



The Atraumatic Metatarsal Fracture: A Clinical Sign of Bisphosphonate-Associated Bone Fragility

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Authors' contributions

This work was carried out in collaboration between both authors. Author WBH managed the literature searches and wrote the original manuscript. Both authors managed the analyses of the study and read and approved the final manuscript.

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ABSTRACT

Beginning with some of the earliest publications suggesting the association between bisphosphonate treatment for osteoporosis and coincident skeletal fractures, the wide range of fractured bones reported have included the metatarsals. This paper presents a survey of the medical literature describing this association. Evidence is offered supporting definitions of inclusion rather than exclusion in seeking to define bisphosphonate-associated fractures. In addition we question the recent trend toward attributing fractures of the metatarsal as well as at other sites to "holidays" from bisphosphonate and other strong antiresorptive drugs. A 2018 paper proposed that the increased metatarsal fracture risk that persists years after stopping bisphosphonate therapy may be explained by the cessation of the antiresorptive drug. We propose instead that the frequency of this association justifies the inclusion of a prevalent or subsequent metatarsal fracture as one of the optional minor features defining the bisphosphonate-associated atypical femoral fracture.

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1. INTRODUCTION

We have previously cited [1] what we believe to be the earliest publication [2] acknowledging an association between bisphosphonate (BP) therapy for osteoporosis and fractures of the metatarsal (MT) bones. Earlier papers [3,4] had reported BP-associated fractures of other bones. All these early reports involved the use of etidronate, a BP which significantly inhibits matrix mineralization at excessive doses [5]. Those etidronate-associated insufficiency fractures which were adequately described were reported to resolve upon cessation of etidronate administration [2].

In July 2003, an article [6] was published reporting fractures combined with high bone density (total body Z-score of +2.5 using a scale [7] developed for children and adolescents) in a young boy treated with high doses of a BP. The effects were described as an induced osteopetrotic change with atraumatic fragility fractures after long-term administration of intravenous pamidronate, a moderately antiresorptive BP which is much less inhibiting of mineralization than etidronate. No MT involvement was reported, but this was the first report to describe the fracturing potential of prolonged BPs in humans. This publication was accompanied by an editorial [8] which sounded a clear warning about BP-associated fracture complications. Remarkably, a similar effect had been observed [9] in experimental animals some 30 years earlier. Mice treated with etidronate or clodronate were described as tending toward "a slowing of bone remodelling with an osteopetrotic skeleton resulting". Osteopetrosis (OPT) is a genetic disorder resulting in fracturing despite the associated high bone mineral density [10].

The relevance of OPT to a discussion of the effects of bisphosphonates on femoral and metatarsal fractures (MTFs) is that, analogous to the deactivating effect of BPs on osteoclasts [11], osteoclasts in OPT are inactive and cannot remove damaged bone [10,12]. This lack of function is associated with fracturing. These two parallel but very different mechanisms –drug-associated or congenital– are associated with similar fractures in the same bones [13], including metatarsals [14,15]. The genetic deficits in the osteopetroses lead to a preponderance of formation without remodeling

repair of damaged areas. The target of the BP drugs is, of course, the osteoclast-mediated resorption of bone. Indeed, subtrochanteric/femoral transverse shaft fractures of lateral origin, meeting the definition of BP-associated atypical femoral fractures (AFFs) [16,17] by the American Society of Bone and Mineral Research (ASBMR), have been described in individuals with congenital OPT. This report [18] included a literature review of the period between 2009-2013 finding 19 additional examples of shaft or subtrochanteric femoral fractures reported in OPT. This paper [18] made no reference to the resemblance to the ASBMR-defined AFFs, a definition which was published in the same year.

Later in 2003, the first observations regarding the general association of intermediate to long-term BP use with fragility fractures were presented [19] at a meeting of the ASBMR. Associated MT fracturing was mentioned and later included in the formal publication [20].

In the present paper, we have surveyed the medical literature regarding the occurrence of MTFs in conjunction with bisphosphonate therapy.

