



Bisphosphonate-associated Atypical Fractures that are not “Atypical Femoral Fractures”

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Authors' contributions

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ABSTRACT

Aims: Responding to the steadily increasing number of unusual subtrochanteric and mid-shaft femoral (ST/FS) fractures in persons treated with the bisphosphonate drugs since the index cases were described in 2003, the American Society of Bone and Mineral Research (ASBMR) convened a committee tasked with finding a precise definition. Their present definition, a composite from two publications, includes the morphological characteristics of low trauma, origin as an insufficiency fracture, transverse/oblique orientation with/without comminution, cortical thickening, and beaking at the cortex when complete. These fractures must occur in mid-femur, below the lesser trochanter and above the supracondylar flare. They became known as Atypical Femur Fractures (AFFs). The index cases included about an equal number of fractures meeting this definition and similar fractures in other locations. Despite this, attention was focused on the ST/FS definition and a large number of publications ensued describing these. However, publications in the medical literature as early as 1986 contained descriptions of non-femur fractures associated with bisphosphonate

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therapy and the number of these reported has grown slowly contemporaneously with reports of femur fractures meeting the ASBMR definition.

The present authors have been following the development of these non-AFF bisphosphonate-associated fractures since 2005 and have collected a large amount of historical and current information on the subject. We find that many useful inferences about the phenomenon can be derived from consideration of it as a systemic rather than localized effect. We aim to provide a summary of this subset up to the present time and to discuss the implications of these data.

Methodology: We queried the OVID Medline database as detailed below.

Results and Discussion: We identified 102 individual or case series which reported more than 166 atypical non-AFF fractures. In the Discussion, we review the current state of the evidence upon which the assumed antifracture benefit of the drugs rests and show that these atypical fractures, when added to the AFFs, reduce even more the typically claimed benefit-to-harm ratio.

Conclusion: We intend this review as a resource for individuals wishing to follow developments in this field. We also present our conclusions about the implications of the accumulated evidence and the general state of associated knowledge.

Keywords: *Atypical; fracture; bisphosphonate; non-femur; alendronate; zoledronic acid; risedronate; ibandronate; etidronate; pamidronate.*

1. INTRODUCTION

Since 2003, there has been a steadily increasing number of fractures reported temporally associated with bisphosphonate (BP) therapy used in the treatment or prevention of osteoporosis. Most cases have involved the middle portion of the femur. Demographic investigations, case reports, and speculation about the potential of bisphosphonate (BP) therapy to increase bone fragility have focused on these laterally-originating subtrochanteric and femoral shaft (ST/FS) fractures, occurring in the longest highly-stressed mostly-cortical portion of the bone [1]. A “task force” convened by the American Society of Bone and Mineral Research reached a consensus on several additional “features” which defined what the committee labeled “atypical femur fractures” (AFFs) [2] for the express purpose of providing a uniform definition for investigators. The task force report clearly stated that the increasing number of reports of fractures associated with BP treatment was the reason it had been convened. The paper identified as of 2010 some 37 case reports or series where the fractures were associated with various combinations of BP therapy. Although there was doubtless some duplication, the cited reports included 335 fractures of which 326 were associated with BP therapy. (For this review, we have identified some 102 case or series reports containing description of more than 166 fractures. All of the included fractures were deemed by the authors to be due to bisphosphonate therapy).

The task force definition consisted of a list of major and minor “features”. Five major features

were all required for a fracture to be designated as an AFF. The first of these, specific location in the femur, excluded fractures above the lesser trochanter and below the supracondylar flare. Association with BP medication was not a major feature but was included as a minor feature based on the assertion that similar fractures occurred in individuals who had not been treated with BPs. There were indeed nine such BP-unassociated fractures identified in the task force summary. We have confirmed the stated non-use of BPs in one of the four cases reported by Bunning [3]. Three non-BP fractures were reported by Girgis [4] as not currently taking BP. No other history was provided; thus these cases cannot be definitively assigned to the non-association category, as these fractures can occur after the BP medication has been stopped [5]. The remaining 5 cases reported in abstract form by Dell and co-workers [6] with reportedly good x-ray evidence were the only other unambiguous exceptions. The task force report included some six possible pathogenic mechanisms observed in preclinical studies of BPs which might rationalize a positive BP association. Furthermore, of the fractures presented from which the definition of the AFF was derived, 97½% were associated with BP therapy. For some reason, the report failed to include the 2003 index case presentation at the 2005 ASBMR annual meeting while nonetheless referencing the abstract at the 2010 meeting which provides 5 of its 6 more or less convincingly cited cases said to be unassociated with BP therapy. The authors of this abstract subsequently stated [7] that they believed that the fractures were rarely observed before the use

of BPs began. An industry-sponsored study [8] confirmed this.

