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Review

American Society of Biomechanics Journal of Biomechanics Award 2013: Cortical bone tissue mechanical quality and biological mechanisms possibly underlying atypical fractures ☆

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ABSTRACT

The biomechanics literature contains many well-understood mechanisms behind typical fracture types that have important roles in treatment planning. The recent association of "atypical" fractures with long-term use of drugs designed to prevent osteoporosis has renewed interest in the effects of agents on bone tissue-level quality. While this class of fracture was recognized prior to the introduction of the anti-resorptive bisphosphonate drugs and recently likened to stress fractures, the mechanism(s) that lead to atypical fractures have not been definitively identified. Thus, a causal relationship between these drugs and atypical fracture has not been established. Physicians, bioengineers and others interested in the biomechanics of bone are working to improve fracture-prevention diagnostics, and the design of treatments to avoid this serious side-effect in the future. This review examines the mechanisms behind the bone tissue damage that may produce the atypical fracture pattern observed increasingly with long-term bisphosphonate use. Our recent findings and those of others reviewed support that the mechanisms behind normal, healthy excavation and tunnel filling by bone remodeling units within cortical tissue strengthen mechanical integrity. The ability of cortical bone to resist the damage induced during cyclic loading may be altered by the reduced remodeling and increased tissue age resulting from long-term bisphosphonate treatment. Development of assessments for such potential fractures would restore confidence in pharmaceutical treatments that have the potential to spare millions in our aging population from the morbidity and death that often follow bone fracture.

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Abbreviations: AFF, atypical femoral fractures; AGE, advanced glycation end-products; ASBMR, American Society for Bone and Mineral Research; BMU, basic multi-cellular unit; BP, bisphosphonate; Cx43, connexin 43; DEXA, dual energy x-ray absorptiometry; E, elastic modulus; FDA, Food and Drug Administration; FTIR, Fourier transform infra-red; HAP, hydroxyapatite; MRI, magnetic resonance imaging; NMR, nuclear magnetic resonance; OB, osteoblast; OC, osteoclast; ONJ, osteonecrosis of the jaw; OVX, ovariectomy; PET, positron emission tomography; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor-κB ligand; SAXS, small-angle x-ray scattering; WAXS, wide-angle x-ray scattering; μCT, micro-computed tomography

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1. Introduction

Relationships between many typical bone fracture types and their mechanisms are well understood, are found in the biomechanics literature, and play an important role in treatment planning. For example, osteoporotic fracture has been associated with decreased bone density at skeletal sites composed predominately of trabecular tissue. Over the past two decades bisphosphonate (BP) therapy has been the gold standard used to reduce osteoporotic fracture risk by suppressing osteoclast-mediated bone resorption. However, increased reports of rare but serious "atypical" femur fracture (AFF) associated with long-term BP therapy have intensified examination by the Food and Drug Administration (FDA) and the orthopaedic research community (Fig. 1) (e.g., Lenart et al., 2008; National Guideline Clearinghouse, 2013). This review summarizes work that may hint at the potential underlying mechanisms behind the bone tissue damage that produces this atypical fracture pattern.

2. Fracture classification

Fractures are classified based on location, the estimated energy that produced them and the resulting breakage patterns. Classification criteria inform a great deal about the biomechanical environment prior to fracture. Fractures due to pathologic conditions such as osteoporosis, Paget's disease, osteogenesis imperfecta, rickets or bone cancer are generally closed, have intact overlying skin, and result from low-energy events. Conversely, high-energy impacts often result in open trauma fractures and are classified by the AO Trauma system (Müller, 1980). These typical fractures include those that have at least one large crack that completely traverses all cortices, including the entire width of the bone. The simple fractures are spiral, oblique and transverse. More complex, higher-energy fractures include burst, comminuted with many small bone fragments and/or impacted.

2.1. Osteoporotic fractures and their prevention

Osteoporotic fractures present with typical patterns. They are the result of age-related metabolic bone wasting characterized by highly porous, low density bone ends with reduced bone strength where trabecular structure is predominantly found (Atkinson, 1965). The wasting is due to rates of osteoclastic bone resorption outpacing osteoblastic bone formation, resulting in a highly porous structure. Hip fractures usually result from falls that would not otherwise produce fractures in non-osteoporotic individuals (Sanders et al., 1998). Collapsing crush fractures of the principally cancellous spinal vertebrae are also common with osteoporosis (Kleerekoper et al., 1985).

While osteoporotic fractures normally occur in the predominantly trabecular ends (metaphyseal region), cortical bone also plays a role in the propensity to fracture. Cortical cross-sectional geometry (i.e., bone structure) includes bone width, cortex thickness and distribution of tissue matrix. Bone width and cortex thickness are important to resisting failure by local buckling, as structures buckle when they have a slender aspect ratio (small width to length) (Beck et al., 2001; Giladi et al., 1987). The distribution of bone about the centroidal axis is important because a smaller periosteal versus endosteal adaptive expansion of the cortex offsets a propensity to fragility due to the effect on structural cross-sectional moment of inertia (Ruff and Hayes, 1982; Smith and Walker, 1964). Thus, bone normally adapts to meet biomechanical needs and some of these abilities, such as cortical thickening, may be observed in the pathogenesis of AFF (Section 3), possibly with imaging techniques (Section 4).

2.1.1. Bisphosphonate mechanisms of action

BPs are the most commonly prescribed drug for the prevention of osteoporotic fracture (FDA, 2011). By suppressing resorption, BPs and other anti-resorptive agents slow the loss of bone mass at the hip and spine (Rodan and Fleisch, 1996). Consequently, fracture risk is reduced (Seeman and Delmas, 2006). Non-nitrogen containing, first-generation BPs have fallen out of favor, especially in the U.S. because they may affect mineralization, although a few are still used clinically including clodronate (Bayer), etidronate (Warner Chilcott) and tiludronate

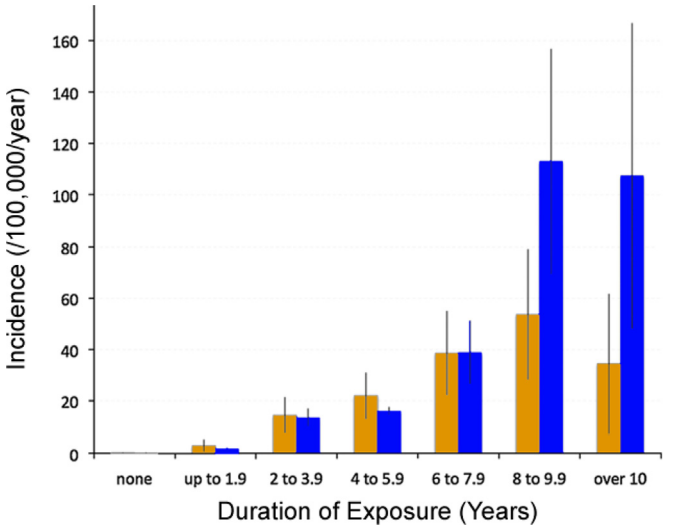

Fig. 1. In the only large, long-term prospective clinical report to date, the incidence of non-traumatic diaphyseal fractures of the femur increased with duration of bisphosphonate (BP) exposure. Reproduced with permission from Dell et al. (2012). Data demonstrate unadjusted (blue) and age-adjusted (yellow) (error bars are 95% confidence intervals) incidence of atypical femur fracture (AFF) in 188,814 patients on BPs for increasing numbers of years (*x*-axis). The study population was over 45 years old, and approximately half of those sustaining AFF were of Asian ancestry. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)