2. MATERIALS AND METHODS

We compiled this review in mid-November 2017 using OVID Medline In-process & Non-indexed (English and non-English), Pubmed, and the Embase database. We have included the material on MT fractures from our earlier publication [1] surveying the literature on non-atypical femur fracture BP-associated atypical fractures, thus bringing the earlier survey up to the current date to the extent that MT fractures are concerned.

References 26-32 indicate publications that appear in Table 1 but not otherwise discussed in the text.

3. RESULTS

A 2012 statistical evaluation [21] of the long-term courses and clinical consequences experienced by 81 persons who had incurred one or more AFFs [16,17] was notable for the high number of MTFs incurred by the same individuals. In some cases the MTFs preceded the AFFs. In all, 34.5% of the individuals with the femur lesion

also developed one or more MTFs. This report did not include the detailed statistics for the MTFs; thus the treatment range in Table 1. is given for the whole group, not specifically for the occurrence of the MTFs. Also, because of the anonymous nature of this analysis, we cannot be certain that some of these MTFs may not also have been reported elsewhere in the medical literature.

Regarding the reports of MTFs in patients treated for multiple myeloma with BPs [22,23], it is unlikely that the fractures were pathologic lesions secondary to the malignancy. A survey [24] of the Mayo Clinic records of 165 persons with the diagnosis of multiple myeloma treated in the years 1945-2001 (before the use of intravenous BP treatments) found no cases of spontaneous or pathologic MTFs.

The last case in the chart [25] included two additional bone-active medications after the last BP infusion. Several months after the last zoledronic acid infusion, the patient was given a 24-month treatment with teriparatide followed by a single infusion of denosumab. Foot pain began about 10 months after that single infusion and 2 months later a spontaneous Jones fracture ensued.

In summary, there are at least 52 cases reported in the medical literature where the individual sustained one or more MTFs in association with BP therapy. More than 60 such fractures were observed in these individuals; the way in which these data were presented does not allow the determination of *how many* more. Four to five times as many atypical femur fractures (AFFs) were summarized in the initial [17] ASBMR survey, but the AFF is a far less common, and therefore more remarkable, fracture. MTFs would not be expected to capture attention, and thus may go unreported or reported without reference to the BP association. An illustration of this is provided by reference 18.

A summary of the cases found is presented in Table 1.

4. DISCUSSION

In the two ASBMR committee reports seeking a definition of the AFF, sets of obligatory "major" and optional "minor" features were defined. We have shown that MTFs in an individual with an AFF can serve as support for defining the major fracture. We propose the inclusion of prevalent

MT fracture(s) as a "minor feature". An example exists in the literature illustrating the importance of minor feature inclusion in identifying the AFF. A 12-year analysis [26] of the incidence of AFFs, defined only by the ASBMR-defined major features (called AFMs), in a large cohort of women ≥ 50 and men ≥ 65 years of age, did not detect an increase in AFFs over the last 10 years of the study. This interval corresponded to the rapid increase of BP therapy for osteoporosis. However, the combined use of the major features and any minor feature (called AFMms) revealed a steady increase in AFFs. (Fig. 1). The difference in the two data sets reflects the fact that 70% of the cohort included in this study had never been exposed to bisphosphonates, thus reducing the sensitivity of the incidence rates of bisphosphonate-related AFFs. But as shown in Fig. 1. the increase in sensitivity obtained by including the AFMms clearly does show an upward trend in AFFs during the 10 year period.

