Bone Reports 2 (2015) 8–13

Contents lists available at ScienceDirect

Bone Reports

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

Original Full Length Article

The effect of osteoporosis treatments on fatigue properties of cortical bone tissue☆

Garry R. Brock [a], Julia T. Chen [a], Anthony R. Ingraffea [b], Jennifer MacLeay [c], G. Elizabeth Pluhar [d], Adele L. Boskey [e], Marjolein C.H. van der Meulen [a,e,*]

[a] Sibley School of Mechanical and Aerospace Engineering, Cornell University, Ithaca, NY, USA
[b] School of Civil and Environmental Engineering, Cornell University, Ithaca, NY, USA
[c] Colorado State University, Fort Collins, CO, USA
[d] University of Minnesota, St. Paul, MN, USA
[e] Musculoskeletal Integrity Program, Hospital for Special Surgery, New York, NY, USA

ARTICLE INFO

Article history:
Received 21 October 2014
Accepted 30 October 2014
Available online 14 November 2014

Edited by Peter Ebeling

Keywords:
Biomechanics
Osteoporosis
Fatigue testing
Bisphosphonate
Raloxifene
Metabolic acidosis

ABSTRACT

Bisphosphonates are commonly prescribed for treatment of osteoporosis. Long-term use of bisphosphonates has been correlated to atypical femoral fractures (AFFs). AFFs arise from fatigue damage to bone tissue that cannot be repaired due to pharmacologic treatments. Despite fatigue being the primary damage mechanism of AFFs, the effects of osteoporosis treatments on fatigue properties of cortical bone are unknown. To examine if fatigue-life differences occur in bone tissue after different pharmacologic treatments for osteoporosis, we tested bone tissue from the femurs of sheep given a metabolic acidosis diet to induce osteoporosis, followed by treatment with a selective estrogen reception modulator (raloxifene), a bisphosphonate (alendronate or zoledronate), or parathyroid hormone (teriparatide, PTH). Beams of cortical bone tissue were created and tested in four-point bending fatigue to failure. Tissue treated with alendronate had reduced fatigue life and less modulus loss at failure compared with other treatments, while tissue treated with PTH had a prolonged fatigue life. No loss of fatigue life occurred with zoledronate treatment despite its greater binding affinity and potency compared with alendronate. Tissue mineralization measured by microCT did not explain the differences seen in fatigue behavior. Increased fatigue life with PTH suggests that current treatment methods for AFF could have beneficial effects for restoring fatigue life. These results indicate that fatigue life differs with each type of osteoporosis treatment.

1. Introduction

Osteoporotic fractures are a substantial public health concern with total fractures and associated costs estimated to continue to rise through 2025 (Burge et al., 2007). Bisphosphonates are a commonly prescribed class of anti-resorptive drug that increases bone mineral density between 0 and 8% while reducing the risk of fracture by up to 50% in osteoporotic patients (Cummings et al., 2002; Liberman et al., 1995). The large decrease in fracture risk despite the modest increase in bone mineral density suggests a material property change in bisphosphonate-treated tissue. Suppression of bone remodeling with bisphosphonates has led to concern over inability to repair damaged and older tissue (Allen and Burr, 2011). To fully understand the reduction in fracture risk, all fracture properties and mechanisms should be examined.

Fracture of osteoporotic bone typically occurs through one of two mechanisms, a single overload (traumatic failure), or repetitive sub-fracture loads (fatigue failure; Fig. 1). Typical osteoporotic hip fractures are due to a mechanical overload, in which the femoral head and neck are subjected to loads that the bone cannot withstand due to reduced bone mass. Fatigue loads are repetitive, sub-failure forces applied to the tissue. Activities of daily living create fatigue loads that in turn create microdamage in the tissue (Taylor et al., 2007). Healthy individuals are unlikely to experience fatigue fractures under normal loading conditions since damage to the bone is typically repaired before fracture can occur. However, the tissue properties may be altered in individuals using anti-resorptive treatments (Donnelly et al., 2012; Bala et al., 2012; Paschalis et al., 2011; Roschger et al., 2008). Knowledge of fatigue on bone tissue has been primarily gained from testing of machined sections of bones and has shown fatigue dependence with temperature, stress amplitude, and bone microstructure (Pattin et al., 1996; Carter

