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PERSPECTIVES

Bisphosphonates and Fatigue Fractures

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Abstract

There are now several case series of fatigue fractures of the femur in patients on long-term bisphosphonate treatment. The association with bisphosphonates has been clearly demonstrated, and a population-based study has recently shown an incidence around 1 fracture per year, per 1000 patients treated for at least 2 years. When combining the published reports, almost half of the patients have bilateral fractures, and a quarter of them are taking corticosteroids. Still, bisphosphonates reduce fracture risk: for each stress fracture associated with this treatment, it is estimated that 15 osteoporotic fractures are avoided.
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Introduction

When bisphosphonate treatment was first introduced to prevent osteoporotic fractures, there were many warnings that decreased remodeling would "freeze" the skeleton, so that microdamage and microcracks would accumulate (1). It was feared that an early reduction of fracture risk would be followed by a later increase. However, as experience grew with time, these warnings appeared unwarranted: the reduction in fracture risk with bisphosphonates has been shown to last for at least a decade (2).

Bisphosphonates remain in the skeleton with a half-life of many years. After a bisphosphonate has attached to a mineralized surface, it may be buried by new bone formation on top of it. This will block even the minor spontaneous dissociation of the drug from the surface that might otherwise have occurred. The only way the bisphosphonate can be removed is by osteoclastic resorption (3). As the molecule is not metabolized by the osteoclast, it will ultimately be released, again in the vicinity of bone, and has a good chance to attach to a mineral surface again (3). This recycling may explain the long duration of the effects of a few years of bisphosphonate treatment, and is a cause for concern if unwanted effects turn up after many years.

Two such unwanted effects have caught attention during the last few years: stress, or fatigue, fractures and osteonecrosis of the jaw. Both are biologically interesting conditions, subject to interesting speculation, based on insufficient data. The focus of this *Perspective* is on bisphosphonate-assocated stress fractures.

Bisphosphonate-Associated Stress Fractures

Stress fractures are a well-known condition in orthopedics, first described in 1855 as local pain and swelling among Prussian military recruits (4), but today occurring mainly in overactive athletes. In the clinic, stress fractures appear as localized pain on loading, with no radiographic findings initially, but later with a modest callus reaction. They are thought to be caused by microdamage accumulation. This can lead directly to larger lesions, as in any overloaded material: microcracks lead to stress concentration, leading to more cracks and gross failure. However, as microdamage is a stimulus for targeted resorption and remodeling (5), it is also possible that localized resorption weakens

the bone and causes the symptoms. Regardless, it is apparent that stress fractures are caused by an imbalance between accumulation of microdamage and reparative remodeling. This was the cause for early concern with bisphosphonates: although elderly osteoporotic individuals are unlikely to overuse their skeleton in track and field activities, reduced remodeling might allow sufficient accumulation of microdamage from their daily living activities.

Recently, a number of publications have reported case series of displaced transverse diaphyseal femoral fractures with minimal trauma in patients after several years of bisphosphonate treatment (Table 1) (6-14). Several of these papers partly describe the same patients, as an increased number of observations has prompted the authors to publish their material again, extended with new patients. The fractures have often been described as “subtrochanteric”, which is not incorrect, but perhaps less appropriate, as the fractures occur in the diaphyseal cortex.

Table 1.

Author	Reference	Year	Patients	Bilateral	Cortisone
Ing-Lorenzini	(11)	2009	8	4	4
Kwek	(7)	2008*	17	9	1
Lenart	(12)	2009*	15	-	-
Odvina	(13)	2009*	10	3	4
Schilcher	(14)	2009	5	1	0
Visekruna	(10)	2008	3	2	3
All			58	19/43	12/43

Notes: Recent case reports regarding femoral fatigue fractures. Patients: number of patients with femoral stress fractures on bisphosphonate treatment. Bilateral: Number of such patients with bilateral fractures. Cortisone: number of such patients on corticosteroid treatment. Lenart *et al*. excluded patients on steroid treatment and do not mention bilateral fractures. Odvina *et al*. also reported 2 fractures in other long bones, which are removed from this table. Bilateral fractures and cortisone are likely to be overrepresented, as they might draw attention to the case, except in Schilcher *et al*., which was a population-based study.
*Part of the material was published previously (6;8;9;19).

A recent study by Lenart *et al*. focused on the relation between fracture type and bisphosphonate use, and made clear that there is an association (12). They classified all fractures referred to them as either typical stress fractures or fractures with a more ordinary radiographic appearance, and then found a higher ratio between the number of bisphosphonate users and non-bisphosphonate users in the stress fractures. However, they excluded all patients on other drugs that could possibly influence bone turnover (12), or did not mention them (9). Therefore the importance of concomitant corticosteroid treatment, for example, was not elucidated. In addition, the number of bilateral cases is unclear.

