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# Comparative Analysis of Local Bone Adaptation in Response to Mechanical Loading and Parathyroid Hormone Treatment Across Cortical Compartment in a Mouse Tibia Model

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## 1. Introduction

Mechanical loading (ML) and Parathyroid Hormone (PTH) treatments are key factors in bone remodelling. Understanding their effects and interaction on cortical and trabecular compartments is essential for planning effective therapies for osteoporosis (Sugiyama et al. (2008) and San Cheon et al. (2021)). This study examines the local effects of ML and PTH on bone adaptation using high-resolution micro-computed tomography (μCT) and an automated analysis pipeline. Following protocols by Sugiyama et al. (2008, 2012), we investigate mean cortical thickness changes along the tibia, from proximal to distal regions, to understand the localized impacts of these treatments on bone remodelling.

## 2. Methods

### 2.1 Experimental design

This study leverages data from the second “iPTH/Mechanical Loading ML” experiment detailed in Sugiyama et al. (2008). Female C57BL/6 mice, aged 13 weeks, were randomized into four groups: three received 6 weeks of intermittent PTH (20, 40, or 80 μg/kg/day) and one vehicle group (PTH0) received no treatment. During the final 2 weeks (17 to 19 weeks of age), the right tibiae and ulnae were subjected to mechanical loading (ML). μCT scanning was recorded at 5 μm resolution.

### 2.2 Adaptation analysis

Our investigation explores the dynamics of mean cortical thickness change ( $\Delta Th.Ct$ ) relative to the control along the bone's length, transitioning from the proximal 20% region to the distal 80%, for different iPTH dosages. By adopting a focused approach, we aim to analyse the dynamics of bone adaptation, particularly in response to the complex interplay between pharmacological intervention and mechanical stimuli.  $\Delta Th.Ct$  is calculated with the following formula:

$$\Delta Th.Ct = \left( \frac{\overline{Th.Ct}_{current} - \overline{Th.Ct}_{vehicle}}{\overline{Th.Ct}_{vehicle}} \right) * 100$$

Where  $\overline{Th.Ct}_{current}$  and  $\overline{Th.Ct}_{vehicle}$  represent the mean cortical thickness per slice of the currently treated bone and the vehicle, respectively.

Linear regression analysis was conducted across two key regions—the proximal (20% to 50%) and middle to distal (50% to 80%) segments—to identify the slopes of  $\Delta Th.Ct$ . These slopes represent the gradient of cortical thickness change along the tibia's z-axis, relative to the vehicle control. This method allows for identifying statistically significant slopes and provides insights into localized bone responses to PTH treatments, enhancing our understanding of bone's adaptive mechanisms.

