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Commentary

Proposed pathogenesis for atypical femoral fractures: Lessons from materials research

B. Ettinger [a,*], D.B. Burr [b], R.O. Ritchie [c,d,e]

[a] Department of Medicine, University of California Medical Center, San Francisco, CA, 156 Lombard Street #13, San Francisco, CA 94111, USA
[b] Dept of Anatomy and Cell Biology, MS 5035, Indiana University School of Medicine, 635 Barnhill Dr, Indianapolis, IN 46202, USA
[c] Department of Materials Science & Engineering, University of California, Berkeley, CA 94720-1760, USA
[d] Department of Mechanical Engineering, University of California, Berkeley, CA 94720-1760, USA
[e] Materials Sciences Division, Lawrence Berkeley National Laboratory, USA

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ABSTRACT

Atypical femoral fractures (AFFs) have been well defined clinically and epidemiologically. Less clear are the underlying mechanisms responsible. This commentary points out the likely sources of decreased resistance to fracture using lessons from bone material studies and biomechanics. We hypothesize that the key element in the cascade of events leading to failure of the largest and strongest bone in the human body is long-term suppression of normal bone turnover caused by exposure to potent anti-remodeling agents, most notably the bisphosphonates (BPs). Suppressed bone turnover produces changes in bone that alter its material quality and these changes could lead to adverse effects on its mechanical function. At the submicroscopic [<1 μm] level of collagen fibrils, suppression of bone turnover allows continued addition of non-enzymatic cross links that can reduce collagen's plasticity and this in turn contributes to reduced bone toughness. Further, adverse changes in hydroxyapatite crystalline structure and composition can occur, perhaps increasing collagen's brittleness. At the microscopic level [~1–500 μm] of the bone-matrix structure, suppressed bone turnover allows full mineralization of cortical bone osteons and results in a microstructure of bone that is more homogeneous. Both brittleness and loss of heterogeneity allow greater progression of microscopic cracks that can occur with usual physical activity; in crack mechanical terms, normal mechanisms that dissipate crack tip growth energy are greatly reduced and crack progression is less impeded. Further, the targeted repair of cracks by newly activated BMUs appears to be preferentially suppressed by BPs. We further hypothesize that it is not necessary to have accumulation of many cracks to produce an AFF, just one that progresses — one that is not stopped by bone's several protective mechanisms and is allowed to penetrate through a homogeneous environment. The remarkable straight transverse fracture line is an indicator of the slow progression of a "mother crack" and the failure of usual mechanisms to bridge or deflect the crack. Research in AFF mechanisms has been focused at the organ level, describing the clinical presentation and radiologic appearance. Although today we have not yet connected all the dots in the pathophysiology of BP-induced AFF, recent advances in measuring bone mechanical qualities at the submicroscopic and tissue levels allow us to explain how spontaneous catastrophic failure of the femur can occur.

Introduction

The purpose of this commentary is to explore the possible mechanisms linking long-term bisphosphonate (BP) use to the occurrence of a rare but catastrophic failure (fracture) of the femur — termed atypical femoral fracture (AFF). First, we describe the AFF clinical entity and subsequently we review current hypotheses that could explain the relationship between BP use and AFF. Bone scientists and clinicians are now well aware of the large number of case reports, cohort studies, and case–control studies that point to a very strong association between BP use and AFF — so strong that today most experts have concluded that BP use substantially contributes to the risk of suffering an AFF [1]. However, the literature on potential AFF mechanisms is currently confusing and occasionally contradictory. Based on expanding knowledge from bone biology and biomechanics studies, we offer a plausible explanation for BP exposure causing catastrophic failure of the femur, the largest, heaviest, and strongest bone in the skeleton.

The final event in the process of an AFF is an insufficiency fracture occurring between the lesser trochanter and the supracondylar flare. An insufficiency fracture is a stress fracture caused by repetitive, normal loading on bone that is unable to functionally adjust to the demands

* Corresponding author at: 156 Lombard Street #13, San Francisco, CA 94111, USA.
E-mail addresses: doc.ettinger@gmail.com (B. Ettinger), dburr@iupui.edu (D.B. Burr), roritchie@lbl.gov (R.O. Ritchie).