☆ Disclosures:Garry R. Brock: no disclosures.Julia T. Chen: no disclosures.Anthony R. Ingraffea: no disclosures.Jennifer MacLeay: current address 3631 SW Stonybrook Drive, Topeka, KS.G. Elizabeth Pluhar: no disclosures.Adele Boskey: grant paid to institution: NIH AR041325. Marjolein C.H. van der Meulen: grant paid to institution: NIH AR053571, NIH EB004321; and board membership: Relievant Medsystems, Scientific Advisory Board.

* Corresponding author at: Sibley School of Mechanical and Aerospace Engineering, Cornell University, 219 Upson Hall, Ithaca, NY 14853, United States. Fax: +1 607 255 1222.
E-mail addresses: grb54@cornell.edu (G.R. Brock), tc468@cornell.edu (J.T. Chen), ari1@cornell.edu (A.R. Ingraffea), jmmacleay@gmail.com (J. MacLeay), pluha006@umn.edu (G.E. Pluhar), boskeya@hss.edu (A.L. Boskey), mcv3@cornell.edu (M.C.H. van der Meulen).

http://dx.doi.org/10.1016/j.bonr.2014.10.004
2352-1872/

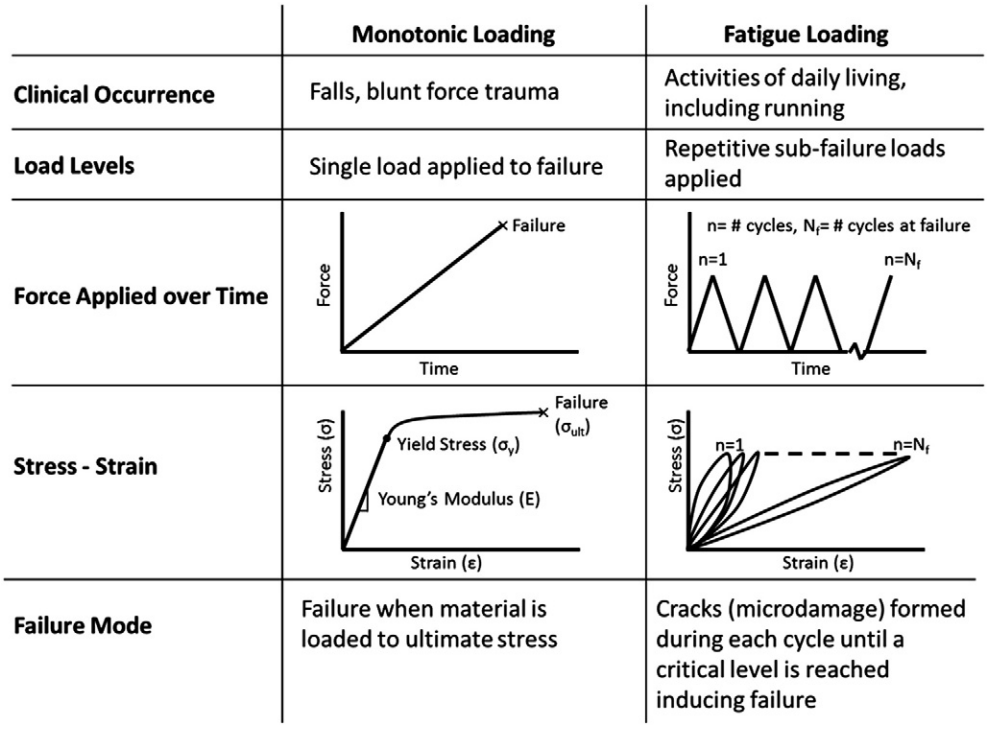

Fig. 1. Comparison of monotonic and fatigue loading. In monotonic loaded samples, force is increased until the sample fails. In fatigue, a repetitive sub-failure load is applied creating damage that eventually coalesces to cause failure.

and Hayes, 1976; Carter et al., 1976). Studies examining fatigue of osteoporotic and treated tissue have focused on microdamage accumulation rather than the material properties of the tissue (Allen and Burr, 2011).