These AFF-type fractures presumably originally attracted attention because they are unusual, standing out in contrast to the more frequent hip fractures of the femoral neck and intertrochanteric region as well as the high-impact fractures typically associated with ST/FS femur [9]. In addition to the very specific anatomic location, attributes assigned to the AFF include atraumatic initiation, prodromal pain, origin as an insufficiency fracture in the lateral cortex, non-comminuted (but not always - see below) transverse breakage, and local cortical thickening causing medial beaking when the fracture is complete. These latter attributes are shared by many non-AFF fractures reported in connection with BP therapy over the last 12 years, but perhaps because these often have been not so unusual as the femur examples, they seem to have attracted only limited attention. Perhaps also the general acceptance of the very specific femoral location has engendered a pervasive but unjustified sense of anatomic specificity [10,11]. Non-AFF femur examples as well as examples in many other anatomic locations have nonetheless been described and often called "atypical" in reference to characteristics similar to the AFFs except for anatomic location.

The ASBMR AFF definition was officially updated in 2014 [12]. At least one of the fractures (reported by one of us in 2006 [13]) which was listed in the 2010 task force report was comminuted and thus inconsistent with the non-comminuted restriction. We also reported in 2012 two additional cases that met the definition except for that restriction [5] and argued at that time that comminuted cases had been observed by us and deserved recognition. We were gratified to see that a modified definition including "limited" comminution was incorporated into the task force update.

The first public presentation [14], specifically identifying a potential association between BP therapy and low-trauma fractures of bones of high cortical content, described five fragility fractures after long-term alendronate (Fosamax™) therapy, only one of which involved the femur. This clinical material was subsequently expanded in the general medical literature with the addition of several more femur examples [15], and this was followed shortly by another femur fracture report [13] associated in

the same individual with an unusual metatarsal fracture. These index cases clearly showed that the associated fractures were not limited to the femur. This has been borne out by many subsequent case presentations. The clinical appearance of these insufficiency fractures, often in highly-stressed bones, is morphologically similar to the AFFs and argues persuasively for a more general process not confined to the ST/FS femur.

2. MATERIALS AND METHODS

In a publication in 2012, we emphasized the growing importance of atypical non-AFF fractures [5]. Two thoughtful reviews of risks associated with antiresorptive therapy [16,17] published in 2011 did not mention non-AFF BP-associated fractures. Several limited reviews published more recently have acknowledged these fractures including those of the ulna [18] and the pelvis [19], although the latter also discussed a broader range of etiologies. These did not include any new cases and are not included in our tabular summary. We compiled this list using OVID Medline In-process & Non-indexed, ePub Ahead of print, and Standard 1946-present, and with a large variety of appropriate key words.

3. A REVIEW OF NON-AFF BISPHOSPHONATE-ASSOCIATED FRACTURES WITH ATYPICAL CHARACTERISTICS

3.1 Early History of Bisphosphonate-associated Fractures

Alendronate was the first BP approved by the FDA for use in post-menopausal DXA-determined osteoporosis. Following that 1995 approval, two scientists prominent in bone physiology suggested that a possible increase in bone fragility might be observed with this new class of drugs. Michael Parfitt warned about this in a 1996 textbook [20]. In 1998, Herbert Fleisch, the Swiss physiologist who, beginning in the early 1970s, discovered and led the exploitation of the antiresorptive properties of the BP class of drugs, expressed [21] similar reservations.

Alendronate and the other bisphosphonates are small organophosphorus molecules based on a pyrophosphoric acid moiety in which the central oxygen atom has been replaced by carbon. The mechanism of action of alendronate is predominantly an inhibition of osteoclastic bone

resorption [22,23]. But before the FDA approval of this drug, interest had focused on etidronate, a BP significantly more potent than alendronate as an inhibitor of mineralization [24,25]. This drug, the subject of many years of clinical investigation, can be pushed to the point of severe osteomalacia. Several etidronate-associated non-AFF fractures were reported. Among three patients treated for osteoporosis off-label with cyclic etidronate, seven stress fractures of the lower extremities were found [26]. Another similar treatment led to the loss of five osseointegrated dental implants [27] – essentially osteolysis, without necrosis, of the all-cortical alveolar bone proper. (This was a complication that, 15 years later, was reported in a patient treated with alendronate [28]). A placebo-controlled trial of etidronate did not demonstrate fracture reduction efficacy but claimed controlled trial evidence for “safety” and “no evidence of generalized osteomalacia” [29].

