

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

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.

1. Introduction

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

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34 In July 2003, an article (6) was published reporting fractures combined
35 with high bone density (total body Z-score of +2.5 using a scale (7)
36 developed for children and adolescents) in a young boy treated with high
37 doses of a BP. The effects were described as an induced osteopetrotic
38 change with atraumatic fragility fractures after long-term administration
39 of intravenous pamidronate, a moderately antiresorptive BP which is
40 much less inhibiting of mineralization than etidronate. No MT
41 involvement was reported, but this was the first report to describe the
42 fracturing potential of prolonged BPs in humans. This publication was
43 accompanied by an editorial (8) which sounded a clear warning about
44 BP-associated fracture complications. Remarkably, a similar effect had
45 been observed (9) in experimental animals some 30 years earlier. Mice

46 treated with etidronate or clodronate were described as tending toward
47 "a slowing of bone remodelling with an osteopetrotic skeleton resulting".
48 Osteopetrosis (OPT) is a genetic disorder resulting in fracturing despite
49 the associated high bone mineral density (10).

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51 The relevance of OPT to a discussion of the effects of bisphosphonates
52 on femoral and metatarsal fractures (MTFs) is that, analogous to the
53 deactivating effect of BPs on osteoclasts (11), osteoclasts in OPT are
54 inactive and cannot remove damaged bone (10, 12). This lack of
55 function is associated with fracturing. These two parallel but very
56 different mechanisms –drug-associated or congenital-- are associated
57 with similar fractures in the same bones (13), including metatarsals (14,
58 15). The genetic deficits in the osteopetroses lead to a preponderance of
59 formation without remodeling repair of damaged areas. The target of the
60 BP drugs is, of course, the osteoclast-mediated resorption of bone.
61 Indeed, subtrochanteric/femoral transverse shaft fractures of lateral origin,
62 meeting the definition of BP-associated atypical femoral fractures (AFFs)
63 (16, 17) by the American Society of Bone and Mineral Research
64 (ASBMR), have been described in individuals with congenital OPT. This
65 report (18) included a literature review of the period between 2009-2013
66 finding 19 additional examples of shaft or subtrochanteric femoral
67 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.

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.

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 (34)	Right, 2nd	1/1	7	The fracture healed after several months.
Wiel/2008 (26)	4 th 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 (27)	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 (28)	Left, 5th	1/1	8½	This was a Jones fracture. Earlier the patient had an AFF after 7 years on alendronate (continued).
Reichmister /2012 (29)	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 (30)	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 (31)	Left	1/1	10	Two years after the MT, continuing alendronate, the patient sustained atraumatic tibial fractures
Muir/ 2017 (32)	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 4. 3 zol	The MT Jones fracture occurred ~ 3 years after the last zoledronic acid infusion.

				Polypharmacy intervened (see text above).
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Table 1 Cases identified in the medical literature

Discussion

In the two ASMBR 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 (33) of the incidence of AFFs, defined only by the ASMBR-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. (Figure 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 Figure 1, the increase in sensitivity obtained by

including the AFMms clearly does show an upward trend in AFFs during the 10 year period.