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being placed on it. Thus, an insufficiency fracture differs from a usual stress fracture, for example those observed in athletes or military recruits, in that it is caused by a problem in the bone rather than by an excessive amount of loading. However, all stress fractures have a number of common characteristics such as horizontal progression nominally perpendicular to the long axis of the bone, slow progression with attempts at cortical repair, and pain at the periosteal repair site.

It has been hypothesized that the site of AFF is determined by femoral shape and the forces brought to bear on it. Typically, the fracture site is located 25% of the distance between the upper end of the femur and the knee [2]. This is where the convex curve of the upper femoral shaft straightens to a large degree and is the area where tensile forces are focused. The lateral location of AFF differs from the medial location observed in stress fractures observed among athletes. AFF is often a bilateral process since the forces generated by usual activities are equally distributed to both legs and the deficiencies in bone quality are generalized. Contralateral AFFs almost always occur at exactly the same site on a patient's opposite femur.

As a crack grows and penetrates through the outer femoral cortex, the osteoblasts in the periosteum produce cartilage and woven bone to form a bridging callus that appears on X-ray as a bump on the lateral aspect of the femur. This is the normal physiologic response to a break in the periosteal surface of bone, is mediated by an inflammatory response, and involves endochondral bone formation. Until the callus becomes calcified, it may not show up well on standard radiographs but will be detected by CT scan, MRI, or scintigraphy. As this stress fracture process continues, a horizontal dark line (the so-called "dreaded black line") progresses medially across the femur and ultimately a completed fracture occurs with little or no external trauma (i.e., spontaneously) [3]. The fracture line is usually transverse or only slightly oblique and the fracture is either not or only minimally comminuted; the relatively clean and smooth fracture line is quite unusual for fractures of this site. At the fracture site, localized periosteal reaction of the lateral cortex (termed "beaking") and thickening of both cortices often may be observed; this may include bone formation on the endocortical surface as well [4].

In 2010, the ASBMR Task Force published the clinical and radiologic criteria for AFF [1]. Required major elements included: 1) location anywhere along the femur from just distal to the lesser trochanter to just proximal to the supracondylar flare; 2) associated with no trauma or minimal trauma, as in a fall from a standing height or less; 3) transverse or short oblique configuration; 4) non-comminuted; and 5) complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex. Optional (minor) features included: 1) localized periosteal reaction of the lateral cortex; 2) generalized increase in cortical thickness of the diaphysis; 3) prodromal symptoms such as dull or aching pain in the groin or thigh; 4) bilateral fractures and symptoms; 5) delayed healing; 6) comorbid conditions (e.g., vitamin D deficiency, rheumatoid arthritis, hypophosphatasia); and 7) use of pharmaceutical agents. Some revisions of these criteria are expected in the forthcoming 2013 Task Force Report.

While review of AFF epidemiology is beyond the scope of this commentary, we recognize that such studies have shown that the incidence of AFF among people exposed to BP is quite low. Further, epidemiologic studies have found AFF cases among those who report no BP exposure.

Bone mechanics

In engineering, a number of terms are used to describe the mechanical quality of materials. In bio-engineering, the material qualities of bone are described in similar terms to other materials such as metal or plastic. The quality of bone is measured by the mechanical effects on the bone material when it is subjected to external forces or deformation. For example, bone strength can be described by the maximum force that a bone can sustain without failure. The modulus of elasticity, or Young's modulus, refers to the elastic stiffness of bone tissue. Brittleness describes the tendency of bone to fracture when it is minimally deformed, which is the opposite of ductility. Bone can be strong and stiff (i.e., sustain large maximum loads and not bend easily) but brittle (break when bent only a little). Toughness is a measure of bone's resistance to fracture, specifically how much work or force the material can endure before catastrophic failure, which for a bone is a fracture. Bone can be strong but still suffer from reduced toughness.