Just before the disclosure of the index alendronate-associated fracture [14] cases, atraumatic bilateral L4 pars fractures were reported [30] in a child treated long-term with high doses of the BP pamidronate. Two years earlier, Susan Ott [31] had pointed out that the data from an extended alendronate trial, which did not carry the placebo comparator beyond the first 3 years, suggested an increase in fractures over baseline with prolonged use. Anatomic locations of the incident fractures in this extended trial [32] were never specified.

The four alendronate patients originally described in the fall of 2003 by Clarita Odvina [14] had incurred 1 “proximal femur” (later specified to be the femoral shaft [15]), 2 pelvic, and 2 sacral, as well as “several metatarsal and metacarpal” fractures. Her subsequent publication of an expanded analysis of nine patients (including the 4 above) reported 2 pelvic, 2 sacral, 1 metatarsal, 1 vertebral, 1 rib, and 6 femoral shaft fractures. Jennifer Schneider [13] then described a comminuted femoral shaft fracture and a subsequent metatarsal fracture in the same individual following long alendronate use. Thus at the beginning of 2006, the reported anatomical locations of fractures associated with long-term oral BP use were equally distributed between those of the femoral shaft and non-ST/FS sites. Certainly there was nothing to suggest that the phenomenon would be observed exclusively in the femur. Rather, these early observations provided the first evidence that the increasingly acknowledged association

[33,34] of long-term BP use with the ST/FS is only part of a larger overall increase in fracture incidence. The present authors reported 81 individual long-term histories of AFFs [5], 35% of whom also experienced one or more metatarsal fractures - after the femoral event. The percentage would have been greater if metatarsal fractures while on the BP but preceding the femur had been included. Nonetheless, it is understandable that the greatest attention has been to more remarkable AFFs, since the fractures in at least some of the other anatomical locations reported in the index cases have a much higher background incidence and thus BP-related examples may go unnoticed in the observational “noise”. To date, fractures with the characteristics of the AFF have been reported in association with BP therapy in the calcaneus, clavicle, cuboid, distal femur, metatarsal, pelvis (pubic rami, ischium, sacrum, acetabulum), radius, rib, scapula, talus, tibia, ulnar, and vertebral bones. These reports are presented in tabular form below. However, several merit individual attention.

3.2 Discussion of Selected Examples

As mentioned above, the index cases were about equally divided between the femurs and the combined pelvis (including the sacrum), metatarsals, vertebrae, and ribs. Reports of similar insufficiency fractures have continued to appear, with increasing frequency. Cases of a non-AFF fracture in the same individual as an AAF and/or ONJ can be found. A remarkable series of insufficiency fractures of the femur, tibia, calcaneus, and talus, eight insufficiency fractures in all, associated with prolonged BP therapy, has been reported [35] in a single individual. In this section we offer a critical appraisal of the implications of some of the papers reviewed.

3.2.1 Proximal femur

A carefully done evaluation [36] of the Danish national database (in a search for atypical femur fractures) revealed that the summed incidence of proximal femur “classical” hip fractures in persons treated with alendronate was significantly greater than in matched comparators who were not treated.

3.2.2 Distal femur

As mentioned above, the ST/FS fractures came to notice because they were felt to be unusual and were of increasing incidence. Evidence has been presented that fractures of the distal femur

increased after the introduction of the BPs. In residents of one county with long-term records [37] at the Rochester Mayo Clinic, there was an 11% increase in distal femur fractures (as defined by the Arbeitsgemeinschaft für Osteosynthesefragen / Orthopedic Trauma Association Category 33 [38] which all fall outside the ASBMR AFF definition) during 1996 - 2007 compared to 1984-1995. Alendronate was introduced for the treatment of osteoporosis in 1995. There have been three strikingly similar reports from independent workers showing the same fracture pattern developing in the distal (condylar) femur associated with BP therapy [39,40,35]. Of course, the ASBMR task force definition of AFFs specifically excluded this femoral region.

3.2.3 Vertebrae

Michael Whyte has been especially instructive about long term BP sequelae resembling osteopetrosis. While the “bone-within-bone” radiological appearance characteristic of congenital osteopetrosis was not seen early in his case [30] of prolonged pamidronate exposure, the patient’s clinical course including bilateral pars fractures was deemed consistent with an acquired osteopetrosis-like state. That initially-missing characteristic radiological sign developed years after the pamidronate was stopped [41] and more fractures ensued (another spondylolysis, a metacarpal and an ulna fracture). Long-term pamidronate in a young patient has been described in another report [42] as inducing an osteopetrotic state mimicking the characteristic bone-in-bone radiological sign. While no fractures are reported in that case, Whyte’s patient’s bilateral vertebral pedicle fractures have also been observed in three separate BP exposed individuals [43,44,45], respectively after 3 years of IV ibandronate, after 4 years of weekly alendronate, and after 10 years of risedronate. In addition, another atraumatic 3-level bilateral pedicle fracture in an elderly man, previously diagnosed two years before as osteoporotic, was reported in 2006. The medication history in this last case was not reported [46] and it is not included in our tabulation.

