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Theoretical analysis of alendronate and risedronate effects on canine vertebral remodeling and microdamage

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ABSTRACT

Bisphosphonates suppress bone remodeling activity, increase bone volume, and significantly reduce fracture risk in individuals with osteoporosis and other metabolic bone diseases. The objectives of the current study were to develop a mathematical model that simulates control and 1 year experimental results following bisphosphonate treatment (alendronate or risedronate) in the canine fourth lumbar vertebral body, validate the model by comparing simulation predictions to 3 year experimental results, and then use the model to predict potential long term effects of bisphosphonates on remodeling and microdamage accumulation. To investigate the effects of bisphosphonates on bone volume and microdamage, a mechanistic biological model was modified from previous versions to simulate remodeling in a representative volume of vertebral trabecular bone in dogs treated with various doses of alendronate or risedronate, including doses equivalent to those used for treatment of post-menopausal osteoporosis in humans. Bisphosphonates were assumed to affect remodeling by suppressing basic multicellular unit activation and reducing resorption area. Model simulation results for trabecular bone volume fraction, microdamage, and activation frequency following 1 year of bisphosphonate treatment are consistent with experimental measurements. The model predicts that trabecular bone volume initially increases rapidly with 1 year of bisphosphonate treatment, and continues to slowly rise between 1 and 3 years of treatment. The model also predicts that microdamage initially increases rapidly, 0.5–1.5-fold for alendronate or risedronate during the first year of treatment, and reaches its maximum value by 2.5 years before trending downward for all dosages. The model developed in this study suggests that increasing bone volume fraction with long term bisphosphonate treatment may sufficiently reduce strain and damage formation rate so that microdamage does not accumulate above that which is initiated in the first two years of treatment.

1. Introduction

Bisphosphonates (BPs) are anti-resorptive drugs that suppress bone remodeling, increase bone volume and bone mineral density, and are used to treat post-menopausal osteoporosis and other bone fragility disorders (Rodan and Fleisch, 1996; Chavassieux et al., 1997; Tonino et al., 2000; Ding et al., 2003; Dufresne et al., 2003; Recker et al., 2005). At the tissue level in humans, BP treatment is associated with decreased bone resorption and turnover (Storm et al., 1993; Rodan and Fleisch, 1996; Eriksen et al., 2002) and, therefore, provides a transient increase in bone volume (filling of pre-existing remodeling spaces). This may be followed by a further trend to increase bone volume by reducing the amount of bone resorbed relative to that formed by basic multicellular units (BMUs) (Boyce et al., 1995). In post-menopausal women, BPs reduce fracture risk by improving the structural properties of bone (Delmas, 2000) and increasing the degree of mineralization (Boivin et al., 2000). However, BP treatment also results in significant microdamage accumulation and a reduction in bone toughness in canine vertebrae (Mashiba et al., 2001; Komatsubara et al., 2003; Allen et al., 2006; Allen and Burr, 2007). The microdamage accumulation is due, at least in part, to decreased remodeling, which is the only mechanism in bone to remove fatigue damage (Burr et al., 1985; Mori and Burr, 1993). These observations, some having positive and others negative implications in bone, indicate the need for a better understanding of BP effects on bone remodeling, structure, and material properties.

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While long term BP studies have focused on alterations to bone mineral density and bone turnover (Miller et al., 1997; Tonino et al., 2000; Bone et al., 2004; Ste-Marie et al., 2004; Borah et al., 2006; Zoehrer et al., 2006), their effects on microdamage accumulation have not been studied beyond 3 years of treatment (Forwood et al., 1995; Hirano et al., 2000; Mashiba et al., 2000, 2005, 2001; Komatsubara et al., 2003, 2004; Day et al., 2004; Allen et al., 2006, Allen and Burr, 2007). Results from canine studies have documented microdamage increases in the vertebral body, rib, and ilium following 1–3 years of BP treatment, but these changes were compensated for by increases in bone mass and structural properties, including ultimate load and stiffness (Allen and Burr, 2007). However, some of these studies also documented significant reductions in bone toughness, the intrinsic ability of the tissue to resist fracture. Since BP treatment in patients with osteoporosis now extends 10 years or more, the long term effects of BPs on microdamage accumulation and bone fragility are of clinical interest.

In the present study, we develop a mathematical model to explore the long term effects of BP treatment on bone. We have previously developed computational models simulating bone mechanics and remodeling in a representative volume of bone (Martin, 1995; Hazelwood et al., 2001; Nyman et al., 2004, 2006). These models simulate BMU activation and remodeling in response to mechanical loading and fatigue microdamage. Our overall goal in developing these mathematical models is to simulate the long term effects of BPs on remodeling and microdamage accumulation in current animal models and, ultimately, in humans. As an initial step, our approach in the current study is to develop a model of remodeling in a representative volume of trabecular bone based on control and 1 year experimental results following BP treatment in the canine fourth lumbar vertebral body (Allen et al., 2006), and subsequently to test its predictions against data from a 3 year alendronate study (Allen and Burr, 2007). Then, in an effort to understand long term bisphosphonate treatment effects over periods similar to those for clinical use in humans, we examine model predictions after 10 years of simulated treatment.

2. Methods

The control and 1 year data used for model development were from skeletally mature female beagles treated daily with saline vehicle or one of three doses of alendronate (ALN: 0.10, 0.20, or 1.00 mg/kg/day) or risedronate (RIS: 0.05, 0.10, or 0.50 mg/kg/day) (Allen et al., 2006). The middle doses of ALN and RIS correspond to the clinical treatment dose, on a mg/kg basis, for post-menopausal osteoporosis. The lower dose of ALN corresponds to the preventative dose for osteoporosis, while the higher dose of both ALN and RIS are approximately equivalent to those used for treatment of Paget's disease. In that study, trabecular bone mineral density (BMD, g/cm^3), volume fraction (BV/TV), activation frequency (Ac.f), and microdamage (crack surface density or Cr.S.Dn) in the fourth lumbar vertebra (L4) were quantified.

