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The Clinical Biomechanics Award 2012 — Presented by the European Society of Biomechanics: Large scale simulations of trabecular bone adaptation to loading and treatment

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ABSTRACT

Background: Microstructural simulations of bone remodeling are particularly relevant in the clinical management of osteoporosis. Before a model can be applied in the clinics, a validation against controlled in vivo data is crucial. Here we present a strain-adaptive feedback algorithm for the simulation of trabecular bone remodeling in response to loading and pharmaceutical treatment and report on the results of the large-scale validation against in vivo data.

Methods: The algorithm follows the mechanostat principle and incorporates mechanical feedback, based on the local strain-energy density. For the validation, simulations of bone remodeling and adaptation in 180 osteopenic mice were performed. Permutations of the conditions for early (20th week) and late (26th week) loading of 8 N or 0 N, and treatments with bisphosphonates, or parathyroid hormone were simulated. Static and dynamic morphometry and local remodeling sites from in vivo and in silico studies were compared.

Findings: For each study an individual set of model parameters was selected. Trabecular bone volume fraction was chosen as an indicator of the accuracy of the simulations. Overall errors for this parameter were 0.1–4.5%. Other morphometric indices were simulated with errors of less than 19%. Dynamic morphometry was more difficult to predict, which resulted in significant differences from the experimental data.

Interpretation: We validated a new algorithm for the simulation of bone remodeling in trabecular bone. The results indicate that the simulations accurately reflect the effects of treatment and loading seen in respective experimental data, and, following adaptation to human data, could be transferred into clinics.

1. Introduction

Osteoporosis is a systemic disease, characterized by reduced bone quality and increased susceptibility to fracture (Kanis, 2002). The symptoms are common in menopausal women and elderly of both sexes (Garnero et al., 1996; Hannan et al., 2000; Melton et al., 1992; Nguyen et al., 2000). At the present, osteoporosis is considered a pandemic in the aging world population (Cooper et al., 1992; Riggs and Melton, 1995). The biggest challenge in the clinical handling of the disease is not identification of those individuals that are suffering from decreased bone quality due to the homeostatic shifts, but detection of those that are prone to developing fractures (Kanis, 2002). Once the first osteoporosis-related fracture is sustained, an individual becomes more likely to suffer repeated incidences of broken bones (Gold, 1996; Lindsay et al., 2001), thus leading to ever decreasing mobility and quality of life, as well as growing financial costs (Chrischilles et al., 1991; Ray et al., 1997; Riggs and Melton, 1995). If identified prior to fracture, osteoporosis can be clinically managed with appropriate physical therapy, pharmacological treatments, or a combination of both (Kanis et al., 2008; Liberman et al., 1995; Neer et al., 2001). In this context, microstructural simulation models of bone remodeling, capable of reflecting changes in the tissue over time, can become a valuable auxiliary tool in clinical prediction and prevention of osteoporosis.

Before a model can be practically applied in the clinics, however, a thorough validation is of major importance (Levchuk and Müller, 2013). An extensive validation routine overview has been presented by Huiskes (1997). Several types and levels of validation for bone adaptation models are proposed prior to clinical transfer. Briefly, numerical validation should establish that the algorithm is functional and does not produce obscure artifacts. Mechanistic validation attests that the model accurately reflects realistic mechanisms and processes. Finally, predictive validation verifies the results of the simulation against controlled reference data. In the first step, model performance according to bone-remodeling phenomena at large should be tested. The next step of predictive validity assessment juxtaposes simulated predictions with the experimental results for a population. Lastly, a specimen-specific quantitative validation has to be performed. This last step has

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always been a bottleneck for in silico models in the past, mainly due to the lack of appropriate in vivo data (Huiskes, 1997; Levchuk and Müller, 2013).

One of the earlier in silico models for the prediction of trabecular bone-remodeling focused on voxel-based surface adaptation by means of combined Gaussian filtration and thresholding as an open-loop control model, and did not include mechanical feedback (Müller, 2005). In another study, mechanical feedback was incorporated in the form of strain gradients, and the algorithm was applied on the data from an ongoing in vivo study, thus allowing for a subsequent indirect validation of the results (Adachi et al., 2001). A different model for examination of bone metabolic expression under load was presented by Ruimerman et al. (2005b). The same group of researchers has also introduced an algorithm where formation was coupled with strain energy density (SED), while resorption was randomized according to a certain probability (Ruimerman et al., 2005a). Finally, a more recent in silico model has been introduced by Schulte et al. (2013). This approach is based on the previously established open-loop control model, which did not include mechanical feedback between iterations of the simulation (Schulte et al., 2011b). In the new algorithm, on the other hand, SED stimuli for local control of formation and resorption sites are calculated for each iteration using the large-scale micro-finite element (μFE) analysis. The inherent approach to strain adaptation allows the algorithm to run in a closed-loop feedback mode (Schulte et al., 2013).

