.5 years. In all cases there were normal bio-
chemical markers of bone turnover on haematological
testing. However, in three of the four patients, bone his-
tomorphometry confirmed decreased bone turnover, and
the authors estimated bone formation rate to be 100 times
less than a normal postmenopausal woman. They also
noted that there were minimal signs of callus formation
whilst on alendronate, and in certain cases, fracture healing
only occurred once alendronate therapy had stopped.

Only a few other cases [2, 13, 38, 51, 53] presented
histomorphometric data collected via bone biopsies. Cer-
tain reports [38, 51, 53] demonstrated severely suppressed
bone turnover following prolonged use of bisphosphonates,
as histological samples showed reduced or absent tetracy-
cline labelling and reduction in osteoclastic and osteo-
blastic surfaces. In other cases [2, 13], biopsy samples
showed normal bone turnover and no evidence of hyper-
mineralisation or microcrack accumulation, arguing against
a potential pathophysiological mechanism. Most of these
reports had substantial confounding factors, including
inconsistent or poorly documented duration of bisphosph-
onate use, concurrent use of other medications that are
known to affect bone physiology and comorbidities. Evi-
dently, these case reports did not provide any scientific
evidence of causality; however, they did highlight the need
for further investigations on this topic.

Retrospective studies

Lenart et al. [33], performed a small case–control study of
41 subtrochanteric or femoral shaft fracture, comparing
them with patients sustaining intertrochanteric/femoral
neck fractures. Among the 41 cases, 15 (37 %) were on
bisphosphonates compared with nine of 82 (11 %) controls
Table 1  Summary of case reports/case series

| Author                        | No. of patients | Age of patient | Fracture site                  | Other risk factors | BPN          | Years of bisphosphonate preceding injury | Histomorphometrically confirmed suppressed bone turnover |
|-------------------------------|-----------------|----------------|--------------------------------|-------------------|-------------|-----------------------------------------|----------------------------------------------------------|
| Aspenberg et al. [2]          | 1 F             | 57             | Subtrochanteric                | RA, pred          | ALN/RSN     | 7                                       | Yes                                                      |
| Capeci and Tejwani [10]       | 7 F             | 61             | Subtrochanteric/femoral shaft  |                   | ALN         | 8.6                                     | No                                                       |
| Cheung et al. [13]            | 1 F             | 82             | Femoral shaft                  | No risk factors   | ALN         | 10                                      | Yes                                                     |
| Das De et al. [16]            | 12 F            | 63.1           | Subtrochanteric Midshaft       | 4× Pred           | ALN         | 4.6                                     | No                                                      |
| Demiralp et al. [17]          | 1 F             | 65             | Femoral shaft                  | Pred              | ALN         | 7                                       | No                                                      |
| Edwards et al. [19]           | 1 F             | 60             | Femoral diaphysis              | Steroid use for 10 years | ALN         | 6                                       |                                                         |
| Goddard et al. [22]           | 1 F             | 67             | Femoral shaft                  | No risk factors   | ALN         | 16                                      | No                                                      |
| Griffing and Nallapaneni [23] |                 |                |                                |                   | HIV         | 8                                       | No                                                      |
| Husada et al. [25]            | 1 F             | 72             | Femoral shaft                  | Osteoporosis      | ALN         | Not stated                              | No                                                      |
| Ing-Lorenzin et al. [26]      | 7 F             | 67.5           | Subtrochanteric                | Steroid and proton pump inhibitor use | ALN 5× ALN 2× Ibradonate | (16 months–8 years) | No |
| Kwek et al. [30]              | 17 F            | 66             | Subtrochanteric                | 1× RA 1× Pred     | ALN         | 4.8                                     | No                                                      |
| Lee et al. [31]               | 1 F             | 73             | Femoral shaft                  | –                 | ALN         | 1.5                                     | No                                                      |
| Lenart et al. [32]            | 15 F            |                | Subtrochanteric/femoral diaphysis | –                | ALN         | 5.4                                     | No                                                      |
| Leung et al. [34]             | 9 F             | 78.2           | Subtrochanteric/femoral diaphysis | 2× Pred           | ALN         | 3.6                                     | No                                                      |
| Odvina et al. [38]            | 13 F            | 64.3           | Midshaft                       | 4× Steroids       | ALN—8.5 ALN—3.3 | Yes 6/13—severe suppression           | 6/13—severe suppression                                   |
| Odvina et al. [39]            | 4 F             | 63             | Proximal/midshaft              | 1× Steroids       | ALN         | 6.5                                     | Yes                                                     |
| Sayeed-Noor and Sjoden [43]   | 1 F             | 72             | Subtrochanteric                | Anorexia          | ALN         | 7                                       | No                                                      |
| Sayeed-Noor and Sjoden [44]   | 2 F             | 66.5           | Midshaft                       | –                 | ALN         | 10                                      | No                                                      |
| Schilcher and Aspenberg [45]  | 5               | 75             | Femoral shaft                  | 1× RA and steroid | ALN         | 5.8                                     | No                                                      |
| Schneider [46]                | 1 F             | 59             | Spiral mid-shaft               | HRT               | ALN         | 7                                       | No                                                      |
| Somford et al. [50]           | 1 F             | 76             | Bilateral femoral shaft        | RA Pred           | ALN         | 8                                       | Yes                                                     |
| Somford et al. [51]           | 3 F             | 73.3           | Subtrochanteric                | 3× RA, pred       | ALN         | 9.3                                     | No                                                      |
| Visekruna et al. [53]         | 3 F             | 62.7           | Subtrochanteric/femoral shaft  | 3× Pred (11.7 years) | ALN         | 8.3                                     | Yes—reduced osteoids                                    |
| Wang et al. [54]              | 7 F             | 72             | Subtrochanteric                | 5× Steroids       | ALN         | 5.9                                     | No                                                      |