3.2.4 Metatarsal

Metatarsal fractures accompanied by two AFFs were reported [47] in a patient with previously undiagnosed adult hypophosphatasia (HPP) who was not taking a BP. In this interesting recent paper, the danger of using a BP in persons with

undiagnosed HPP is discussed. HPP produces [48] elevated levels of pyrophosphate (PPi) secondary to low levels of alkaline phosphatase. Despite opinions to the contrary [24], the dual biological activity of PPi has been shown to be similar the BPs [49,50,51]. Like the bisphosphonates illustrated in this paper, PPi has both antiresorptive (cellular) and mineralization inhibitory activity. This case illustrates the similarity in the resulting pattern of skeletal fractures in metabolic economies affected by PPi or BPs, a similarity which has been noted before [52]. The authors specifically enjoined the use of BPs despite multiple fractures in similar patients. However, Timothy Bhattacharyya at the NIH studied [53] the DNA of a series of patients with prior AFFs and found no statistical correlation of incident AFF with preexisting HPP.

3.2.5 Ulna

A review [18] of BP-related ulnar fractures and several additional ulnar reports [54,55] are available. Some of these fractures were deemed a result of stress placed by walking aids on the arms. Ulna fractures in the absence of BP therapy are occasionally reported as incident with walking aids as well.

3.2.6 Pelvis

BP-related fractures of the pelvis have been reported since the index cases [56,57]. One series with biopsies included femur, pelvis, rib, metatarsal, and ankle fractures [58].

3.2.7 Metatarsus

Metatarsal fractures following the femur fractures occurred in 35% of the AFF patients we reported [5] and in 50% of another shorter series [59].

3.2.8 Alveolar bone proper

An osseointegrated dental implant failure [28] following alendronate initiation shows that osteolysis can occur with a remodeling-dominant BP as well as with etidronate.

Table 1 lists all the papers up to November 2016 that we have discovered. These are Level IV anecdotal case report examples. We recommend consideration of this evidence in the context of the Bradford Hill analysis (see below). No cases are listed unless the author attributed the fracture(s) to a BP.

Table 1. Atypical non-AFF fractures 1986-2016

Author/Year/Ref (Chronological)	Non-AFF atypical fracture site	Patients/no. of non-AFF fractures	Brief details
Mautalen/1986/[60]	Tibia, ulnas, rib, vertebra	2/5	Fractures, through non-Paget bone, attributed to etidronate; there was also one transverse insufficiency fx of the femoral diaphysis originating laterally
Eyres/1992/[61]	Bilat tibias	1/2	Fractures through non-Paget bone after etidronate; osteomalacia (osteolysis) seen and resolved after stopping drug and starting calcitonin
Guanabens/1994/[26]	Distal tibial metaphysis	1/1	Etidronate used off-label, never approved for osteoporosis; these insufficiency fracture (s) healed spontaneously
"	Cuboid; second metatarsal	1/2	
"	Both calcani; prox tibia; dist tibia x 2	1/5	
Starck/1995/[27]	Alveolar bone proper	1/1	Osteolysis released osteointegrated alveolar implants after etidronate started
Whyte/2003/[30,41]	L4, L3 spondylolysis metacarpal, ulna,	1/2 bilat then +3	Child had putative hyperphosphatasemia; given high doses of pamidronate He developed 3 more atypical fractures years after stopping the BP
Odvina/2003/[14]	Pelvis	2/2	Alendronate. Femur, metatarsal, metacarpal, and rib fractures were also
"	Sacrum	2/2	mentioned in the abstract but only 1 femur fx was described in detail
Odvina /2005/[15]	Sacrum	1/1	In this series, 7 femoral shaft fractures were also reported
"	Vertebra, rib	1/2	as occurring in some of the patients listed with non-femur fractures
"	Sacrum, ischium	1/2	
"	Pubic rami	1/2	
"	Metatarsal	1/1	
Schneider/2006/[13]	Metatarsal	1/1	Alendronate; had prior AFF on alendronate
Imai/2007/[56]	R pubis, L ilium	1/2	Alendronate for 3 years
Lee/2007/[62]	Sacrum	1/1	After 9 months alendronate, 2 undisplaced AFFs were also noted.
Kazimoglu/2009/[63]	Bilateral distal tibia	1/2	Insufficiency undisplaced distal shaft fractures on alendronate
Arribas- Garcia/2009/[64]	Ilium	1/1	ONJ patient suffered fracture of iliac crest on biopsy
Doita/2009/[65]	Bilat pedicle	1/2	Had VCF at L5; 3 mths later bilat pedicle fractures at L4; no BP history
Armamento- Villareal/2009/[58]	Metatarsals bilat	1/2+	After 8 years on BP
"	Multiple ribs	1/2+	After 7 years on BP
"	Metatarsal bilat	1/4+	After 8 years on BP
"	Multiple ribs		
"	Fibula	1/1	After 4 years on BP
"	Ribs	1/1+	After 8½ years on BP
"	Ribs, metatarsals	1/3+	After 6 years on BP; patient also had an AFF
"	Metatarsal	1/1	After 3½ years on BP

