Treatment with Parathyroid Hormone Following Daily Loading Does Not Attenuate Osteoarthritis Progression

Omar Dervisevic[1], Ana Witkowski[1], Marjolein C. H. van der Meulen[1,2]
[1]Cornell University, Ithaca, NY [2]Hospital for Special Surgery, New York, NY
od73@cornell.edu

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Introduction: Pain and joint dysfunction are the primary reasons for which patients seek treatment for osteoarthritis (OA). Early-stage OA is characterized by increased bone remodeling, prompting interest in subchondral bone modifying treatments as potential therapies. Parathyroid hormone (PTH), an FDA-approved anabolic therapy for osteoporosis, promotes bone formation[1]. In surgical OA models, PTH treatment attenuated joint degradation and pain[2,3]. Eight weeks of PTH pretreatment before loading enhanced cartilage thickness and bone mass and mitigated cartilage damage following daily cyclic tibial loading[4]. In this study, we investigated whether PTH can alleviate OA pain and protect joint integrity when administered concurrently with daily loading. We hypothesized that PTH treatment would reduce pain-related behaviors, attenuate cartilage damage progression, and increase bone mass.

Methods: With IACUC approval, the left hindlimbs of 26-wk-old male C57BL/6J mice underwent 6 weeks of daily cyclic tibial loading (9N, 1200 cycles, 4Hz)[5,6]. The right hind limbs were not loaded and used as contralateral controls. Male mice develop more cartilage damage than female mice[7]. Mice were randomized into 2 treatment groups and injected with saline (VEH, SQ, n=8-10, 5d/wk) or PTH (40µg/kg/day, SQ, n=8-10, 5d/wk) immediately following each bout of loading. Static weight bearing was performed every 2 weeks to measure load distribution between right and left hindlimbs. Mice were euthanized 6 weeks after the start of loading; knees were dissected and prepared for microCT imaging and Safranin-O staining[3]. Cancellous bone in the epiphysis and cortical bone of the subchondral plate were analyzed by microCT. Cartilage damage in the tibia was quantified by OARSI scoring of Safranin-O-stained slides for total plateau and posterior and anterior compartments. Using a linear mixed-effects model Treatment and Loading effects for bone morphology and OARSI score were determined with a Tukey post-hoc analysis. Treatment, Loading, and Duration effects on static weight bearing were determined similarly.

Results: Significant cartilage damage was evident after 6 weeks of daily loading. PTH treatment did not improve cartilage damage compared to VEH treatment (Figure 1A, 1B). When examined by location, the most severe damage was present in the posterior-medial compartment of the tibia. Over the 6 weeks hindlimb weight bearing shifted to an increased reliance on the contralateral limb. PTH treatment did not alleviate this pain-related behavior (Figure 1C). Loading decreased the epiphyseal bone volume fraction (BV/TV), epiphyseal tissue mineral density (TMD), trabecular number (Tb.N), trabecular thickness (Tb.Th), cortical thickness (Ct.Th), and cortical TMD. As expected, PTH increased the epiphyseal BV/TV (Fig. 2A). The effect of loading on epiphyseal TMD differed with PTH treatment, which increased the reduction in bone mass in loaded limbs (Fig. 2B).

Discussion: PTH treatment reduced pain and cartilage damage in surgical models of OA[2,3]. Additionally, PTH pretreatment had protective effects on both bone and cartilage in load-induced OA[4]. In the present study, PTH administration initiated concurrently with load-induced OA did not reduce pain or cartilage damage. These discrepancies across preclinical OA models may stem from the effects of mechanical loading on cartilage and/or the combined impact of PTH and loading on cartilage health. PTH treatment increased bone mass in the epiphysis, reflecting its anabolic effect on bone. Loading reduced epiphyseal TMD, indicating bone remodeling, with a greater reduction in PTH-treated limbs, perhaps highlighting an enhanced remodeling response to combined PTH and loading. Although tibial bone microarchitecture improved, cartilage damage and pain related behaviors were not attenuated with combined daily loading and PTH administration, suggesting that our prior results reflected improved cartilage properties with PTH pretreatment. The mechanisms underlying the effects of PTH treatment on cartilage with loading merit further investigation.

Significance: No disease-modifying treatments exist for OA. PTH reduces cartilage damage in surgical models but has not been studied in load-induced OA.

References: [1]Yuan+ 2014, [2]Sun+ 2021, [3]Sampson+ 2011, [4]Antoinette & Ziemian+ 2024, [5]Fritton+ 2005,[6]Ko+ 2013, [7]Temp+ 2020

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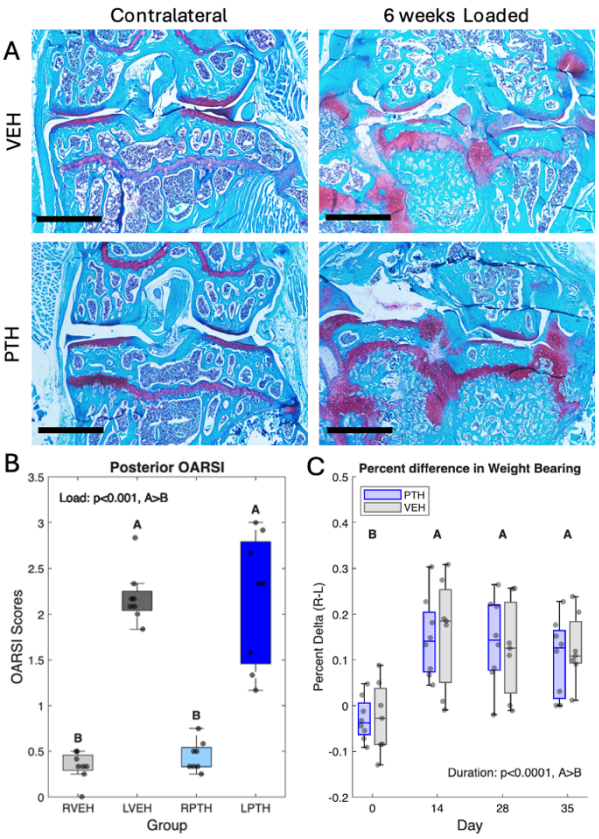

Figure 1: A) Representative sections of the proximal tibia of loaded and control limbs for VEH (Top) and PTH (Bottom) treatments. B) OARSI Scores in the posterior compartment of the tibia increased with daily loading; C) Weightbearing on the contralateral limb increased with experimental duration as measured by static weightbearing (% difference R-L).

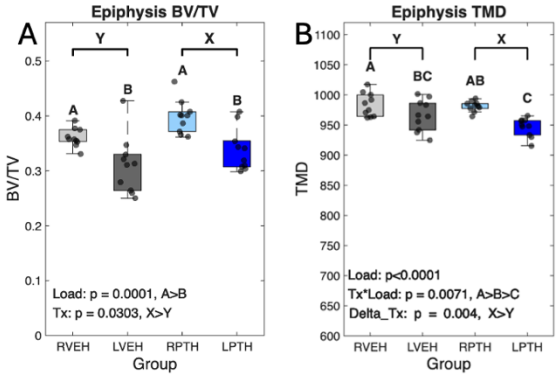

Figure 2: A) Epiphysis BV/TV decreased with loading (p=0.0001, A>B) and increased with PTH Treatment (p=0.03, X>Y). B) The effect of PTH treatment on epiphysis TMD differed with loading (Tx*Load p=0.0071) and increased the difference between PTH-treated limbs (Delta_Tx p=0.004, X>Y).