Bone turnover is accomplished by millions of microscopic bone metabolic units (BMUs; the final architectural product of a BMU is sometimes called a bone structural unit or BSU), each consisting of a resorption side and a formation side, the former accomplished through osteoclasts and the latter through osteoblasts. These two "sides" are closely linked by local chemical signalers — thus, osteoclasts can "talk" to osteoblasts and vice versa. As a result, in the normal skeleton, there is an active renewal of bone tissue accomplished by a balanced effort between resorption and formation.

In all postmenopausal women, these two "sides" become imbalanced to a lesser or greater degree. Because the amount of resorption is greater than the amount of formation, some bone mass is lost within each created BSU. Ultimately if this imbalance is severe, bone loss will result in deterioration of skeletal microscopic architecture and that will contribute to bone fragility (a tendency to fracture easily) — defined as osteoporosis.

Newly completed BSUs can be thought of as "young bone." Maturation of these "young bone BSUs" involves increasing mineralization and maturing collagen. Hydroxyapatite crystals are embedded in newly formed collagen fibrils at regular intervals along its protein helices. Crystal growth here occurs in two phases; the first, referred to as "primary" is estimated to occur within a few weeks while, "secondary" mineralization continues over many months to a few years [5]. At the same time, collagen fibrils undergo progressive cross-linking by enzymatic creation of deoxypyridinoline and pyridinoline connections both within and across adjacent fibrils. Both mineralization and collagen cross-linking substantially add strength to developing bone; however, we hypothesize that excessive mineralization and cross-linking can embrittle it.

Bisphosphonate is beneficial by reducing bone turnover

Bisphosphonates (BPs) are a pyrophosphate-like class of drugs that seek out and become incorporated into bone by attaching to hydroxyapatite crystals there. Through a complex series of biochemical and cellular changes, BPs suppress osteoclast function and reduce bone turnover. The immediate effect of BP administration is to alter the usual imbalance in which bone resorption outpaces formation. Temporarily, BPs induce a new imbalance between bone resorption (which is suppressed) and bone formation (which is not suppressed), thus allowing erosion pits created before treatment to fill in with new bone while reducing the creation of new resorption sites. However, in time (usually within 3 to 6 months after BP initiation), bone formation, because it is closely linked to resorption, also becomes suppressed. This 3 to 6 month period of filling in the remodeling space produces a measureable increase (usually 3–5%) of bone mineral density (BMD). With longer duration BP administration, bone becomes quiescent with both resorption and formation suppressed, but existing bone continues to mature as evidenced by changes in collagen structure and mineralization.

BP treatment, by filling in the remodeling "space", by increasing mineralization of bone, and by preventing new resorption activity, can make bone more resistant to injury and thereby reduce the risk of fracture, specifically by preserving bone architecture. The beneficial effects of BPs are most marked in cancellous bone that exists in the vertebra and in the ends of the long bones (i.e., hips and wrists).

Cancellous bone structure is particularly affected by osteoporosis and the associated bone fragility is largely mediated by excessive resorption cavities (or pits) that can cause microscopic damage from perforation and discontinuities of trabecular plates.

Patients with both low bone density and poor bone microarchitecture (osteoporosis) stand to gain the most from this effect of BPs. Clinical trials have shown a reduction in the risk of vertebral [6] and non-vertebral fractures [7] for women with osteoporosis within 6–12 months of BP initiation — long before large changes in BMD have accrued.

Bisphosphonates can markedly suppress bone turnover

The careful microscopic measurements of bone surfaces in bone biopsies allow calculation of a number of bone turnover parameters. Tetracycline, usually administered for 3 days 3 weeks prior and for 3 days one week prior to the biopsy, is incorporated into mineralizing bone matrix and should produce 2 fluorescent lines; the separation between these lines allows measurement of bone formation during the 2-week interval between the two tetracycline labels.