Author/Year/Ref (Chronological)	Non-AFF atypical fracture site	Patients/no. of non-AFF fractures	Brief details
"	Ankle	1/1	After 4 years on BP
Breglia/2010/[66]	Tibial diaphysis	1/1	12 years alendronate
Thaya/2010/[67]	Femoral head	1/1	3 years alendronate after suffering VCFs before the BP was started
Bjorgul/2011/[55]	Ulna	1/1	Pt had 4 femoral fractures
Tang/2011/[68]	Ulna, tibia	1/2	Alendronate; the two fractures occurred over 7 month interval
Waterman/ 2011/[69]	Metatarsals	6/6	Pts on long-term BP for mult myeloma
El Rachkidi/2011/[70]	Vertebral pedicles	1/2	bilat, L5, atraumatic, not assoc with VCF 10 years on risedronate
Stathopoulos/2011/[71]	ulna	1/1	Pt had 2 AFFs after 6 yrs IV zol, 2 yrs teriparatide, and 1 year more IV zol
Schneider/2012/[5]	Metatarsal	28/28	All 28 incurred an AFF before the metatarsal fracture
Pradhan/2012/[72]	5 th metatarsal	1/1	On alendronate; had prior AFF on alendronate
Hoppé/2012/[73]	Tibia rib fibula ulna	1/4	On etidronate 20 yrs for Pagets; these fx in non-pagetic bone
Subramanian/2012/[28]	Alveolar bone proper	1/1	Starck (1995) experience with etidronate revisited; osseointegrated implants failed after 7 years alendronate: osteolysis/osteomalacia with alendronate
Imbuldeniya/2012/[40]	Bilat tibial metaphysis, distal femoral metaphysis	1/3	Pamidronate every 3 months, chronic administration although duration not specified. Fractures were non-displaced insufficiency type. Femur fracture possibly bilateral.
Reichmister/2012/[59]	4 metatarsals, rib, sacrum	3/6	These patients also sustained one or two AFFs. BP therapy had been given for 14, 15 and 5 years
Ang/2013/[74]	Ulna, bilat	1/2	Walker for ambulation; 15 years of BP; prior introchanteric fx on BP
Patel/2013/[57]	Upper & lower pubic rami	1/2	After 8 cumulative years on BPs; after 5 years BP use she had an AFF
Moon/2013/[75]	Ulna	1/1	All three fractures showed characteristic beaking
"	Radius	1/1	Pt presented with insufficiency bilateral AFFs as well; 12 yrs alendronate
Bissonette/2013/[76]	Tibia	1/1	Insufficiency fracture of radius, bilat hypertrophy FS cortex; 8 yrs aln
Grace/2014/[54]	Ulna	1/1	Insufficiency fracture
Watson/2014/[77]	Pelvis	1/2	After 9 years on alendronate; patient used cane as a walking aid
Tantavisut/2014/[78]	Acetabulum	1/1	2 fractures R hemipelvis after yrs of BP; later had femoral neck fracture
Vun 2014/[79]	clavicle	1/1	Periprosthetic, after 7 years of zoledronate infusions q 6 weeks
Ayanaoğlu/2015/[80]	Ilium; pubic rami	1/3	Alendronate 7 yrs
Tournis/ 2015/[81]	Ischiopubic ramus	1/1	8 years BP therapy
Karabay/2015/[44]	Pedicle, mult. bilat	1/8	Alendronate 4 yrs, teriparatide 18 months then alendronate 4 more years
Al-Azzani/2015/[82]	Metatarsal	1/1	L1-L4 all affected; history of BP medication
Kim/2015/[43]	L4 pedicles bilat	1/2	5 yrs alendronate, 1 year holiday, 4 yrs ibandronate; followed by AFF
Osada/2015/[83]	ulna	1/1	3+ yrs of IV ibandronate; patient also had 2 ST/FS insufficiency fractures
			7 years of alendronate; histology provided

