The spatial relationship between bone formation and bone resorption in healthy and ovariectomized mice treated with PTH, bisphosphonate or mechanical loading

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Introduction

Bone is continuously remodeled to remove damage, to adapt to changes in mechanical demands and to regulate calcium homeostasis. The first goal is accomplished by coupled bone formation and resorption whereas adaptation requires sites of formation to differ from those of resorption. The regulation of circulating ions is probably achieved by a stochastic remodeling.

Aims

Here, we investigated these different aspects of remodeling in healthy and ovariectomized mice treated with PTH, bisphosphonate or cyclic mechanical loading.

Methods

15-week old female C57BL/6J mice were divided into: untreated ovariectomized (OVX, n=17) and sham operated (SHM, n=8); treated daily with PTH (PTH, n=9), treated once with zolendronate (BIS, n=9) and treated with cyclic mechanical loading (8N, 10Hz, 3000 cycles) at the 6th caudal vertebra (CML, n=17). Treatment started 11 weeks after ovariectomy and micro-CT measurements were performed at start of the treatment (w0) and after 2 (w2) and 4 (w4) weeks. Registration of consecutive scans allowed clustering the image voxels into formed, resorbed and quiescent bone (Fig. 1) [1]. The relative amount of surface voxels in the formation, resorption and quiescent clusters within the first two-weeks time interval (i.e., w0-w2) was defined as the probability for a remodeling event to occur at the bone surface [2]. By comparing the spatial locations of the remodeling events within two consecutive time intervals (i.e., w0-w2 and w2-w4) we estimated the probability of bone formation/resorption to occur at surfaces previously undergoing either formation, resorption or quiescence. One-way ANOVA with Bonferroni's correction was used to assess differences among groups.

Results & Discussion

Compared to OVX, only PTH and CML increased the probability of bone formation (Fig 2a), whereas the probability of bone resorption significantly decreased for all treatments (Fig. 2b). Moreover, PTH decreased the probability for the bone surface to remain quiescent (Fig 2c) and BIS significantly increased it (compared to SHM). Treatment with PTH made more likely that bone formation occurred either at surfaces previously undergoing formation or being quiescent (Fig 3a). The latter is in agreement with the evidence that PTH converts lining cells to osteoblasts [3]. All treatments significantly decreased the probability of detecting bone resorption on previously resorbed surfaces (Fig. 3b). The probability of coupled bone formation/resorption to occur was always less than 5% and in some cases not higher than the registration error of about 1% (dash line, Fig. 4). Nevertheless, coupled bone resorption significantly increased by a factor 3 for OVX and by a factor 2 for PTH compared to SHM. Considering that it is mechanically irrational that newly formed bone gets immediately removed, coupled bone resorption could be due to stochastic untargeted remodeling.

References

[1] Schulte, Lambers, et al., Bone 2011, 48:433–442
[2] Schulte, Ruffoni et al., PloS ONE 2013, 8:e62172
[3] Kim, Pajevic, et al., JBMR 2012, 27:2075-2084

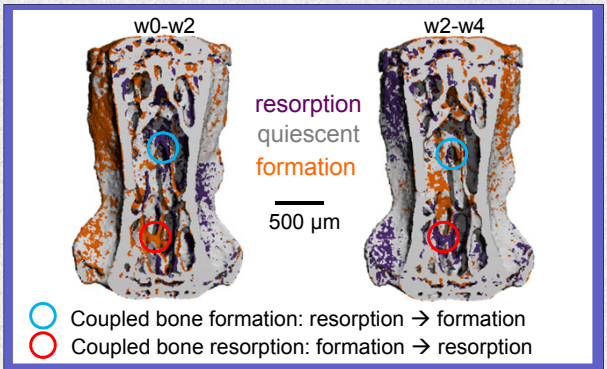

Fig. 1: Bone formation and resorption sites measured with *in vivo* micro-CT over 2 weeks for two consecutive time intervals, i.e. w0-w2 (left) and w2-w4 (right). The spatial locations where coupled bone formation and coupled bone resorption take place are highlighted.

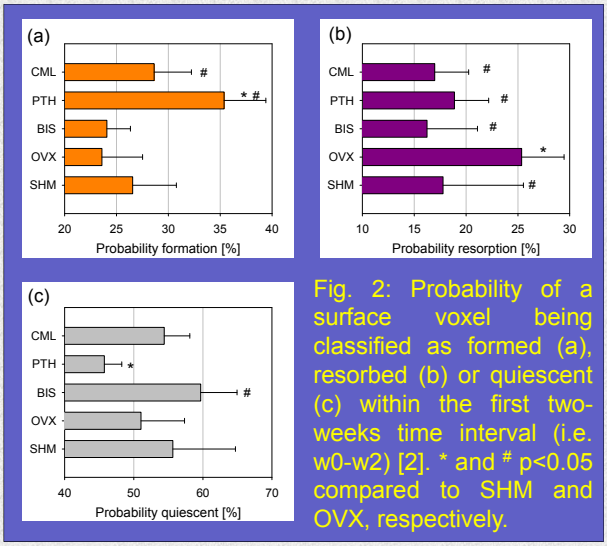

Fig. 2: Probability of a surface voxel being classified as formed (a), resorbed (b) or quiescent (c) within the first two-weeks time interval (i.e. w0-w2) [2]. * and # p<0.05 compared to SHM and OVX, respectively.

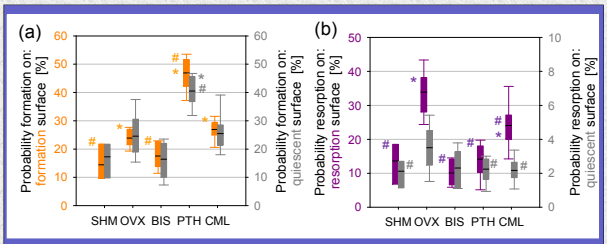

Fig. 3: Probability of bone formation (a) and resorption (b) on previously formed/resorbed and quiescent surfaces. * and # p<0.05 compared to SHM and OVX, respectively.

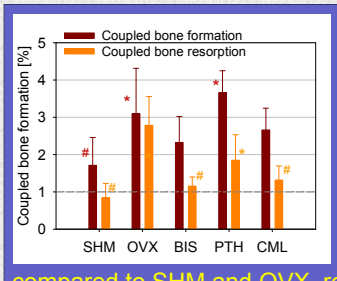

Fig. 4: Probability of coupled bone formation (i.e., bone formed at locations where it was resorbed) and coupled bone resorption (i.e., bone resorbed at locations where it was formed). * and # p<0.05 compared to SHM and OVX, respectively.