Low-level cyclic tibial compression attenuates osteoarthritis progression after joint injury in mice

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INTRODUCTION: Mechanical loading, exercise, and joint health have a unique relationship in the onset and progression of osteoarthritis (OA). High levels of loading lead to cartilage degradation by decreasing proteoglycan synthesis [1] and inducing chondrocyte apoptosis [2]. Conversely, mild exercise involving low levels of mechanical loading can benefit cartilage by preventing injury-induced cartilage degradation [3,4], maintaining thicker cartilage [5], and increasing proteoglycan synthesis in vitro [6]. To date, the majority of models used to study the effects of beneficial loading were either in vitro cell culture and cartilage explant experiments [6] or involved in vivo exercise [4,5]. In vitro models do not represent the entire joint. Exercise leads to systemic effects, such as muscle growth and weight loss, causing difficulty in determining factors that specifically benefit the joint [7]. Thus, we sought to isolate the beneficial effects of in vivo mechanical loading using cyclic tibial compression. Previously, cyclic tibial compression at moderate (4.5N) and high (9.0N) loads induced OA-like pathology in mouse knee joints [8]. Here, we examined whether daily cyclic compression would directly benefit the joint by applying low-level cyclic compression after surgical induction of post-traumatic OA, using the destabilization of the medial meniscus (DMM) model. We hypothesized that low-level cyclic compression would attenuate post-traumatic OA symptoms induced by DMM.

METHODS: Fifty-one 10-wk-old C57BL/6J male mice underwent DMM surgery on the right knee. After a 5-day recovery period (+0-wks), we applied cyclic compression to the right tibiae of mice at low (DMM+1.0N, DMM+2.0N) and moderate (DMM+4.5N) peak loads for 2 or 6 wks (n=7-8/group). Loading consisted of 1200 cycles/day at 4 Hz for 5 days/wk. An additional group received daily doses of anesthesia without cyclic tibial compression (DMM-only). Contralateral limbs served as controls (Ctrl). We assessed cartilage damage using the OARSI scoring system [9]. We also evaluated changes in osteophyte size and maturity, subchondral bone sclerosis, cellularity, apoptosis, and aggrecanase activity. All experimental techniques were approved by the Cornell IACUC. Data were compared using ANOVA followed by Tukey’s post-hoc test (p<0.05). All results presented are significant.

RESULTS: Low-level cyclic compression attenuated DMM-induced cartilage degradation, osteophytes formation, and subchondral bone sclerosis. In addition, low-level loading had subtle beneficial effects on cellularity and cleaved aggrecan levels. After 6 wks, focal cartilage erosion occurred in the DMM-only group, whereas the cartilage surface was intact in both the DMM+1.0N and DMM+2.0N groups (Fig. 1A). Cartilage damage was limited to proteoglycan loss with low-level loading, reflected by lower OARSI scores compared to the DMM-only group at +6-wks (Fig. 1B,C). Moderate loading (4.5N) did not attenuate DMM-induced cartilage degradation. In addition, 1.0N-loading suppressed DMM-induced osteophyte formation in the posterior region of tibial plateau in 5 of 7 animals. Loading at any magnitude suppressed increases in tissue mineral density in the subchondral bone plate associated with DMM. Cellularity was lower in the +6-wk DMM-only group compared to +0-wk DMM-only levels, but not different between the +6-wk DMM+1.0N group and +0-wk DMM-only levels.

DISCUSSION: Our results support the hypothesis that low-level cyclic compression can attenuate DMM-induced OA progression. Low-level loading (1.0N, 2.0N) reduced the severity of the structural cartilage erosion following DMM. In addition, low-level loading had beneficial effects on osteophytes and the subchondral bone plate. Based on our tissue-level results, the beneficial response to low-level cyclic axial compression in the cartilage was comparable to responses reported with other noninvasive techniques, such as treadmill exercise or transverse loading of the knee [3,10]. However, low-level loading was more effective in inhibiting osteophyte formation compared to similar approaches [10]. The success of loading following DMM may reflect the limited joint instability associated with the model [11]. Our findings demonstrate the potential of using low-magnitude cyclic compression as a preventative therapy after joint injuries. Treatment protocols after injury often immobilize the affected joint to allow time for healing. Our results suggest that applying controlled loading during the healing process may maintain cartilage health and attenuate post-traumatic OA progression.

SIGNIFICANCE: Rehabilitation protocols after joint injury may benefit from controlled, low-level cyclic compression to maintain healthy cartilage and attenuate the development of post-traumatic OA.


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Figure 1. A) Representative Safranin O/Fast-Green stains showing beneficial effects of low-level loading post-DMM. Arrows indicate proteoglycan loss; arrow heads indicate cartilage erosion. Scale bars=100 μm. B) OARSI scores comparing Ctrl, DMM-only, and DMM+1.0N groups at 0, 2 and 6 wks. C) OARSI scores for all load levels at +6-wks. Bars indicate mean ± standard deviation with individual data points overlaid. Bars not sharing the same letter have different means (p<0.05).