Author/Year/Ref (Chronological)	Non-AFF atypical fracture site	Patients/no. of non-AFF fractures	Brief details
Cecchetti/2015/[35]	5 tibial, 1 distal femur, 1 calcaneus, 2 talus	1/9	8 years risedronate (2002-2010) The fractures listed occurred between 2007 and 2013 Last talar dome fracture occurred after the initiation of teriparatide in 2012
"	scapula	1/1	Alendronate 6 yrs
"	Tibial diaphysis	1/1	Alendronate 5 years
Sharma/2015/[84]	Distal tibia diaphysis	1/1	Unilateral increased cortical density with incipient beaking after 2 yrs on IV pamidronate
Al-Wattar/2016/[39]	Bilat prox tibias; unilat distal femur	1/3	Fractures were in the corresponding metaphyses and were insufficiency-type.
Murray/2016/[85]	Metatarsal; bilateral distal fibula shaft	1/3	Metatarsal after 10 years alendronate therapy; continued for a total of 12 yrs, stopped, and bilateral distal tibial fractures occurred 5 months later
Haque/2016/[86]	Scapula	1/1	10 years on alendronate; fracture was associated with no fall or trauma
Van der Laarschot/ 2016/[87]	Tibia	1/1	Transverse atypical tibial fx after 7 yrs IV BP; AFF occurred 2 yrs later
Vasanwala 2016/[88]	Tibia	1/1	After 15 pamidronate cycles; fracture was followed by three ST/FS AFFs
Erdem/2016/[89]	Ulna	1/2	One new, 1 partially healed transverse fx in same ulna; 7 years alendronate

4. DISCUSSION

4.1 Causality of Bisphosphonate-related Fractures

It has been commonplace to assert that BP causation of femoral shaft fractures "has not been established". The ASBMR task force papers included this declaration. Despite this, the current FDA-approved BP label, part 17, acknowledges causation [34]. There is a widespread claim that only a randomized blinded placebo-controlled null hypothesis trial designed to differentiate the drug and placebo side effects can "prove" such causation. Such a trial powered to detect these uncommon events would be very large, very expensive, and thus very unlikely. The NHLBI Women's Health Initiative is an example of such a mammoth trial. This assertion has been the defense of the frequently-reiterated statement that the causation has not been "proved". However, an independent consensus has developed steadily over the last 20 years that this kind of "proof" is neither necessary nor desirable [90,91], especially when considering uncommon side effects. Yet, in each BP PI Warnings & Precautions section, a claim against causation is still currently advanced: "Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates". This is an

invocation of lack of specificity to disprove causation. The FDA has endorsed a [92] soft approach to settle this simple logical fallacy known as *the fallacy of the single cause*. This is the Bradford Hill methodology. The legacy analysis of Austin Bradford Hill [93] is viewed on the USFDA website as appropriate methodology for deciding the question of causation of uncommon side effects. This methodology is especially sensitive to the specificity issue: quite different initial events [94,95] progressing to the same result *by the same mechanism* are not regarded as inconsistent with specificity. In other words, assuming that one cause of an event is invalidated if another cause can be found is unfounded, and in fact is a recognized logical fallacy. Rather, the Bradford Hill reasoning views such as confirmatory of causality if it can be demonstrated that there is a commonality of mechanism. In the examples given, the commonality lies in the prevalence of excessive PPI or its equivalent, a BP. In other words, this analysis supports the conclusion that a causal relationship exists between bisphosphonate use and atypical fractures.

The Bradford Hill causation analysis also seeks analogy support for causation even though as formulated it states that such support will often not be forthcoming. In the present case, there is ample analogy support. Spontaneous atypical

AFF-like femur fractures are observed on osteopetrosis [94], a hereditary failure of osteoclast activity analogous to the known osteoclast dysfunction induced by the BPs.

Another hereditary syndrome, adult hypophosphatasia [95,52], includes failure of adequate alkaline phosphatase synthesis, causing high blood levels of pyrophosphate. The physiologic action of pyrophosphate was the model for the discovery of the BP antiresorptive activity [96,51]. AFF-like femur fractures, metatarsal fractures, and alveolar bone dysfunction are observed in adult hypophosphatasia. A third analogy can be found in the history of phosphorus chemistry. In the mid-19th to early 20th centuries, mid-femoral fractures occurring with no trauma were observed in factory conditions where there was exposure to smoke and fumes from accidental white phosphorus fires [97,98]. This smoke contains a significant amount of pyrophosphate [97,98]. This exogenous PPi origin is comparable to the endogenous origin of the PPi excess associated with hypophosphatasia. Both result in bone fragility resembling that associated with the bisphosphonates.