The key bone turnover parameters from a bone biopsy report are 1) percentage of bone surface showing single tetracycline label, 2) percentage of bone surface showing double tetracycline label and 3) a weighted score of single label (×0.5) plus double labeled (×1.0) mineralizing surfaces as a percentage of bone surface. This latter parameter is abbreviated MS/BS.

Ott has summarized a number of histomorphometric studies that reported bone turnover levels among postmenopausal women, both healthy and those diagnosed with osteoporosis [8]. The median MS/BSs for 13 reported studies were similar, most in the range of 5–7%, however, the spread of values among these untreated women was quite wide and included a small proportion with low turnover. For example, Kimmel and co-workers showed that 5 out of 90 biopsies from untreated postmenopausal women failed to show double tetracycline label, indicating very low turnover [9].

As far back as 1997, Chavassieux in Meunier's laboratory in Lyon, France, reported an approximately 90% reduction in MS/BS after 2 and 3 years in patients taking 10 mg alendronate daily compared to those taking placebo [10]. In this cohort, bone formation rates were also about 90% reduced compared to placebo. Biopsies from patients taking 5 mg alendronate daily showed somewhat lesser and later onset of markedly reduced turnover. The turnover reductions were observed in both trabecular type bone and bone beneath the dense outer cortex (endocortical area).

In 2000, Bone and co-workers reported on a double-blind, placebo-controlled two-year clinical trial comparing alendronate alone, conjugated equine estrogens 0.625 mg alone, and the combination of the two [11]. The median MS/BS was 0.3% and 0.1% in the alendronate and alendronate plus conjugated equine estrogen groups, respectively; these values are 90% and 95% lower than the 5.0% median MS/BS value observed in this study among women receiving placebo.

In 2005, Odvina and co-workers [12] described several patients with "severely suppressed bone turnover" (SSBT) in a publication that described the markedly reduced histomorphometric bone activity that was found among users of BPs suffering unusual low-energy fractures, some of which were in the femoral diaphysis. Odvina used the term SSBT based on observation from iliac bone biopsies performed after double tetracycline labeling.

In 2007, Chapurlat and co-workers reported on histomorphometric studies of iliac bone biopsies in 37 patients taking oral alendronate 10 mg/day, 10 patients taking oral risedronate 5 mg/day, and 3 receiving intravenous pamidronate quarterly [13]. All were exposed to BPs for 3 years or more (mean 6.5 years). Biopsies from 12 cadavers were used as comparators. One third of all the BP users in this study showed no double tetracycline label. The median MS/BS parameter among alendronate users was 0.4%, a value about 90% lower than what should be expected for post-menopausal women.

How could bisphosphonate suppression of bone turnover be harmful?

The hierarchical structure of bone is a useful paradigm in which to consider the interplay of various factors that affect resistance to fracture [14,15]; biomechanical functions of bone can be considered from the submicroscopic level to the organ (whole bone) level — and an understanding of the interplay of structure-function (or altered structure-dysfunction) can be valuable in showing the hypothesized mechanism for AFF.

While some aging of bone is beneficial, experimental evidence points to problems at all structural levels when bone ages excessively (or prematurely). Accumulation of "old bone" occurs when the process required for its replacement is slowed; in other words, when bone turnover is too low to maintain a continued supply of "new bone". While the chain of events leading up to the drug-induced insufficiency fracture involves a number of putative mechanisms at various structural levels (Fig. 1), suppression of bone remodeling is the likely driving force. Table 1 summarizes the evidence that supports these hypothesized mechanisms, categorized by the level of bone structure involved.

At the submicroscopic (<1 μm) level of collagen fibrils, several molecular changes occur over time; the effects of various additions to native collagen's mechanical functions have been theoretically summarized in a mathematical model [16]. Early on, these include increases in the ratio of pyridinoline to deoxypyridinoline cross-links and changes in the ratio of alpha to beta collagen fibril isomers, both measures of normal collagen maturation. Over a number of years, non-enzymatic collagen cross links such as pentosidine, derived from end-products of the Amadori reaction, become more prominent [17]. These glycation additions to proteins, so-called "advanced glycation end-products" (AGEs) are observed in many tissues, the most widely known of which is the glycation of hemoglobin in the red blood cell (glycohemoglobin) a key marker for diabetes mellitus glycemic control. Whereas glycohemoglobin levels are limited by red blood cell removal from the circulation, long-term persistence of collagen in bone allows extensive accumulation of AGEs. Under conditions of markedly reduced bone turnover, AGE-loaded collagen suffers reduced plasticity and this in turn contributes to reduced bone toughness [18].