Evidence has accumulated of bisphosphonate-associated MTFs, as well as fractures in many other sites [1]. Added to the fact that many of the MTFs described here either preceded or followed an AFF, these findings support the use of a BP-associated MT fracture as an optional minor feature important in defining the full incidence of BP-associated fractures. In the first report [16] of the ASBMR committee which was convened to address the mounting concerns about BP-associated femur fractures, one of the "major features" required for a given fracture to satisfy the AFF definition was "non-comminution". By 2010, when this report was published, the atypical Femur Fracture Support Group managed by Jennifer Schneider and associates [21] already had accumulated details of a number of convincing cases where the BP-associated fractures were comminuted. We deemed that ASBMR feature to be one of exclusion, providing no evident advantage for the recognition of this problem and limiting the appreciation of its full extent. In fact, the first complete individual AFF case reported in the literature [27] was of a comminuted fracture. This report, which preceded the ASBMR report by 4 years, was covered extensively in the news media, with repeated use of the preoperative plain film as an illustration of an AFF. When we published, in 2012, a statistical summary [21] of that portion of our case histories which was acceptable to the editors of the *Journal of Clinical Endocrinology and Metabolism*, four comminuted fractures were included. We stated "we strongly feel that the restriction of the AFF definition reached by the

ASMBR Task Force to noncommittated fractures excludes many cases that clearly deserve consideration". About that time the United Kingdom [28] and European Union [29] authorities had issued criteria making non-comminution optional, thus *de facto* reducing it to a minor feature. Two years later [17], the ASBMR revised its definition somewhat, broadening but not abandoning the excluding character by retaining it as a major feature.

Table 1. Cases identified in the medical literature

Author/ Year (Ref)	MT fracture features	# of Individuals /# of MT fractures	Years of BP Use	Remarks
Guañabens/1994 [2]	Left, 2nd, mid- shaft	1/1	7 months	Patient was in 1st month of second 3-month etidronate cycle
Odvina/ 2003 [19]	n/a	"several"	various	In the preliminary presentation, no MT details were given. Alendronate was the only BP.
Odvina/ 2006 [20]	n/a	1/1	4	Only one MT fracture after alendronate was described in the followup publication.
Schneider/ 2006 [27]	Right, 2nd	1/1	7	The fracture healed after several months.
Wiel/2008 [30]	4th basilar (2)	2/2	n/a	One on ibandronate, the other on risedronate. Both were atraumatic fractures. A bisphosphonate association was not recognized.
Armamento-Villareal/ 2009 [31]	n/a	4/7+ One pt had "multiple bilateral" MTFs	3½-8	Subsequent clinical courses were not described.
Waterman/ 2011 [22]	2nd (1), 4th(3), 5th (4), L(4), R(4)	6/8	5(1), 7(2), 8-10(3)	All were being treated for multiple myeloma with sequential IV pamidronate then zoledronate, or only IV zoledronate. (see MM clarification in text above).
Pradhan/ 2012 [32]	Left, 5th	1/1	8½	This was a Jones fracture. Earlier the patient had an AFF after 7 years on alendronate (continued).
Reichmister/2012 [33]	Left, 2nd (1 pt) Left (1 pt) Bilateral (1 pt)	3/4	12 14 5	First case MT fractured after alendronate 12 yrs, experienced an AFF 3 years later. The 2nd case MT fx on aln after 14 years, had an AFF 1 year later. The 3rd case had MT and AFF fx after 5 years on alendronate; then another MT fx and another AFF subsequently.
Schneider/ 2012 [21]	n/a	28/28+	1½-15	Details of the cases including MT fractures were not described but several of the AFF cases reported suffered more than one MT. (see text above)
Adam/ 2013 [23]	2nd	1/1	34 months	Czech paper read in abstract only. Atraumatic nature of the MT fracture was emphasized.
Al-Azzani/ 2015 [34]	Right, 5th	1/1	9	The individual described was treated with aln and then ibandronate. The MT fx preceded an AFF by several months
Murray/ 2016 [35]	Left	1/1	10	Two years after the MT, continuing alendronate, the patient sustained atraumatic tibial fractures
Muira/ 2017 [36]	Right, 5th	1/1	6½	The MT Jones fracture occurred spontaneously six months after bilateral AFFs
Hinshaw/ 2017 [25]	Right, 5th	1/1	13 alen 1. 3 zol	The MT Jones fracture occurred ~ 3 years after the last zoledronic acid infusion. Polypharmacy intervened (see text above).

