

## Altered mechanosensitivity can explain the substantially increased bone mass in hypoparathyroidism

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**ALTERED MECHANOSENSITIVITY CAN EXPLAIN THE SUBSTANTIALLY INCREASED  
BONE MASS IN HYPOPARATHYROIDISM**

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**INTRODUCTION**

Hypoparathyroidism (HypoPTH) is characterized by low or absent parathyroid hormone (PTH). It is mainly associated with a drastic suppression of bone turnover by around 80% (Rubin et al., 2008) and a substantial increase in bone mass in the range of 10-32% (Rubin et al., 2008; Abugassa et al., 1993).

It is known that PTH can affect bone cells, but how it would lead to such a high net formation in HypoPTH is unclear. In *hyperparathyroidism* studies it was found that elevated PTH up regulates RANK production in osteoblasts causing increased bone resorption via binding to RANKL expressed on osteoclasts. This suggests that during *HypoPTH*, RANK would be down regulated thus reducing turnover, which is in agreement with clinical measurements (Rubin et al., 2008). As a result of this reduced turnover, an increase in bone mass would be expected due to filling of the resorption space. However, given that the resorption space accounts only for approx. 5% of the total volume, this effect cannot fully explain the substantial gain in bone mass during HypoPTH

As an additional effect of PTH on bone cells, we hypothesize that the sensitivity of the cells to mechanical loading is altered, as already proposed by Frost (Frost, 1987). Support for this hypothesis came later from experiments in which it was shown that osteoblast-like cells are more sensitive to mechanical stimulation *in vitro* (Ryder and Duncan, 2000; Carvalho et al, 1994) and *in vivo* (Chow et al., 1998) when PTH is added.

To investigate if this hypothesis can explain the marked increase in bone mass seen with HypoPTH, we simulated the proposed effects of HypoPTH using a well established computer model for the simulation of bone remodeling. Simulations were performed for models representing bone biopsies obtained from the iliac of HypoPTH patients at different time points and compared to experimental data.

**MATERIALS AND METHODS**

**Human iliac bone biopsies**

Human iliac crest bone biopsies prepared and documented in another study (Rubin et al., 2010) were used. There, HypoPTH was diagnosed when serum calcium and PTH concentrations were below normal limits during two measurements and this condition had to be present for at least 3 years. Two biopsies per subject were taken with a time lag of one year and micro-computed tomography (micro-CT) was used to assess the microarchitecture. In our study, the micro-CT images of the first biopsies (n=7) were cropped to cubic subvolumes of  $3.2 \times 3.2 \times 2.6 \text{ mm}^3$  and transformed into voxel-based micro-finite element (micro-FE) models with an element size of 40  $\mu\text{m}$ .

**Bone remodeling simulations**

For the bone remodeling simulations, a previously developed and tested load-adaptive bone remodeling algorithm (Ruimerman et al., 2005; Huiskes et al., 2000) was used. The model is based on the theory that osteocytes within the bone sense mechanical loading, calculated using the micro-FE analysis, and send a signal to the osteoblasts on the bone surface that form bone accordingly. Bone formation only takes place if the total osteocyte signal received at the surface exceeds a certain formation threshold  $k$ . Bone resorption, on the other hand, is assumed to occur spatially random with the activation frequency  $f_{res}$  based on the assumption that also microcracks or osteocyte apoptosis occur in that manner.

HypoPTH conditions were simulated by reducing the osteoclast activation frequency  $f_{res}$  by 80% according to clinical data (Rubin et al., 2008) and, by increasing the bone cell mechanosensitivity, represented by the formation threshold  $k$ , i.e. stepwise decreasing its value by 0%, 10%, 20%, and 30%. Simulations were based on initial structures that were first adapted to a compressive load in the longitudinal direction and tension in the transversal direction (Fig. 1).

## RESULTS

HypoPTH simulations showed an increase in bone mass (BV/TV) of 4.2%, 10.6%, 18.4%, and 27.8% when the formation threshold was decreased by 0%, 10%, 20%, and 30% respectively.

In all four simulations osteoclast activity dropped sharply whereas osteoblast activity lagged behind or even temporarily increased, if the formation threshold was altered, before both activities were balanced at a lower bone turnover (Fig. 2).

## DISCUSSION

HypoPTH simulations based on human iliac bone biopsies revealed that decreased osteoclast activity by 80% and an increased sensitivity by 20% cause a net bone formation of 18.4% which is in good agreement with the amount of bone mass gained during HypoPTH. This supports the hypothesis that certain hormones alter the sensitivity of bone cells to mechanical loading as already speculated by Frost (Frost, 1987). If only bone resorption was suppressed, bone mass was increased by only 4.2% since in that case only the resorption space was filled, which is limited to around 5%.

Interestingly, the bone remodeling dynamics during the simulations were similar to clinical measurements after parathyroidectomy (Yajima et al., 2007). They showed that within the first weeks after surgery, bone resorption drops down sharply and bone formation peaks first before it is balanced again with resorption at a lower level. Therefore, our HypoPTH simulations show similar features as clinical measurements, at least in terms of bone remodeling dynamics.

In conclusion, the HypoPTH simulations revealed that an increase in osteoblast mechanosensitivity of 20% in combination with osteoclast suppression by 80% can explain the substantial gain in bone mass during HypoPTH. This corroborates the hypothesis that certain hormones, such as PTH, might trigger the sensitivity of bone cells to mechanical loading.

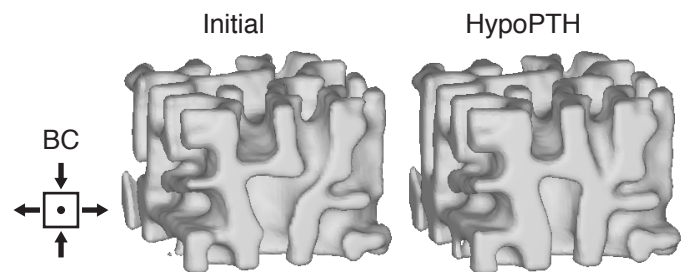
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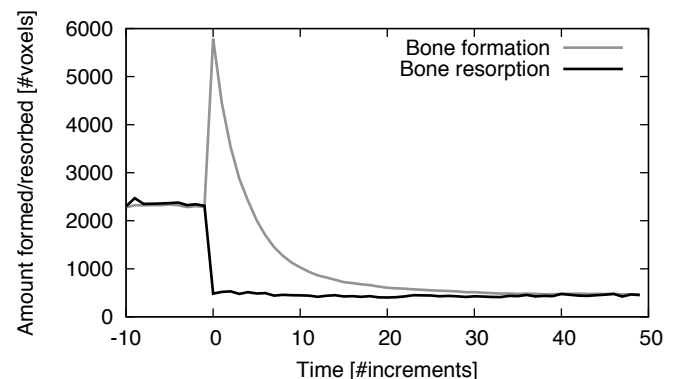
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**Figure 1: Human iliac bone biopsy microarchitecture and boundary conditions (BC) prior to (Initial) and after the HypoPTH simulation (HypoPTH) with 20% decreased formation threshold.**



**Figure 2: Bone remodeling dynamics of the HypoPTH simulation with 20% decreased formation threshold.**