Cortical bone mechanical response is different under compression and tension stimulation

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INTRODUCTION: Bone adapts its structure according to the external force that it experiences [1]. Due to the structure of the bone, the strain distribution in the loaded tibia varies at different locations. Studies have found that bone cells respond differently under different mechanical stimulation types and patterns *in vitro* [2]. Molecular signals such as sclerostin, RANKL, OPG, cathepsin K, and periostin have been reported to participate in bone modeling and remodeling [3,4]. However, how these proteins have been regulated in the cells in response to different mechanical stimulations *in vivo* is still unclear. Thus, we used μCT and FE modeling in this study to identify strain distribution in mouse tibia and bone modeling/remodeling events in response to uniaxial tibial loading. We measured protein expressions and cellular responses at different locations (compression or tension regions) by histology staining.

METHODS: Female C57B1/6J mice (n=11) underwent *in vivo* μCT scan once per week for 5 weeks starting at 14 weeks of age. At the age of 16 weeks, the right tibia of each mouse was subjected to uniaxial compression loading for 2 weeks, and the contralateral tibia served as the non-loaded internal control. Weekly scanned images were registered, and 3D dynamic *in vivo* histomorphometry quantified bone volume changes at the voxel level. Separate age-matched mouse was scanned to measure the strain distribution using FE-modeling. After final μCT scanning, mouse tibia was harvested and fixed in 4% paraformaldehyde. 10% EDTA has been used to decalcify bone for 2 weeks. Paraffin-embedded samples were sectioned longitudinally, and IHC and TRAP staining were used to measure protein expression and pre-osteoclast/osteoclast number (n=4). Data are presented as mean ± standard deviation and statistical analyses were performed using a paired-t test. This study was approved by IACUC.

RESULTS: Under uniaxial tibia loading, cortical bone can be divided into tensile and compressive strain regions, and FE-modeling results showed that posterior/ lateral regions are compression-dominated, and anterior/ medial regions are tension-dominated with peak principal strains ranging from -3500 με to 2000 με (**Fig. 1A**). After 2 weeks of mechanical loading, both tension and compression sites increased bone formation and reduced bone resorption. The bone resorption was almost abolished at the peak compression region but not in the tension region after the loading (**Fig. 1B**). Bone remodeling was increased after mechanical loading in the compression site but not in the tension site (**Fig. 1C**). Periostin expression was decreased significantly in the compression region but slightly increased in the tension region (**Fig. 1D**). For the protein expression in osteocytes, sclerostin was inhibited in response to the loading both in compression and tension regions, but more significant in tension region. Oppositely, cathepsin K expression in osteocytes has been upregulated, and this mainly showed in compression site (**Fig. 1E**). Moreover, like the μCT results, osteoclasts-induced bone resorption was decreased, and more significantly in compression site as showed in Trap+ surface result (**Fig. 1F**).

DISCUSSION: In this study, the mechanical response in cortical bone is different under tension and compression. Although they have similar trends in modeling and remodeling, the signaling pathways involved may be different as they have different cellular changes. Our FE-modeling indicates the different strain distributions under uniaxial mechanical loading over cortical bone, and the IHC results suggest the different cellular responses under different strain stimulation. Periostin and cathepsin K change mainly in the compression site and sclerostin changes more significantly in the tension site. These observations suggest that compression and tension activate different cell signaling pathways and regulate bone homeostasis. Future studies may be needed to enhance our study, such as registration of μCT-based modeling/remodeling with histology slides to study cellular changes at different locations specifically. Also, according to the recent findings that mechanical responses are different from periosteal and endosteal surfaces, further separating regions based on outside and inside may be necessary better to understand the mechanism of mechanical responses in cortical bone.

SIGNIFICANCE: This study helps to reveal the mechanism of cortical bone mechanical responses under different stimulation regimes and provides insight into finding better treatments for bone strength improvement by combining physical exercise with pharmaceutical treatments.

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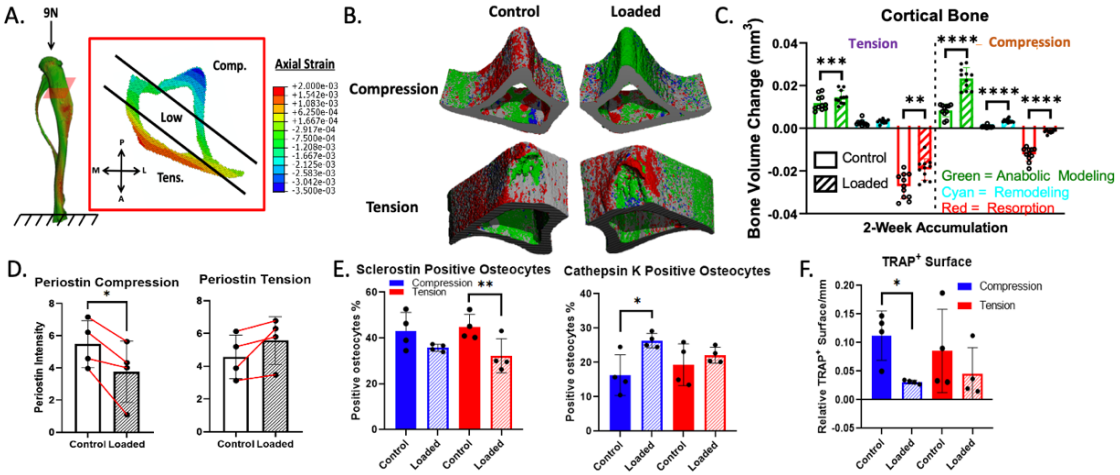

Figure 1. (A) FEA model of the strain distribution in cortical bone due to the uniaxial tibial loading. (B) μCT images of cortical bone anabolic modeling (green), catabolic modeling (red) and remodeling (blue) after 2 weeks loading. (C) Quantification of modeling and remodeling events in tension and compression regions (n=11). (D) Periostin staining intensity in periosteum at cortical compression and tension locations. (E) Quantification of sclerostin positive osteocytes and cathepsin K positive osteocytes in different locations after mechanical loading. (F) Quantification of TRAP$^+$surface in periosteum at compression and tension site after mechanical stimulation. N =4 mice/group. *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001. Vertical bars represent mean ± SD.