The recent study by Schilcher and the current author (14) was based on a population survey, and for the first time could specify a number for the yearly incidence of femoral stress fractures in women taking bisphosphonates, which was around 1/1000 (95% CI, 0.2-2). Women not taking bisphosphonates had an incidence of 0.02/1,000 (95% CI, 0.004 to 0.1), which is over 40 times less. Considering that not all stress fractures have a typical appearance, and that they do not always occur in the femur, the incidence of bisphosphonate-related stress fractures may be higher. Still, it is important to remember that bisphosphonates decrease the overall fracture rate. For each stress fracture associated with this treatment, it is estimated that roughly 15 osteoporotic fractures are avoided (14). We are now repeating the study on a national basis in Sweden, and hope to soon be able to present more accurate numbers.

Bilateral fractures occurred in about half of the patients discussed in published studies thus far, and corticosteroid treatment in one-quarter. However, these numbers may be erroneously high, since, for example, a contralateral stress fracture will draw

attention to the case and increase the likelihood of a case report. This effect appears to lie behind a very recent report on 7 bilateral fractures, where the number of unilateral bisphosphonate-associated fractures was not even provided (15) (and therefore was not included here in Table 1). However, also in the population-based study by Schilcher and the current author (14), there was 1 bilateral case in 5 (and actually another one after the paper was submitted).

These fracture patients usually had a history of thigh pain for months before the displacement occurred, which suggests they had an undisplaced stress fracture for a long time. The natural cause of such undisplaced fractures in bisphosphonate-treated patients is unknown. It is possible that only a minority of the cases go to complete fracture. This would be similar to stress fractures in young people. However, because such a large proportion of the patients have bilateral, displaced fractures, it is likely that most cases progress to displacement. Possibly, bisphosphonate treatment might be responsible for unhindered propagation of the crack until dislocation occurs.

It is likely that concomitant treatment with other drugs increases the risk. This appears obvious for corticosteroids. Moreover, Ing-Lorenzini *et al*. recently noted that 7 of their 8 patients were on proton-pump inhibitors, which are known to be associated with an increase in fracture risk (11;16).

The mechanisms behind corticosteroid-induced osteoporosis appear to be complex, and include impaired osteocyte and osteoblast survival (17;18). This suggests a speculative explanation of how corticosteroids and bisphosphonates might act synergistically: bisphosphonates would allow the cortical bone to become aged, with accumulated microdamage, and osteocyte apoptosis due to corticosteroids would preclude targeted remodeling at the sites of microdamage. On the other hand, fractures in corticosteroid-treated patients sometimes have an appearance suggestive of bone fatigue also in the absence of bisphosphonates.

The high incidence of bilateral fractures suggests that patients with these fractures might differ from the general population of bisphosphonate users. If the risk of fatigue fractures was evenly distributed among all bisphosphonate users, they would almost never be bilateral. Instead there is a strong dependence between the left and the right femur in an individual, suggesting that there is an individual risk factor, for example, an atypical form of osteoporosis based on individual genetic proclivities.

Ordinary idiopathic osteoporosis is a hypermetabolic state, and bisphosphonates act by slowing down remodeling. This is the mechanism that reduces fracture risk. One would assume that patients who already have low bone turnover, or a weakened ability to form bone, as with corticosteroids, would benefit less from bisphosphonate prophylaxis than others. This is not the case, however. A meta-analysis of 9 randomized studies on corticosteroid-treated patients shows that bisphosphonates reduce fracture risk considerably, and within a short time, in these patients. The bisphosphonate users had a relative risk of vertebral fractures of 0.63 (95% CI, 0.49-0.80) (17). The explanation for this paradox may be that the rapid bone loss after initiation of corticosteroid treatment is due to osteoclastic resorption without much coupled formation, whereas the increased risk of fatigue fractures is likely to be related to osteocyte apoptosis. Even though the risk of stress fractures with bisphosphonates may also be low in corticosteroid-treated patients, the ratio between induced stress fractures and avoided osteoporotic fractures might be less favorable than for patients with idiopathic osteoporosis. Until this has been clarified, it is possible that one should consider replacing bisphosphonates with PTH more often for this patient category.

Another problem is the risk of an epidemic of fear. It is easy to imagine the consequences of an article in the Murdoch-type press with the title “Drugs against fractures cause fractures – a new scandal in health care. Are you at risk?” Thus far, however, this seems not to have happened, and since we now

have an incidence number (14), the risk for such problems has lessened.

Future research should aim at larger population-based studies, elucidating co-morbidities and concomitant drug treatment. There is also room for detailed mechanistic studies.

Conflict of Interest: Dr. Aspenberg reports owning shares in a company developing methods for local treatment with bisphosphonates.

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