F Female, M male, RA rheumatoid arthritis, Pred prednisolone, BPN bisphosphonate, ALN alendronate, RSN risedronate, HRT hormone replacement therapy
[odds ratio (OR) 4.4; confidence interval (CI) 1.8–11.4; 
\( p = 0.002 \)]. Furthermore, their study showed that the 
characteristic radiological pattern associated with insuffi-
ciency fractures was highly associated with the use of 
bisphosphonates (OR 15.3; CI 3.1–76.9; \( p < 0.001 \)). 
However, it is important to note that pretreatment radio-
graphs were not available for comparison, raising the 
possibility that these radiological differences could be the 
result of anatomical variations between patients. Interest-
ingly, this problem was addressed by Issac et al. [27], who 
examined 100 patients with low-energy femoral shaft 
fractures before and after bisphosphonates became avail-
able. The study compared the radiographs of 21 patients 
with this type of fracture before the availability of bis-
phosphonates (period 1995–1997) and compared them with 
79 patients presenting with the same fracture over the 
period 2007–2009. Interestingly, none of the patients from 
the 1995 to 1997 period had the characteristic radiological 
features of insufficiency, whereas 41 patients from the 
bisphosphonate group had these features.

One of the largest studies was carried out by Park-
Wyllie et al. [41], who performed a population-based 
observational study of women >68 years who were started 
on a bisphosphonate orally between 2002 and 2008. Over 
the 7-year period, 205,466 women were started on bis-
phosphonates, with 716 women sustaining a subtrochan-
teric/femoral shaft fracture (411 and 305 women, 
respectively). They suggested that long-term bisphospho-
inate treatment (>5 years) was associated with higher risk 
of subtrochanteric/femoral shaft fracture compared with 
transient use (<100 days) of bisphosphonates (adjusted OR 
2.74; 95 %CI 1.25–6.02). Interestingly, shorter durations 
(>100 days–5 years) were not shown to be associated with 
an increased risk. The authors were also able to assess the 
validity of their study design by investigating the effect of 
long-term bisphosphonate use on femoral neck and inter-
trochanteric fractures. Indeed, the study confirmed the 
well-documented effect of bisphosphonates on these types 
of fractures, as it demonstrated their protective effect 
(adjusted OR 0.76; 95 %CI 0.63–0.93). Despite the sta-
tistical significance achieved in the study, it is worth 
emphasising the small absolute risk of subtrochanteric/ 
femoral shaft fractures detected, as among 52,595 women 
on a minimum of 5 years on bisphosphonates, a fracture 
was seen in only 188 women. As seen in most studies 
investigating the role of bisphosphonates and atypical 
fractures, that study did not use radiological features of 
insufficiency or atypia for identifying cases. The study 
outcome was reached by confirming the absence of trauma 
and radiological identification of the fracture site.

Another retrospective review, by Nevisier et al. 
[36], reported 70 low-energy femoral shaft/subtrochan-
teric fractures. Twenty-five patients were taking 
bisphosphonates; however, the duration of bisphosphonate 
use was only collected for 16 patients (6.2 years). Three 
independent, blinded orthopaedic surgeons where asked to 
review the radiographs of these 70 cases and identify those 
with characteristic radiological features suggestive of 
insufficiency fractures (simple, transverse, or short-oblique 
pattern in areas of cortical thickening with a unicortical 
beak). The authors concluded that the characteristic frac-
ture pattern was much more common in patients on bis-
phosphonates (76 %) compared with only 2 % not on 
bisphosphonates. They also found that this pattern was 
98 % specific to alendronate users. Adding further evi-
dence to their conclusion was their finding that patients 
taking alendronate for longer (6.9 years) were more likely 
to have the classical radiological features than those on a 
shorter duration (2.5 years). Apart from the study being 
retrospective, other limitations included limited patient 
numbers and that confounding factors such as glucocorti-
coid use and other patient comorbidities were not taken 
into account.

Giusti et al. [21] performed a systematic review of 141 
atypical fractures that occurred in patients taking bisphos-
phonates, with a mean age of 68.8 and duration of 
5.95 years bisphosphonates therapy. Their work suggested 
there was no association between bisphosphonate use and 
atypical fractures, as patients who took bisphosphonates for 
<5 years, were more likely to have femoral shaft fractures 
compared with those taking it for >5 years. Nevertheless, 
the quality of this study emphasised the actual quality of 
most reports, as vital information such as patient adherence 
to medication, comorbidities, other medications, dose of 
bisphosphonates and bone turnover markers were often not 
recorded. More importantly, the authors reported that in 
>50 % of case reports, important data was not adequately 
reported or was completely missing.