4.2 Does the Benefit-to-harm Ratio Really Make the BP-induced Fractures Rare Compared to Those Prevented?

Pleas [99] to increase BP treatment in the face of decreasing utilization by the target population fail to take into account that while BP use declined by more than 50% during 2006-2010, hip fractures still declined significantly between 2008 and 2012. ST/FS fractures rose steadily and significantly during 2002-2011, but abruptly dropped in 2012 [100]. The absolute incidence of BP-related fractures has been thoughtfully assessed in several communities [101,8]. The varying technical quality of such estimates aside, this incidence is invariably compared to a benefit derived from the bisphosphonate pivotal clinical trials [for example 102]. "Fractures incurred" can be measured, even if the methodologies used can be disputed; "fractures prevented" seem never to be questioned, despite being measured only by a surrogate endpoint [103] since these cannot be measured in any other way. This endpoint is the clinical trial result. The applicability of such surrogate comparison to normalized populations has been questioned [103,104]. Nelson Watts [105] published a "Perspective" seeking to justify the use of regular DXA screening of patients under treatment for

osteoporosis by asserting that many patients seen *and treated* in clinical practice would not have been deemed eligible for the clinical trials. He referenced one osteoporosis center where 97% of those treated would not have been allowed to participate in at least one of the trials. Watts acknowledged that the BMD data from the trials would not necessarily carry over to the general clinical population. The fracture-prevention benefit postulated by these isolated trials is uncertain for exactly the same reason. All participants in the FIT (alendronate) pivotal trial were recruited together [106]. An FDA statistical analysis of the fracture reduction results from the entire recruitment did not reach the required level of significance [107]. It has become important to give serious consideration to the fact that the reduction in fracture risk noted in the so-called "FIT-1" sub-analysis [102] and the osteoporotic-portion of the "FIT-2" study [108] cannot be expected in the real world (the osteopenic portion sub-analysis in FIT-2 did not demonstrate anti-fracture efficacy [108,109]). These results call into question the familiar opening line of hundreds of papers to the effect that BPs are *known to have prevented many fractures* despite whatever harm is about to be documented in that particular paper.

A meta-analysis [110] of all published BP trials (not real world studies) of sufficient length to prevent one hip fracture found that treatment for 525 woman-years was required to prevent a single hip fracture. A case-control study [111] in a large northwestern clinic population found fracture risk over 10 years did not differ in persons who received BPs and persons who did not. A province-wide Canadian case-control study [101] did not find a significant reduction in hip fractures until 5 years use, the same interval required to detect a significant association with femoral shaft fractures, and the upper limit of the treatment interval now being recommended [112]. University-based refereed meta-analyses funded by the British Columbia Ministry of Health found clinical benefits from BP treatment to be sufficiently small as not to outweigh serious harms [113]. Similar exhaustive reviews [114,115] of all published BP trials and meta-analyses went further to conclude that the risk-to-harm ratio could be unfavorable when the indication is for the prevention or treatment of osteoporosis, that is, long term treatment for chronic disease rather than for metastatic bone pain, a separate indication for some of the bisphosphonates. Another Canadian analysis found even benefits limited to secondary prevention (individuals with

prevalent fractures) were unclear due to the small magnitude and calculated high risk of bias in the trials [116], especially considering the extensive use of sub-group analyses. 68% of the 81 femoral shaft fracture patients whose long-term histories we published [5] had been prescribed a BP despite a bone mineral density in the osteopenic or normal range, a group acknowledged by the original lead author of FIT-2 to enjoy no expectation of fracture risk reduction from treatment [108,109]. This, aside from any claims about secondary prevention, adds significantly to the harm side of any equations calculating the therapeutic ratio. The addition of the non-femur fractures and the possible toll of induced but as yet unrecognized additional non-AFFs [117] clearly influences the therapeutic ratio calculated on the basis of the pivotal trials.

4.3 What Does the Origin of AFFs in the Lateral Femoral Shaft Signify?

The lateral side of the middle section of the femur is the longest portion of the whole bone subject to the greatest strain, followed by the shorter superior portion of the femoral neck [1]. Despite efforts mentioned above to attribute anatomic or metabolic causes to explain the specificity of the ST/FS region for the new type of fracture, the high strain on this area is likely to be the real explanation [118] for most insufficiency fractures. This concept receives support from the increased incidence of AFFs in populations where bowing of the upper femur shaft is more prevalent [119]. Such bowing would increase the tensile strain on the lateral ST/FS. The likelihood that mechanisms reducing the resistance of the lateral shaft to fracture might operate similarly at other high-stress locations in any bone is supported by the distribution of fracture locations in the early reports between 2003 and 2007. So far as we have been able to determine, a comparison of the specific types of fractures incurred in the bisphosphonate pivotal trial drug and placebo arms (especially in the extensions) has never been published. We have illustrated the many examples of fractures associated with bisphosphonate therapy which fall outside the restrictive definitions proposed by the ASBMR task force. Whether some of these types of fractures might have occurred in the drug arm of the pivotal and pivotal-extension trials cannot be determined from published data.