Studies of the hydroxyapatite crystalline structure, either by spectroscopy or X-ray diffraction, suggest that prolonged exposure to BP causes less perfect crystalline structure, changes in the chemical composition of the crystals, and greater homogeneity of crystalline maturity [19]. Although evidence is lacking, it has been hypothesized that these crystalline changes also may reduce bone quality, perhaps through increasing collagen's brittleness.

At the microscopic level (~1–500 μm) of bone structure, suppressed bone turnover allows full mineralization of cortical bone osteons. This in turn allows greater progression of microscopic cracks that can occur with physical activity. It has been postulated that microcracks actually save bone from fracturing under the stress of injury and further, that microcracks are an important way that bone health is maintained. Specifically, limited microcracking is a form of "plasticity" (or more precisely inelasticity) in bone and can help dissipate energy from high applied stresses. In the bones of the healthy young, cracks have limited progress as their path is stopped by differences in mineral density and structure. For example, a crack might be thwarted by the cement line of an osteon or the differing density of interstitial versus osteonal bone. In bone that is old, structural homogeneity allows the crack path to be less impeded. Studies of crack progression through bone indicate the formation of "daughter cracks" ahead of the advancing crack tip in young bone — these are essentially protective microcracks in that they help dissipate the tip energy

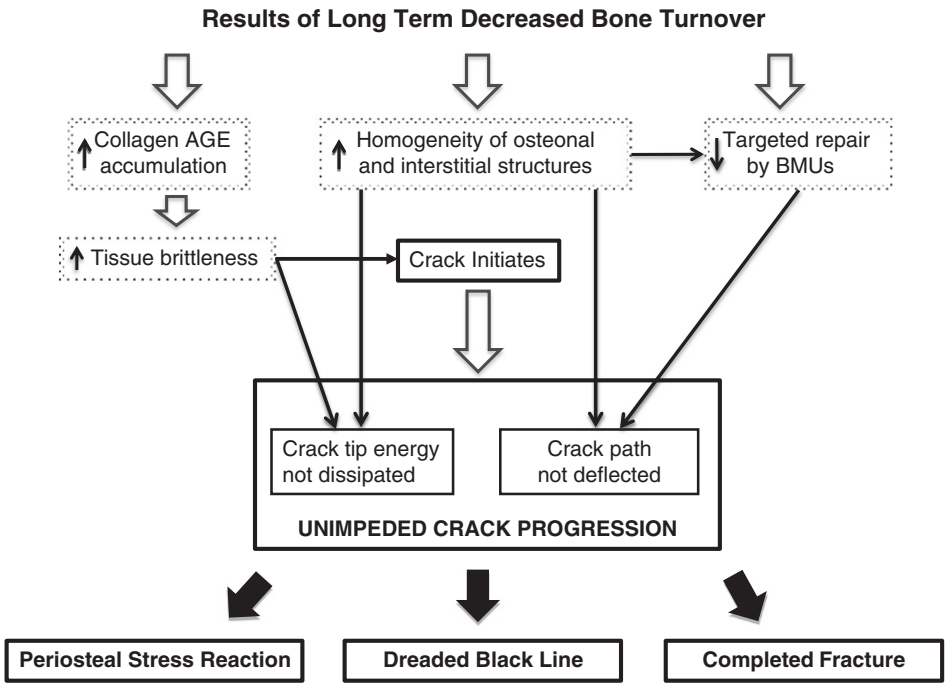

Fig. 1. Flow diagram of pathophysiological steps leading from suppression of bone turnover to atypical femoral fracture. AGEs = advanced glycation end-products; BP = bisphosphonate exposure; BMU = bone metabolic unit; AFF = atypical femoral fracture.