Bisphosphonates act through osteoclast inhibition, which leads to reduced bone turnover, increased bone mass and increased mineralization (Reszka and Rodan, 2003). However, injury within the tissue cannot be remodeled leading to an accumulation of microdamage (Mashiba et al., 2000, 2001; Yamagami et al., 2013; Allen and Burr, 2007). Reduced bone turnover with bisphosphonate treatment increases mineralization and collagen maturity in bone tissue as measured by Fourier transform infrared spectroscopy (FTIR) (Gourion-Arsiquaud et al., 2010). Tests on whole bones after bisphosphonate therapy indicate an increase in monotonic strength and stiffness at corticocancellous sites without concomitant changes to the tissue-level modulus or ultimate strength (Allen and Burr, 2007, 2011). A loss of toughness and energy dissipation in cortical and cancellous tissue has been found with bisphosphonate treatment (Allen and Burr, 2011). Fatigue properties are likely altered with bisphosphonate treatment; however, minimal data regarding these properties have been published (Allen and Burr, 2011). Increased microdamage in both cortical and cancellous tissue with bisphosphonate treatment may reflect an inability to repair damage within the tissue (Mashiba et al., 2000, 2001; Yamagami et al., 2013; Allen and Burr, 2007). Alendronate reduced the fatigue life in beams created from rib bones from healthy canines; however, the dosing was supraphysiological and osteoporosis was not induced prior to treatment (Bajaj et al., 2014).

Long-term bisphosphonate use is associated with atypical femoral fractures (AFFs) (Isaacs et al., 2010; Schilcher et al., 2011). AFF incidence with bisphosphonate use is relatively low, but is associated with considerable morbidity (Lo et al., 2012). The mechanics of these fractures indicate critical differences from typical osteoporotic fractures (Shane et al., 2010, 2014). Association with low loads indicates that AFFs result from repetitive (fatigue) loading rather than a single traumatic incident. The transverse nature of the fractures suggests altered material properties with the tissue becoming more brittle.

Bisphosphonates are the most common therapy prescribed for osteoporosis treatment, but other treatments exist. Selective estrogen receptor modulators (SERMs) reduce osteoporotic vertebral fracture risk by 30–50% (Ettinger et al., 1999). SERMs bind to the estrogen receptors with an affinity similar to estradiol (Rey et al., 2009). Teriparatide (PTH) has been beneficial in patients who experience AFFs by inducing increased bone remodeling, removal of older more fully mineralized tissue and replacement with new less fully mineralized tissue (Chiang et al., 2013). Mechanical property data for SERM and PTH treatments of bone have focused on monotonic failure properties and have not included fatigue.

The purpose of this study was to examine the fatigue and fracture properties of bone tissue after different osteoporosis treatments using a sheep model of osteopenia to determine if a correlation exists between fatigue life and treatment type. Osteopenia was induced in sheep and followed by an osteoporosis treatment or vehicle. Beams of known geometry created from the femoral diaphysis of these sheep were loaded in four-point bending fatigue to failure. Given the inhibition of remodeling, and increased mineralization and collagen maturity reported with bisphosphonate treatment, we theorized that a shorter fatigue life will occur with bisphosphonate treatment.

2. Materials and methods

2.1. Animal model

(Table 1) samples used in this study were from remaining femur tissue from previously published and in progress studies (Burket et al., 2013). For all studies we fed a metabolic acidosis (MA) diet to skeletally mature sheep to induce osteopenia (MacLeay et al., 2004a). In the first study, sheep fed a normal diet served as healthy controls for the experiment (C, n = 6). In the second study, sheep were fed the MA diet for 12 months and given alendronate (ALN; n = 2), raloxifene (RAL; n = 2) or a vehicle (MA1; n = 3) treatment during months 7–12. The low sample sizes were not planned and reflect factors beyond our control in the experiment. To further examine bisphosphonate treatment, a third