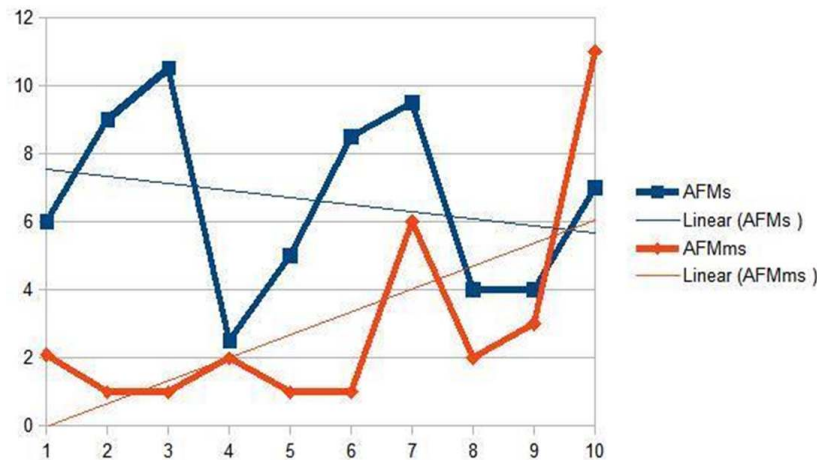


Fig. 1. (adapted from reference 30: last 10 years of the study plotted against the # of identified fractures) AFMs show the annual incidence of AFFs using only the ASBMR major criteria [ref 14]

*AFMms show the annual incidence these AFFs that also had one or more minor criteria
The least-squares regression technique was used to generate the trend lines*

A 2018 report [37] suggested that a "drug holiday" from bisphosphonate therapy may be associated with an increased risk of MTFs during the holiday interval. The assumption of causality brought on by the "drug holiday" must be challenged in the light of three important facts. First, the persistence of BP medications in bone is very long. The published pharmacodynamic data on the BPs is sparse but in a limited study [38] of menopausal women, who received 7.5 mg of alendronate IV daily for 4 consecutive days, the *maximum* individual calculated half life of the drug (half remaining unexcreted) was 17.4 years. There is no justification for an assumption that a bisphosphonate holiday will be accompanied by the significant clearance of the drug from the skeleton. Second, the incidence of second, contralateral, AFFs is reduced (but not eliminated) by stopping BP treatment in comparison to continuing the treatment after the first AFF [21]. Third, we [21] and others [33,36] have reported prior occurrence, during BP treatment, of MTFs which herald rather than follow an AFF. MTFs while on BP therapy have also been reported as preceding other types of fractures that have been associated with bisphosphonate therapy [1,34]. These facts are inconsistent with the choice of MTFs as a marker of increased holiday risk.

5. CONCLUSION

The declared objective of the ASBMR Task Force on Atypical Subtrochanteric and

Diaphyseal Femoral Fractures was to develop a case definition "so that subsequent studies report on the same condition". This was a proper concentration of effort when there were many voices denying any connection between the BP drugs and these fractures. But as we have shown in this and earlier publications, many contributors to the medical literature currently assume that this connection extends far beyond the confines of the ASBMR definitions which narrowly define a subset of femur fractures. We conclude that the time has arrived to change the assumptions implicit in this policy of exclusion, which was designed to make the definition as precise as possible, but as a result excludes many supportable cases from the statistical analyses of potential risk. One example is exclusion of comminuted femoral fractures. As legitimate evidence appears of BP-associated fractures in addition to the original AFFs, such as the atraumatic MTFs we have illustrated here, our understanding of the scope of the impact of these drugs will depend on a recognition of all the characteristic effects. Accordingly we propose that the frequency of this association justifies the inclusion of a prevalent or subsequent MTF as one of the optional minor features defining the bisphosphonate-associated atypical femoral fracture.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author WBH has provided legal consultation and testimony in matters concerning the BP drugs. Author JPS has declared that no competing interests exist.

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