The intermediate term BP effects in animal models [120,121] include reduction in the work-

to-fracture (increased brittleness/decreased toughness) and increased homogeneity [122] which reduces the resistance to crack propagation. There is no physiologic reason to expect that these effects would somehow be limited to the femoral shaft. On the contrary, the all-cortical low-turnover character of the femoral shaft might suggest less opportunity for bisphosphonate binding there [22]. BP pharmacokinetic studies [123,124] in humans have been limited to a study of the retention and excretion of an initial or small number of doses, which ignores the critical fact that the remodeling surface available to bind the drug steadily decreases [125] with regular dosing, or as presciently realized by one authority, recognition of the nature of the activity of the BP on the target (bone) could be expected to affect the pharmacokinetics [126]. Claims that the rate of retention of alendronate was similar for single and multiple doses [127] fail to take into account the inevitable reduction in absorption after long term multiple dosing. The ASBMR review of BP-associated femur fracture calculated the average time to fracture to be about 7 years [2]. In our published series, it was about 9 years [15]. Early estimates of the half-life of alendronate in cortical bone were as long as 40 years [128].

In summary, the interest in these effects on the femur has resulted from the simple fact that the shaft fractures happen to involve the largest and strongest bone in the body where fractures are usually associated with significant trauma. This strength protects the bone from fracture and thus magnifies the significance when fractures are observed in association with insufficiency and low trauma. The upper lateral portion of the shaft is the longest high-stress zone when standing. Atypical femoral fractures are commonly reported to occur when the individual was standing or rising to a standing posture. But given the very widespread prescribing of BP drugs and the increasing awareness of AFFs, it is inevitable that fractures might begin to be noticed, after being alerted by the femoral susceptibility, at other stressed bones predominantly but not exclusively of high cortical content. One can only speculate as to whether yet other fractures not sharing these easily identifiable characteristics may also be due to the effects of the drugs. A recent analysis of the fractures in a FIT trial extension was limited to the "placebo" arm [129], i.e., patients who had in fact received alendronate in the earlier pivotal trial although not in the extension. The fractures described were grouped as "clinical" with no additional

characterization. As emphasized above, a comparative distribution analysis of fractures in the two arms of a pivotal trial has never been published. Another analysis [130] of the short term FIT (alendronate) and HORIZON (zoledronic acid) trials and the FLEX FIT-extension confined analysis to femur fractures only, again revealing nothing about fracture distribution.

5. CONCLUSION

In the reported index cases, the increased fragility of highly-stressed cortical bone at several locations due to BP treatment implies a more general skeletal effect than might be expected from the recent preponderance of the femur in published cases. The steadily increasing number of non-femur cases reported and reviewed here confirms this. To date, cases associated with BP therapy and resembling the physical characteristics of the AFFs have been reported in at least 14 non-AFF sites, as well as in osteolytic failure of the alveolar bone proper, the latter having no pathological resemblance to the many reported cases of bisphosphonate-related osteonecrosis of the jaw. The evidence that the BPs increase fragility of more bones than only the femur implies that a portion of the fractures occurring in long-time users at more common but less easily distinguished sites such as the intertrochanteric femur could well be associated with the therapy rather than the underlying "disease". Several real-world epidemiological studies were unable to confirm the efficacy claimed from the randomized controlled trials; additionally, the cited Canadian and Finnish meta-analyses call the trial data into question. These reports suggest that therapeutic benefit-to-risk ratio assumed by most authorities may not be as favorable to the BPs as claimed. These reports imply a need for additional efficacy investigations and a comparative analysis of the pattern of fractures in the placebo and active trial arms, especially the life-threatening and severely debilitating fractures rather than the often asymptomatic morphometric vertebral compressions added to the more serious types. Such studies might challenge the assumed risk-benefit ratio of the BP drugs based on the pivotal clinical trials. It is to be expected that an accelerating number of reports of non-femur BP-related fractures will continue to appear, lending support to this hypothesis.

The management of the various atypical fractures that are not atypical femur fractures is evidently

dependent on the local orthopedic medical consensus of how best to treat breaks at the particular site. The papers cited deal with the particulars in almost every case. All of the more recent papers also strongly advocate stopping the bisphosphonate medication, a proviso which was not so prevalent at the time we wrote our analysis of case histories in 2012.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Author WBH has provided expert testimony in civil litigation concerning bisphosphonates. Author JPS states that she has no competing interests.

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