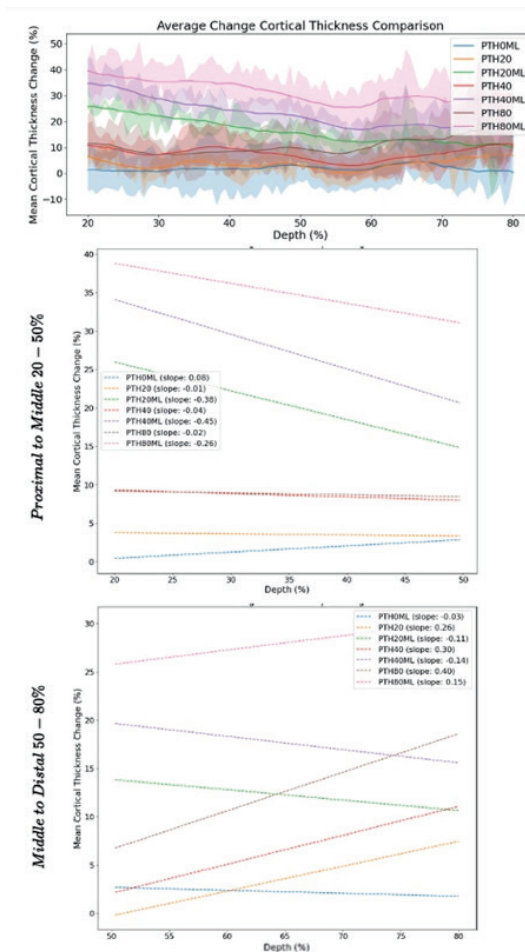
### 3. Results and discussion

A detailed depiction of this analysis is presented in Figure 1, where we illustrate the evolution of  $\Delta Th$ . Ct across all 7 groups (top figure), followed by the regression analysis plot from the proximal to middle 20-50% region (middle figure), and finally the regression analysis from the middle to distal 50-80% region (bottom figure). Within the transition from the proximal to the middle region, notable distinctions emerge in the adaptation gradient influenced by PTH combined with ML (see Table 1.). Specifically, the PTH40ML treatment showcases the most significant decrease, with a slope of  $-0.451$  ( $p < 1.10e-16$ ), and PTH20ML similarly exhibits a substantial reduction with a slope of  $-0.376$  ( $p < 1.11e-12$ ). The observed slopes indicate a dynamic pattern of cortical thickness change across the bone, with a pronounced increase in the proximal region. This nuanced interaction between PTH and mechanical stimuli suggests that while their synergistic effects boost bone adaptation

**Table 1.** Regression slopes and p-values by treatment group across examined region.

Group	Slope	p-values
20% Proximal to 50% Middle		
PTH0ML	0.082	0.0025†
PTH20	- 0.014	0.739
PTH20ML	-0.376	1.11e-12†
PTH40	-0.045	0.233
PTH40ML	-0.451	1.10e-16†
PTH80	-0.024	0.515
PTH80ML	-0.260	9.22e-09†
50% Middle to 80% Distal		
PTH0ML	-0.030	0.476
PTH20	0.257	4.28e-08†
PTH20ML	-0.107	0.015†
PTH40	0.299	4.57e-12†
PTH40ML	-0.137	0.002†
PTH80	0.399	4.50e-10†
PTH80ML	0.149	0.009†

†  $p < 0.05$ .



**Figure 1.** Variation in mean cortical thickness change (%) along the tibia, illustrating mean changes across its length (top plot), regression analysis from proximal to middle region (middle plot), and from middle to distal region (bottom plot).

and formation near the bone's proximal end, the impact becomes less pronounced, leading to a more gradual adaptation as we progress towards the middle. This underscores the complexity of bone adaptation mechanisms under combined treatment modalities. In contrast, the PTH-only treatments maintain a relatively steady adaptation rate across this segment that is not statistically significant, underscoring the distinct responses elicited by combined versus singular treatment approaches.

In the transition from the middle (50%) to the distal (80%) segment, the PTH alone effect became significant, like PTH20 (slope: 0.257,  $p = 4.28e-08$ ), PTH40 (slope: 0.30,  $p = 4.57e-12$ ), and PTH80 (slope: 0.40,  $p = 4.50e-10$ ), showing an increased bone formation and adaptation towards the distal end, at higher slopes increased with the PTH dosage. Combined PTH and ML treatments

still display negative spatial gradient moving to the distal region, with the PTH20ML (slope: -0.107,  $p=0.015$ ) and PTH40ML (slope: -0.137,  $p=0.002$ ). However, an exception is observed with PTH80ML, which uniquely demonstrates a positive slope (slope: 0.149,  $p=0.009$ ), suggesting a saturation or reversal of the combined treatments' effects at this higher dosage.

#### 4. Conclusions

In this study, we explored bone adaptation locally in response to Parathyroid Hormone (PTH) and Mechanical Loading (ML) and their interactions. Our analyses focus on the spatial gradient of the mean cortical thickness change across the depth of the tibia, to observe the dynamics of bone formation locally across all the regions. Notably, treatments combining PTH with ML showcased the most significant adaptation gradient variation along the length of the tibia compared to the vehicle scans, pointing to the complexity of the dynamics of bone formation with combined medical treatments and mechanical loadings.

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#### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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