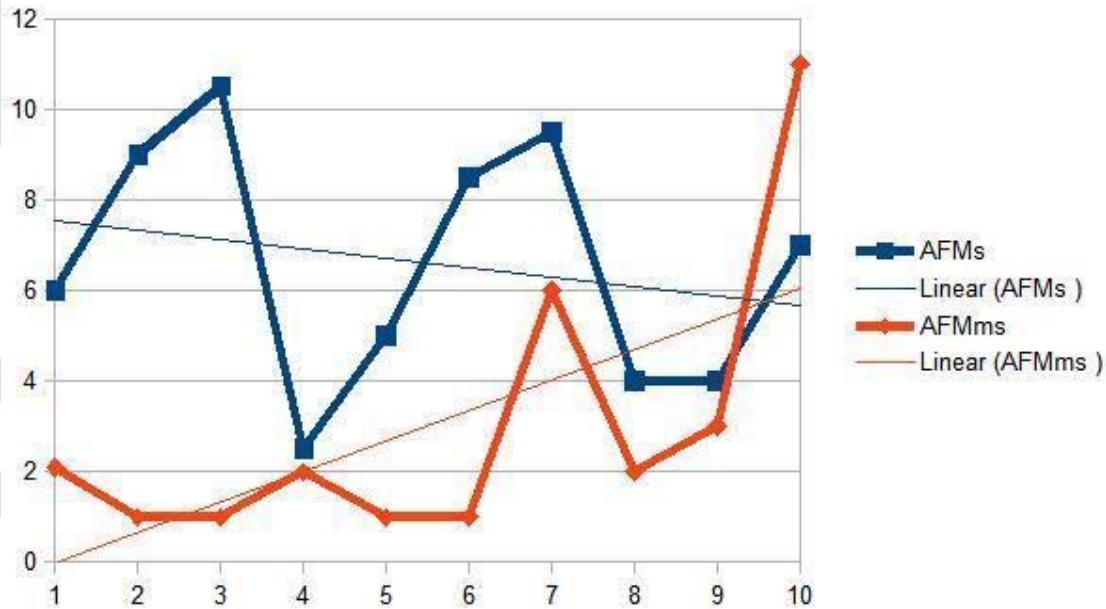


Figure 1 (adapted from reference 30: last 10 years of the study plotted against the # of identified fractures) AFMs show the annual incidence of AFFs using only the ASBMR major criteria (ref 14) AFMms show the annual incidence these AFFs that also had one or more minor criteria The least-squares regression technique was used to generate the trend lines

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

167 this report was published, the atypical Femur Fracture Support Group
168 managed by Jennifer Schneider and associates (21) already had
169 accumulated details of a number of convincing cases where the BP-
170 associated fractures were comminuted. We deemed that ASBMR
171 feature to be one of exclusion, providing no evident advantage for the
172 recognition of this problem and limiting the appreciation of its full extent.
173 In fact, the first complete individual AFF case reported in the literature
174 (34) was of a comminuted fracture. This report, which preceded the
175 ASBMR report by 4 years, was covered extensively in the news media,
176 with repeated use of the preoperative plain film as an illustration of an
177 AFF. When we published, in 2012, a statistical summary (21) of that
178 portion of our case histories which was acceptable to the editors of the
179 *Journal of Clinical Endocrinology and Metabolism*, four comminuted
180 fractures were included. We stated "we strongly feel that the restriction
181 of the AFF definition reached by the ASBMR Task Force to
182 noncomminuted fractures excludes many cases that clearly deserve
183 consideration". About that time the United Kingdom (35) and European
184 Union (36) authorities had issued criteria making non-comminution
185 optional, thus *de facto* reducing it to a minor feature. Two years later
186 (17), the ASBMR revised its definition somewhat, broadening but not
187 abandoning the excluding character by retaining it as a major feature.

A 2018 report (37) suggested that a "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 "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 (29, 32) 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, 30). These facts are inconsistent with the choice of MTFs as a marker of increased holiday risk.

Conclusions

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.

Ethical approval and consent: NA

References

(1) Hinshaw WB, Schneider JP. Bisphosphonate-associated Atypical Fractures that are not “Atypical Femoral Fractures”, Brit J Med Res. 2017;19(7):1-17. Doi: 10.9734/BJMMR/2017/31269.

(2) Guañabens N, Peris T, Monegal AL, Collado A, Muñoz-Gómez. Lower extremity stress fractures during intermittent cyclical etidronate treatment for osteoporosis. Calc Tiss Internat.1994;54(5):431–43.

(3) Mautalen C, Gonzalez D, Blumenfeld EL, Santini Araujo E, Schajowicz F. Spontaneous fractures of uninvolved bones in patients with Paget's disease during unduly prolonged treatment with disodium etidronate (EHDP). Clin Orthop Relat Res.1986;207:150-5.

(4) Eyres KS, Marshall P, McCloskey E, Douglas DL, Kanis JA. Spontaneous fractures in a patient treated with low doses of etidronic acid (disodiumetidronate). Drug Safety. 1992;7(2):162-5.