In this study, we extended Schulte in silico framework to simulate trabecular bone remodeling in response to loading and pharmaceutical treatment. Scans obtained directly from in vivo micro-computed tomography (μCT) measurements were used input for the model, thus allowing systematic time-lapsed comparison of the simulation results with the biological changes in experimental subjects. The study incorporated a total of 180 genetically inbred mice, subjected to controlled experimental conditions. This parallel setup of in vivo and in silico studies has allowed us to carry out an extensive validation of the algorithm, covering full range of pre-clinical validity testing. Here, we report on the results of this large-scale validation of the closed-loop strain adaptive algorithm against three-dimensional (3D) in vivo reference data of bone adaptation due to pharmaceutical treatments and mechanical loading in mouse vertebrae.

2. Methods

2.1. In vivo reference data

All animals used in the validation study were ovariectomized at the age of 15 weeks to create a state of estrogen depletion, and mimic the effect of osteoporosis (CTR, control group). All animal procedures were performed under isoflurane anesthesia (2–2.5%, 0.4 L/min) delivered through a nose mask, and were approved by the local authorities (Kantonales Veterinäramt Zürich, Zurich, Switzerland). The studies were subdivided into two time-dependent groups in order to emulate the consequences of and treatment effects during initial rapid bone loss, as well as at the later stage of osteopenia (Lambers et al., 2012; Parfitt, 1984). In the early treatment (ET) group treatment intervention started 5 weeks post-operatively or at the 20th week of life for the animals. In the late treatment (LT) study, a lag period of 11 weeks was allowed prior to the start of treatment in the 26-week-old mice (Kuhn et al., 2011). The animals in the ET group were losing bone during the first half of the study period, and consequently recovering some of the loss in the second half. In the LT group, on the other hand, the bone condition could be described as osteopenic at the onset of the treatment, and there was no further bone loss observed during the entire study period. Therefore, the in vivo experiments have been designed in this manner to investigate the effects of preventive and curative treatments. The experimental study was based on an established mouse model for bone adaptation (Webster et al., 2008), in which sixth caudal vertebra (CV6) of the female C57BL/6 mice underwent mechanical loading (ML) through the metal pins inserted into CV5 and CV7. In the experiment, a sinusoidal force of 8 N was applied at the frequency of 10 Hz for 5 min/day, three times a week, for 4 weeks. Pharmacological treatments included parathyroid hormone (PTH; hPTH 1–34, Bachem AG, Bubendorf, Switzerland), administered at a dose of 80 μg/kg for 4 weeks, or bisphosphonate (BIS; Zometa 4 mg/5 mL; Novartis Pharma Schweiz AG, Bern, Switzerland) administered once at the start of the treatment at a dose of 100 μg/kg.

A total of 12 studies investigating single and combined effects of loading and pharmacological treatments at different stages of bone loss have been used in the validation, where all experimental procedures have been carried out as part of a doctoral thesis (Weigt, 2012). Changes in bone microstructure were monitored bi-weekly, starting at the beginning of treatments with in vivo μCT (vivaCT 40, Scanco Medical, Brüttisellen, Switzerland) at an isotropic voxel resolution of 10.5 μm.

2.2. Computational algorithm and μFE analysis

A strain-adaptive feedback algorithm for the simulation of trabecular bone remodeling has recently been developed in house (Schulte et al., 2013). While the experimental data in this project would allow investigation of biological changes in both cortical and cancellous bones, the algorithm was developed exclusively for the simulations of changes in the trabecular bone tissue. The model itself is based on the principles of mechanical control, which has not been shown to have the same impact on the cortical bone as it does on the trabecular bone (Pearson and Lieberman, 2004; Woo et al., 1981). In silico bone adaptation was derived from the mechanostat theory proposed by Frost (2003) and is computed by moving bone surface through adding or removing bone volume depending on local mechanical stimuli. In short, as represented in Fig. 1, a segmented imaged of an in vivo μCT scan is used as input. μFE analysis is then applied on the input image for the calculation of local mechanical signals represented by strain energy density (SED). μFE analysis was performed following a previously established protocol (Webster et al., 2008), where simplified disks were applied on each side of the full vertebra to ensure even force distribution. Material properties of the segmented input images were based on the assumption of tissue homogeneity. Young's Modulus of 14.8 GPa and a Poisson ratio of 0.3 were assigned to all elements (Webster et al., 2008), and the model was solved on a super computing system (CSCS, Lugano, Switzerland) (Arbenz et al., 2008). The amount of bone loss or gain is calculated with the advection equation based on the model input parameters (Table 1) and SED values. A total of four parameters that control the algorithm can be adjusted individually for each simulation. These include bone formation and resorption rate per SED value (τ), upper and lower SED thresholds for the formation and resorption (SED_{upp} and SED_{low}), and maximum remodeling velocity (u_{max}). The output image is created by moving the bone surface in the direction normal to the surface. This image is then used as input for the subsequent iteration loop (Fig. 1).

2.3. Selection of parameters

For all simulations bone formation and resorption rate was kept constant, while the remodeling saturation level and SED thresholds were optimized to produce the best match of bone volume fraction (BV/TV) with in vivo data across all measurement time point. Matches in all other morphometric and dynamic parameters were the outcome of this optimization, and reflect the accuracy of the algorithm.

An initial parameter set was carried over from the previous study performed on C57B/6 data (Schulte et al., 2013). Similarly to the reported method, mechanostat theory was assumed to act on the osteocytic network, where signals for the remodeling are released in response to change in mechanical environment, and has a certain radius of action