A previous bone remodeling algorithm (Hazelwood et al., 2001; Nyman et al., 2004) was modified to simulate remodeling in a 1 cm^3 volume of canine L4 vertebral trabecular bone under uniaxial cyclic loading. The model describes histomorphometric variables governing bone mechanical properties (Table 1). The cancellous bone structure was assumed to be isotropic with a uniform bone volume fraction, BV/TV. The continuum-level elastic modulus (E) was assumed to be related to BV/TV by

$$E = E_0(\mathrm{BV/TV})^b, \tag{1}$$

where $E_0 = 19{,}735$ MPa and $b = 2.4217$ were obtained by fitting experimental data from control and 1 year BP-treated dogs to Eq. (1) (Table 2). Peak strain was calculated as

$$\varepsilon = \sigma/E, \tag{2}$$

where σ is the peak stress applied during cyclic loading.

A loading potential, Φ, was defined to characterize the mechanical environment as it affects remodeling (Hazelwood et al., 2001)

$$\Phi = R_L \varepsilon^q, \tag{3}$$

Table 1
Model state variables.

	State variable
E	Elastic modulus (MPa)
BV/TV	Bone volume fraction
N.Rs.BMU	Number of resorbing BMUs (# BMU/mm^2)
N.F.BMU	Number of refilling BMUs (# BMU/mm^2)
Ac.f	BMU activation frequency (# BMU/mm^2/day)
Ac.f$_{year}$	BMU activation frequency (# BMU/year)
BS/TA	Bone surface area per section area
Cr.S.Dn	Microdamage (mm/mm^2)
σ	Peak stress of cyclic compressive loading
ε	Peak strain of cyclic compressive loading
Φ	Mechanical stimulus (cycles per day, cpd)

where R_L is the loading frequency (assumed to be constant at 3000 cycles per day), and $q = 4$ adjusts the relative contribution of peak strain and loading frequency to the loading potential.

2.1. Microdamage

Microdamage (Cr.S.Dn) was defined as cumulative microcrack length per unit cross-sectional area of bone (mm/mm^2). The damage formation rate was assumed to be proportional to the loading potential

$$\left(\frac{\mathrm{dCr.S.Dn}}{\mathrm{dt}}\right)_F = k_D \Phi, \tag{4}$$

where k_D is chosen to make the damage formation and removal rates equal under steady state conditions (Hazelwood et al., 2001).

The fatigue microdamage removal rate was modeled as (Martin, 1995)

$$\left(\frac{\mathrm{dCr.S.Dn}}{\mathrm{dt}}\right)_{Rs} = \mathrm{Cr.S.Dn} \cdot \mathrm{Ac.f} \cdot \mathrm{Rs.Ar} \cdot F_s, \tag{5}$$

where Ac.f is the BMU activation frequency, Rs.Ar is the resorption space area, and F_s is a "steering factor" to account for targeted damage removal (Martin, 1985). Hence, the net damage accumulation rate is

$$\frac{\mathrm{dCr.S.Dn}}{\mathrm{dt}} = \left(\frac{\mathrm{dCr.S.Dn}}{\mathrm{dt}}\right)_F - \left(\frac{\mathrm{dCr.S.Dn}}{\mathrm{dt}}\right)_{Rs}. \tag{6}$$

2.2. Bone volume fraction

The time rate of change of bone volume fraction, d(BV/TV)/dt, was assumed to be a function of the mean bone resorption (Rs.Ar/Rs.P) and refilling (FAr/FP) rates within individual BMUs, and the mean densities of resorbing (N.Rs.BMU) and refilling (N.F.BMU) BMUs (Martin, 1985)

$$\frac{\mathrm{d(BV/TV)}}{\mathrm{dt}} = \frac{\mathrm{FAr}}{\mathrm{FP}}\,\mathrm{N.F.BMU} - \frac{\mathrm{Rs.Ar}}{\mathrm{Rs.P}}\,\mathrm{N.Rs.BMU}, \tag{7}$$

$$\mathrm{N.F.BMU} = \int_{t-(\mathrm{Rs.P+Rv.P+FP})}^{t-(\mathrm{Rs.P+Rv.P})} \mathrm{Ac.f}\,\mathrm{dt}', \tag{8}$$

$$\mathrm{N.Rs.BMU} = \int_{t-\mathrm{Rs.P}}^{t} \mathrm{Ac.f}\,\mathrm{dt}', \tag{9}$$

where Rs.Ar and FAr are the mean resorption and refilling areas and Rs.P and FP are the mean resorption and refilling periods, respectively, of individual BMUs (Table 2). The shape of the BMU resorption cavity was modeled as a semi-ellipse having a mean cross-sectional area of 0.014 mm^2 as measured from the control dogs (previously unpublished data (Allen et al., 2006)).

2.3. BMU activation frequency

BMU Ac.f (BMUs/mm^2/day) was assumed to be a function of disuse, microdamage, and the available surface area for remodeling, BS/TA. This leads to the equation

$$\mathrm{Ac.f} = (\mathrm{Ac.f_{damage}} + \mathrm{Ac.f_{disuse}})\frac{\mathrm{BS/TA}}{(\mathrm{BS/TA})_{max}}, \tag{10}$$