- 253 (5) Fleisch H. Bisphosphonates in the treatment of osteoporosis.
254 Scandinav J Rheum. 1998;27(sup107):64.
255 Doi:10.1080/03009742.1998.1172076.
256
- 257 (6) Whyte MP, Wenkert D, Clements KL, McAlister WH, Mumm S.
258 Bisphosphonate-induced osteopetrosis, N Engl J Med. 2003;349(5) 457-
259 63.
260
- 261 (7) Bachrach LK, Hastie T, Wang M-C, Narasimhan B, Marcus R. Bone
262 Mineral Acquisition in Healthy Asian, Hispanic, Black, and Caucasian
263 Youth: A Longitudinal Study. 1999; J Clin Endo Met. 84(12):4702-12.
264
- 265 (8) Marini J. Do Bisphosphonates Make Children's Bones Better or
266 Brittle? N Engl J Med. 2003;349(5):423-26.
267
- 268 (9) Reynolds JJ, Murphy H, Muhlbauer RC, Morgan DB, Fleisch H.
269 Inhibition by Diphosphonates of Bone Resorption in Mice and
270 Comparison with Grey-Lethal Osteopetrosis. Calc Tiss Res. 1973;12:59-
271 71.
272
- 273 (10) Shapiro F. Osteoporosis: Current Clinical Considerations, Clin
274 Orthop Relat Res. 1993;294(9):34-44.

(11) Sato M, Grasser W, Endo N, Akins R, Simmons H, Thompson DD, et al. Bisphosphonate Action. Alendronate Localization in Rat Bone and Effects on Osteoclast Ultrastructure. J Clin Invest. 1991;88(12):2095-2015.

(12) Fraser D, Kooh SW, Chan AM, Chernian AG. Congenital osteoporosis - A failure of normal resorptive mechanisms of bone. Calcif Tiss Res.1968;2(Supp):52.

(13) Yates CY, Bartlett MJ, Ebeling PR. An Atypical Subtrochanteric Femoral Fracture From Pycnodysostosis: A Lesson From Nature. J Am Soc Bone Miner Res. 2011;6(6):1377–1379.

(14) Hassenhuttl K. Osteopetrosis: Review of the Literature and Comparative Studies on a Case with a Twenty-four-Year Follow-up. J Bone Joint Surg Am. 1962;44:359-370.

(15) Chawla A, Kwek EBK. An unusual presentation of patella and fifth metatarsal base fractures. J Clin Orthop Trauma 2018;95:S45-S51. in a patient with osteopetrosis

297 (16) Shane E, Burr D, Ebeling PR, Abrahamsen B, Adler RA, Brown TD,
298 et al. Atypical subtrochanteric and diaphyseal femoral fractures: Report
299 of a task force of the American Society for Bone and Mineral Research.
300 J Bone Miner Res. 2010;25(11):2267–2294.

301

302 (17) Shane E, Burr D, Abrahamsen B, Adler RA, Brown TD, Cheung A,
303 et al. Atypical subtrochanteric and diaphyseal femoral fractures: Second
304 report of a task force of the American Society for Bone and Mineral
305 Research. J Bone Miner Res. 2014;29(1):1-23.

306

307 (18) Aslan A, Baykal YB, Uysal E, Atay T, Kirdemir V, Baydar ML et al.
308 Surgical Treatment of Osteopetrosis-Related Femoral Fractures: Two
309 Case Reports and Literature Review. Case Rpts in Orthoped 2014:
310 Article ID 891963, 7 pages. Doi:10.1155/2014/891963.

311

312 (19) Odvina CV, Rao DS, Pak CYC, Maalouf N, Zerwekh JE. Adynamic
313 bone disease during bisphosphonate therapy: Should we be concerned?
314 American Society of Bone and Mineral Research Annual Meeting, 2003.
315 Presentation number SU344.

316

(20) Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CYC. Severely suppressed bone turnover: A potential complication of alendronate Therapy. J Clin Endocrinol Metab. 2006;3:1294–1301.

(21) Schneider JP, Hinshaw WB, Su C, Solow P. Atypical femur fractures: 81 individual personal histories. J Clin Endocrinol Metab. 2012;97(12):4324-4328.

(22) Waterman GN, Yellin K, Jamshidinia K, Swift RA, Tamkin JA, Andell RA, et al. Metatarsal stress fractures in patients with multiple myeloma treated with long-term bisphosphonates: A report of six cases. J Bone Joint Surg – Amer. 2011;93(18):18:e106.