Evidence against an association between bisphospho-
nates and atypical subtrochanteric fractures also comes 
from the work of Abrahamsen et al. [1]. They performed a 
register-based matched cohort analysis and found that the 
ratio of typical osteoporotic fractures and atypical subtro-
chanteric fractures was identical in alendronate-treated 
fracture patients and their matched untreated controls. 
Nevertheless, the main limitation of their study was that 
they were unable to truly identify the number of atypical 
subtrochanteric fractures. Fracture diagnosis was based on 
the International Classification of Diseases (ICD)-10 cod-
ing used in the health register, and it was therefore not 
possible to differentiate between high- and low-energy 
fractures, which are one of the key diagnostic criteria. 
Furthermore, because of the study design, it was not pos-
sible to perform any radiological assessment of the fracture 
sites and thus no criteria for defining atypical/insufficiency 
fractures were used.
Randomized controlled trials

Bone et al. [9] performed a randomised, double-blind, placebo controlled trial of the effects of alendronate on bone density and histomorphometry in 425 postmenopausal women. They found that alendronate alone or in combination with oestrogen did not affect histomorphometry and concluded that alendronate produced favourable effects on BMD. Despite the strength of the study design, there were certain limitations. Firstly, patients were only on alendronate therapy for a maximum of 2 years, and as previously suggested, this might not be long enough. Secondly, of the 425 patients, only 98 underwent bone biopsies, and there was no mention of the selection process and reasons for selection.

The largest study was by Black et al. [7], who performed secondary analyses of three large randomised controlled trials of bisphosphonates. Two trials were based on alendronate therapy: the Fracture Intervention Trial (FIT) [5] and FIT Long-Term Extension (FLEX) [47]; a third trial was based on zoledronic acid: the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly—Pivotal Fracture Trial (HORIZON–PFT) [20]. In the FIT trial, 6,549 women over the age of 65 years were randomised to either receive alendronate or placebo for 3–4.5 years. The FLEX continued follow-up in 1,099 of the 6,549 women in the FIT trial over the subsequent 10 years. In the HORIZON–PFT trial, 7,736 women were randomised to either receive zoledronic acid or placebo over 3 years. Between the three trials, 284 hip fractures were found, and only 12 were subtrochanteric or midshaft femoral fractures. Due to the low incidence of these insufficiency fractures, Black et al. concluded that there was no increased risk associated with prolonged bisphosphonate therapy. Despite the large numbers of patients on alendronate therapy, the authors themselves eluded to the fact that their study was underpowered for definitive conclusions. Further weaknesses include the short duration of bisphosphonate therapy in most cases. Only 1,000 of 15,384 patients took bisphosphonates for >4 years. Another limitation in the process was the lack of radiographs, and therefore the inability to assess for signs of atypia. The diagnosis of insufficiency fracture was again based on fracture site as per radiological report and history of a low-energy fracture.

The same limitations are also encountered in another report by Bilezikian et al. [4], who reported the incidence of these atypical fractures in a randomized, placebo-controlled, phase III trial of the use of risedronate in postmenopausal women with osteoporosis. The trial, which enrolled >15,000 patients, found no causal relationship between risedronate use and this type of fracture. Nevertheless, the mean duration of bisphosphonate use was only 1.9 years, an observation that, as explained previously, could potentially alter the outcome of the study.

Conclusion

Based on the published literature, femoral insufficiency fractures appear to be a different pathology compared with standard osteoporotic fractures, and the atypical features of the fracture are rarely seen without long-term bisphosphonate therapy. Even so, evidence from other studies suggests that these fractures are, in reality, part of the natural history of osteoporosis. Due to the rarity of these fractures, however, there are a limited number of cases published and very few adequately powered studies. Almost all evidence is derived from retrospective observational studies, and in the majority of cases, data are either incomplete or complicated by several confounding factors. Evidently, there is some evidence collected from randomized controlled trials; however, it is worth emphasising the fact that these trials were not designed to investigate this association and are therefore weakened by the lack of important data.

Nevertheless, evidence from the literature confirms the existence of a type of fracture that has specific radiological features and could potentially be associated with the use of bisphosphonates. It is therefore important to consider that even if a causal relationship is shown, it would still be extremely difficult to question the clinical use of bisphosphonates. The risk/benefit ratio of bisphosphonates has been documented in multiple good-quality studies. This ratio is unlikely to be significantly shifted, as both the incidence of these fractures—31 per 10,000 patient years in women receiving alendronate—[1], and the potential absolute risk associated with the use of bisphosphonates seems to be relatively small. Even so, caution should be used before continuing therapy for >5 years, and prodromal symptoms should be taken into consideration. More well-designed studies are needed to establish the presence of a causal relationship.

Conflict of interest None.

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