Bone 55 (2013) 495–500

Contents lists available at SciVerse ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

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

ARTICLE INFO

Article history:
Received 8 January 2013
Revised 9 February 2013
Accepted 11 February 2013
Available online 16 February 2013

Edited by: Thomas Einhorn

Keywords:
Atypical femoral fractures
Bisphosphonates
Bone turnover
Aging
Bone quality
Bone biomechanics

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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http://dx.doi.org/10.1016/j.bone.2013.02.004

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).