(23) Adam Z, Sprláková-Puková A, Chaloupka R. Atypical fracture of metatarsal bone in a patient with multiple myeloma who was treated long-term with bisphosphonates. Vnitri Lekarstvi 2013;59(11):1022-6.

PMID: 24279448

(24) Melton LJ, Kyle RA, Achenbach SJ, Oberg AL, Rajkumar SV. Fracture risk with multiple myeloma: a population-based study. J Bone Miner Res. 2004;20(3):487-493. DOI: 10.1359/JBMR.041131.

339 (25) Hinshaw WB, Schneider JP. Bisphosphonate-associated bilateral
340 atraumatic ulna fractures. Internat J Med Pharmaceut Case Rep.
341 2017;9(1):1-6.2017. DOI:10.9734/IJMP/2017/33170.

342

343 (26) Weil L, McEneaney PA, Prezioso J. Treatment of Fourth Metatarsal
344 Base Fracture Non-Unions in Middle Aged Women with Osteoporosis: A
345 case study, Foot Ankle J. 2008; 1(7):5-11.

346

347 (27) Armamento-Villareal R, Napoli. N, Diemer K, Watkins M, Civitelli R,
348 Teitelbaum S, et al. Bone turnover in bone biopsies of patients with low-
349 energy cortical fractures receiving bisphosphonates: A case series. Calc
350 Tissue Int. 2009;85(1):37-44.

351

352 (28) Pradhan P, Saxena V, Yadav A, Mehrotra V. Atypical metatarsal
353 fracture in a patient on long term bisphosphonate therapy. Indian J
354 Orthop. 2012;46(5):589–592.

355

356 (29) Reichmister R, Jay P. Atypical fractures associated with long-term
357 bisphosphonate use. Clin Geriatr. 2012;20(2):17-21.

358

359 .(30) Al-Azzani WAK, Evans L, Speight L, Lea-Davies M, Stone MD, Lau
360 D, et al. Hyperpharmacotherapy in ageing cystic fibrosis patients: The

first report of an atypical hip fracture. *Respir Med Case Rep.*
2015;16:148e150.

(31) Murray JC, Audet MC, Bédard M, Michou L. Bilateral distal fibula
fractures in a woman on long-term bisphosphonate therapy. *Osteoporos*
Int. 2016;27(2):833–836.

(32) Miura LN, Srikantom SV, Schenck J, Double Fixation: Bilateral
Bisphosphonate-Related Hip Fractures. *Am J Med* 2017;130(1):e13-15.
DOI:10.1016/j.amjmed.2016.06.044.

(33) Feldstein AC, Black D, Perrin N, Rosales AG, Friess D, Boardman
D, et al. Incidence and Demography of Femur Fractures With and
Without Atypical Features. *J Bone Miner Res* 2012;27(5):977–986.

(34) Schneider JP. Should bisphosphonates be continued indefinitely?
An unusual fracture in a healthy woman on long-term alendronate.
Geriat. 2006;61(1):31-33

(35) [https://www.gov.uk/drug-safety-update/bisphosphonates-atypical-](https://www.gov.uk/drug-safety-update/bisphosphonates-atypical-femoral-fractures)
[femoral-fractures](https://www.gov.uk/drug-safety-update/bisphosphonates-atypical-femoral-fractures). Accessed 11/12/2017.

- 383 (36) http://www.ema.europa.eu/docs/en_GB/document_library/Referrals
384 [_document/Bisphosphonates_31/WC500117118.pdf](#). Accessed
385 11/12/2017.
- 386
- 387 (37) Bindon B, Adams W, Balasubramanian N, Sandhu J, Camacho P.
388 Osteoporotic fractures during bisphosphonate drug holiday. Endocrine
389 Practice. 2018;24(2):163-169. DOI:10.4158/EP171975.OR.
- 390 (38) Khan SA, Kanis JA, Vasikaran S, Kline WF, Matuszewski BK, McCloskey EV,
391 et al. Elimination and Biochemical Responses to Intravenous Alendronate in
392 Postmenopausal Osteoporosis. J Bone Miner Res. 1997;12(10):1700-1707.