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Research paper

Prediction of denosumab effects on bone remodeling: A combined pharmacokinetics and finite element modeling

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ABSTRACT

Denosumab is a fully human monoclonal antibody that inhibits receptor activator of nuclearfactor-kappa B ligand (RANKL). This key mediator of osteoclast activities has been shown to inhibit osteoclast differentiation and hence, to increase bone mineral density (BMD) in treated patients. In the current study, we develop a computer model to simulate the effects of denosumab treatments (dose and duration) on the proximal femur bone remodeling process quantified by the variation in proximal femur BMD.

The simulation model is based on a coupled pharmacokinetics model of denosumab with a pharmacodynamics model consisting of a mechanobiological finite element remodeling model which describes the activities of osteoclasts and osteoblasts.

The mechanical behavior of bone is described by taking into account the bone material fatigue damage accumulation and mineralization. A coupled strain-damage stimulus function is proposed which controls the level of bone cell autocrine and paracrine factors. The cellular behavior is based on Komarova et al.'s (2003) dynamic law which describes the autocrine and paracrine interactions between osteoblasts and osteoclasts and computes cell population dynamics and changes in bone mass at a discrete site of bone remodeling. Therefore, when an external mechanical stress is applied, bone formation and resorption is governed by cell dynamics rather than by adaptive elasticity approaches. The proposed finite element model was implemented in the finite element code Abaqus (UMAT routine).

In order to perform a preliminary validation, in vivo human proximal femurs were selected and scanned at two different time intervals (at baseline and at a 36-month interval). Then, a 3D FE model was generated and the denosumab-remodeling algorithm was applied to the scans at t_0 simulating daily walking activities for a duration of 36 months. The predicted results (density variation) were compared to existing published ones performed on a human cohort (FREEDOM).

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1. Introduction

Skeletal bone remodeling is a dynamic process mediated by two distinct cell types: osteoclasts which mediate the production of acids and enzymes to dissolve bone minerals and proteins to resorb bone, and osteoblasts which form new bone. An imbalance between osteoclastic and osteoblastic cell functions generates osteoporosis, a disease that results in significant bone loss, bone fragility and increased susceptibility to fracture.

Various drug treatments against osteoporosis that influence the turnover of bone have been developed, including the administration of estrogen (Clemett and Spencer, 2000; Moen and Keating, 2008), bisphosphonates (Rodan and Martin, 2000; Pillai et al., 2004), parathyroid hormone (PTH) (Blick et al., 2008), ranelate of strontium (Brennan et al., 2006, 2007) and denosumab (Bekker et al., 2004; Lewiecki et al., 2007).

Denosumab (Prolia, Amgen Inc., Thousand Oaks, CA) is approved for treating osteoporosis. Denosumab exerts its effects by binding to the receptor activator of nuclear factor KB ligand (RANKL). RANKL is a cytokine expressed by osteoblasts and is necessary for osteoclastogenesis. This RANK/RANKL/OPG system is regulated by various cytokines, hormones, and mesenchymal transcription factors (Hofbauer and Heufelder, 2001) and determines osteoclast activity. Overproduction of RANKL is hypothesized to contribute to the development of postmenopausal osteoporosis (Miller, 2009; Miller et al., 2011). By binding to RANKL, denosumab inhibits osteoclastgenesis which in turn decreases bone resorption and bone turnover (Miller, 2009; Hofbauer and Schoppet, 2004).

Investigation of the effects of such drugs on osteoporotic patients is very time consuming, expensive and clinically difficult due to complex mechanical and biological multiscale interactions between the bone cells governing bone remodeling combined with the applied local mechanical stress and fatigue damage at a given bone site.

Model-based drug development is a promising alternative to assess osteoporosis therapies. Thus, there is a need for models that utilize drug pharmacokinetics (PK) and pharmacodynamics (PD) to predict changes in bone organ BMD. While PK/PD models have been developed in the past to describe the time courses of biomarkers for ibandronate (Pillai et al., 2004), pamidronate (Cremers et al., 2005) and denosumab (Marathe et al., 2011; Scheiner et al., 2013) in osteoporosis, the 3D numerical simulation of drug effects on bone remodeling is still lacking.

Given the continuously increasing capability of computer simulations and modeling algorithms, computer modeling of bone drug effects has proven promising. The gold standard of mathematical modeling of a given drug effect consists generally in coupling PK models (quantifying the "availability" of the drug at sites of interest) with PD models (quantifying the time-dependent effect of the drug on the overall physiological system).

Recently, several PK models of denosumab coupled with biological remodeling models were proposed by different authors (Marathe et al., 2008, 2011; Scheiner et al., 2013; Tobias et al., 2014). These models have achieved some success in predicting the effect of denosumab. They have however three major deficiencies. First, they do not include mechanical stimulus effects in the remodeling models. Second, PK/PD models are dimensionless mathematical models not designed to investigate the simulated effects of drugs on a whole living organ. Third, none of these models were implemented into a finite element (FE) code to simulate real 3D bone organ remodeling processes from a mechanobiological perspective considering interactions between cell activities and the mechanical reaction of bone and the PK of denosumab. Recently, Wei et al. (2015) developed a simple phenomenological FE model to simulate the effect of denosumab on bone remodeling. In their work, the authors described the effects of the drug by adding one parameter representing the influence of denosumab. When its value was equal to 0, no drug was used; when the value was lower than 0, the remodeling model was adjusted in such a way as to inhibit bone resorption. The main limitations of this study are that (i) the PK model of denosumab was not considered and (ii) the remodeling model was based on a phenomenological description without considering interaction between the bone cells and denosumab.

To the best of the authors' knowledge, computational combined PK and FE models of denosumab effects have not yet been developed. In the current work, a combined PK and PD based FE (PK/PD_FE) model was developed and implemented into a FE code (Abaqus) to simulate the effects of denosumab (dose and duration) on proximal femur remodeling in terms of BMD, degree of mineralization and fatigue damage accumulation variation. The integrated model is based on coupling a PK model of denosumab and a mechanobiological FE model of bone remodeling.

The denosumab PK model is based on the work of Scheiner et al. (2013) which describes the absorption of denosumab in blood serum. The remodeling model is based on a previously developed mechanobiological FE model of osteoblast and osteoclast cell activities (Hambli, 2014).

The link between the PK and FE models (PK/PD_FE) is described by the modulation in the FE model of the autocrine factors representing the RANKL-OPG-RANK regulation by the concentration of denosumab in blood serum.

To investigate the potential of the proposed unified denosumab PK/PD_FE model, three remodeling simulations on a 3D osteoporotic proximal femur model (female, 72 years old, 52 kg) were performed for a duration of three years with three loading cases: Case 1: normal daily applied force without denosumab; Case 2: low daily applied force without denosumab treatment; Case 3: low daily applied force with a dose of 60 mg every 6 months.

We show here that the implementation of an integrated PK/PD_FE model provides a realistic prediction strategy to assess the drug effects on bone remodeling compared to existing experimental results.

2. Material and method

The proposed integrated PK/PD_FE model was built to predict the effect of denosumab on bone remodeling in 2 steps (Fig. 1):

(i) **Step 1**: PK simulation of absorption of denosumab in blood serum based on experimental results.

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