[14]. Additionally, in bone that has normal plasticity, bridges of bone (so-called ligaments) in advance of the crack tip help dissipate local crack growth energy [15]. In brittle bone, seen with aging, these energy-dissipating mechanisms are not seen and thus cracks can progress more easily [15]. We hypothesize that BP exposure, by reducing bone turnover, causes a type of premature aging of bone, rendering it more brittle and less likely to impede crack tip progression. Further, growing cracks are usually targeted for repair by newly activated BMUs [25]; this could also impede crack progression. However, bisphosphonates, attracted to metabolically active bone sites, appear to preferentially suppress the targeted repair process [26]. In bone with normal turnover, targeted repair not only could stop progression of a microcrack but results in bone that is "younger" due to appearance of new BSUs at the site of micro crack repair. These new BSUs can also help to maintain bone's heterogeneous microstructure.

We propose that homogeneity in bone is an important etiologic factor in causation of AFF. The characteristic transverse appearance of the fracture line indicates the relatively unimpeded path of "the mother of all cracks". An analogy would be the ease with which cracks spread through glass, a homogeneous material, compared to other heterogeneous materials such as concrete or fiberglass. Although increased microcrack number has been produced in animals given

Table 1
Evidence that supports suppression of bone turnover contributing to reduced bone material quality, by level of bone structure.

Level of evidence	Evidence	How it is measured	Intermediate results	End results	Key citations
Nano- to micro-scales of mineral and collagen fibrils (<1 μm)	AGE addition to collagen	Modeling HPLC	Equations ↑ with age	↓ sliding of fibrils ↑ stiffness	[15] [16]
	AGE accumulation	X-ray scattering (SAXS)	↑ with BP	↓ ability to absorb strain	[17]
	Mineralization degree and perfection	X-ray diffraction FTIR spectroscopy	↓ mineral perfection ↓ variability of collagen mineralization	(↓ toughness) ↑ homogeneity	[18] [19] [20] [21]
Micrometer scale (~1–500 μm) of bone tissue	Osteonal mineralization	Quantitative micro-radiography Backscattered SEM	Higher and narrower peak	↑ homogeneity ↓ tissue resistance to crack initiation and growth	[22] [14] [23]
	Resistance to fatigue damage	Ex vivo stress/strain fracture toughness measurements	↓ crack bridges allowing ↑crack progression	↑ stiffness ↑ brittleness ↓ BMU targeted repair	[24] [25]
	Resistance to crack progression (fracture)	Pre-cracked 3-point bend testing	↑ plastic deformation resistance (R curves)		
	Crack-associated BMUs	Histomorphometry	BMU association with cracks		
Millimeter scale of organ	Lateral femur periosteal stress reaction	Radiograph Scintigraphy	Localized cortical thickening, periosteal/endosteal callus formation, "hot spot" on scan	Prodromal pain Dreaded black line (horizontal)	[1] [3]
	Progression of crack across femur	MRI/CT		Spontaneous fracture	[2]
	Atypical femoral fracture	Surgical specimen: gross and microscopic	Crack substantially transverse laterally, medial spike Location within femoral diaphysis, within region of maximal tensile force	Contralateral stress reaction or fracture at same location.	

AGEs = advanced glycation end-products; HPLC = high pressure liquid chromatography; SEM = scanning electron microscopy; MRI = magnetic resonance imaging; CT = computed tomography; SAXS = small angle X-ray scattering; FRIR = Fourier transform infrared spectroscopy; BMU = bone metabolic unit.

bisphosphonates, it is unclear whether bone biopsies in humans exposed to bisphosphonates show increased numbers or length of microcracks [27,28], or whether microcracks are the primary contributor to reduced bone toughness [29]. We hypothesize that it is not necessary to have accumulation of many cracks to produce an AFF, just one that progresses — one that is not stopped by the protective processes of BMU initiation and one that penetrates through a homogeneous osteon/interstitium environment. The remarkable straight transverse fracture line is an indicator of the slow progression of a "mother crack" due to the paucity of usual bone material protective mechanisms.

