IN SILICO EXPLORATION OF OSTEOPOROSIS DRUG EFFECTS ON BONE ADAPTATION BASED ON REMODELING AND MODELING

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Introduction

Bone-forming activity of osteoblasts is divided into remodeling-based and modeling-based bone formation depending on the presence or absence of coupling with bone resorption by osteoclasts. Osteoporosis drugs have been reported to have different effects on remodeling and modeling based on their specific mechanisms of action [1]. However, it is still unknown how the drug effects on remodeling and modeling contribute to the mechanical adaptation of the bone microarchitecture. In this study, we developed a mathematical model that enables to analyze drug effects on remodeling and modeling and explored effects of bone-forming drugs on the mechanical adaptation of the bone based on cellular dynamics and bone morphometry.

Methods

Bone metabolism was modeled by describing spatial and temporal evolution of cell activities regulated based on mechano-biochemical interactions where mechanical stimuli sensed by osteocytes trigger signaling cascades of the major molecules such as receptor activator of nuclear factor-κB ligand, osteoprotegerin, and sclerostin [2]. To explicitly describe remodeling and modeling, we modeled osteoclast–osteoblast coupling by a well-known matrix-derived coupling factor [3]. According to the concentration of these signaling molecules and mechanical stimuli sensed by osteocytes, probability of cell genesis and apoptosis of osteoclasts and osteoblasts were determined. By using a finite element cubic model of a cancellous bone obtained from a swine femoral head, drugs effects of romosozumab and teriparatide, major bone-forming drugs, on the mechanical adaption of the bone microarchitecture were explored through drug administration simulation.

Results

To validate the model, we investigated drug effects on bone volume fraction (BVF) and cell activities. While BVF decreased overtime without treatment, it increased with romosozumab and teriparatide administration (Fig. 1A). Romosozumab suppressed remodeling and promoted modeling-based bone formation, whereas teriparatide promoted both remodeling and modeling (Fig. 1B). Because these results are consistent with known drug effects, the model was shown to be valid. To explore the drug effects on the mechanical adaptation of the bone, we further performed drug administration simulation under the condition that the principal stress directions were rotated 45 degrees. As a result, the adaptive change of the cancellous orientation was attenuated with romosozumab treatment but enhanced with teriparatide treatment, in comparison to that without treatment (Fig. 2).

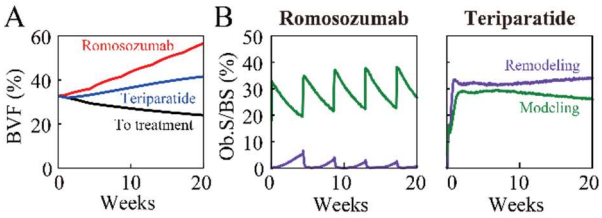

Figure 1: Model validation simulation. (A) Bone volume fraction (BVF). (B) Osteoblast surface (Ob.S/BS).

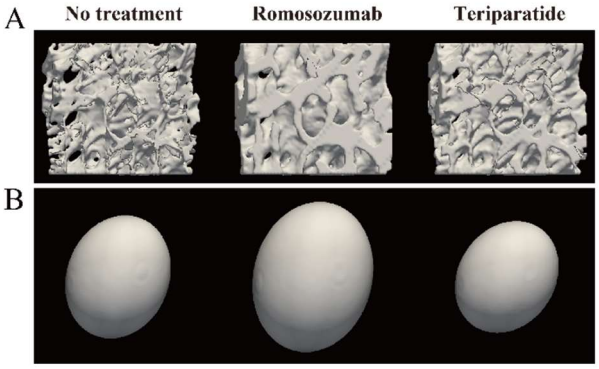

Figure 2: Drug effects on the mechanical adaptation. (A) Cross section of the cubic cancellous bone. (B) Fabric ellipsoid of the cubic cancellous bone.

Discussions

The above results suggests that differential drug effects on remodeling and modeling could lead to drug-specific effects on the mechanical adaptation of the cancellous orientation, which would bring a new perspective to osteoporosis treatment. Our in silico approach would pave the way for new pharmacological strategies for the patients with skeletal diseases.

References

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