Bisphosphonate exposure can be both beneficial and harmful: the "Goldilocks effect"

There has been a widely held belief that the greater the suppression of bone turnover the more bone benefit will accrue from an antiresorptive drug. Evidence from clinical trials of various antiresorptive drugs with varying antiresorptive effects indicates that this is not the case. While a treatment that reduces turnover by 20–30% may be "too little", reducing turnover by 70–90% may be "too much" in terms of adverse effects on bone quality.

Opposing beneficial and harmful effects of BPs on bone mechanical properties may play out differently over time. In the initial months to few years of exposure, beneficial effects predominate and may subsequently plateau [30]. With long-term BP exposure, after a few years, harmful effects on bone mechanical properties can occur. It is our opinion that these opposing effects explain the temporally observed skeletal benefits and later adverse effects from BPs.

Biological changes occurring in bone due to bisphosphonate exposure would be expected to slowly evolve as cortical bone in the femur must slowly lose its microscopic heterogeneity. These changes would be expected to take some years to develop. Additionally, the process of AGE addition to collagen causes loss of plasticity over its lifetime (many years). This timing hypothesis is in keeping with the findings of Dell and co-workers that showed a progressive and marked increase in AFF risk with duration of BP exposure [31]. Indeed, in a large case series the median onset of AFF in those exposed to BPs is about 7 years [1].

It would be further expected that reversal of these bone mechanical properties following BP discontinuation would be slow. However, Schilcher and co-workers found in a case–control study that risk of a first AFF decreases 70% for each year after a BP is stopped [32]. If targeted repair of microcracks were to recover more quickly than bone structural changes after BP discontinuation, then AFF risk could be reduced by creation of new BMUs that would impede progression of microcracks. We do not know for how long a person who has suffered an AFF will continue to be at risk for a second AFF; indeed, many second AFFs have occurred some years after the initial ones [33].

More knowledge is needed of the material properties of bone in patients exposed to long-term BP and those suffering an AFF. Future research in this area should be particularly focused on the following:

- Through submicron-scale experiments involving in situ tensile tests with simultaneous (real time) small angle X-ray scattering and wide angle X-ray diffraction, assess BP-induced changes in the amount of strain carried by collagen versus its associated mineral. This will permit an examination of potential BP effects on bone strength and plasticity (via fibrillar sliding).
- Though micron-scale bending tests, define the mechanistic effects of long-term BP exposure on the separate properties of strength and toughness in precracked or micronotched bones. The objective here would be to discern the extent of homogenization (if any) of the bone matrix structure at the microscale and whether this has any influence on the crack-growth toughness as measured by crack path deflection.

Conclusion

There is a substantial body of evidence that the escalating occurrence of AFF observed over the past decade is related to the use of BP. We know from histomorphometry that some postmenopausal women develop severely suppressed bone turnover after a few years of BP use and we know that suppressed bone turnover can induce changes in bone that affect its material quality and that these changes could lead to adverse effects on bone mechanical function. Research in understanding AFF mechanisms has been largely focused on the organ level, describing the clinical presentation and radiologic appearance. Although today we have not yet connected all the dots in the pathophysiology of BP-induced AFF, recent advances in measuring bone mechanical qualities at the submicroscopic and tissue levels allow us to explain how spontaneous catastrophic failure of the femur can occur when a crack can progress unimpeded through bone.

Conflict of interest

Dr. Burr has received research grants from Eli Lilly and AMGEN. He has served as a consultant to Agnovos Healthcare LLC, and been on the Global Experts Panel for Merck. Dr. Ettinger has received honoraria for lectures from Eli Lilly and has served as a consultant to AMGEN. He has also received payments for acting as an expert witness in litigation involving Merck's Fosamax. Dr. Ritchie reports no potential conflicts of interest.

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