The Effect of Low- and Moderate-intensity Exercise on Post-traumatic Osteoarthritis Progression after ACL Rupture in Mice

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INTRODUCTION: The anterior cruciate ligament (ACL) is one of the most commonly injured joint structures for those playing sports or exercising, particularly for jumping and cutting sports such as soccer and basketball. Approximately 1 in 3,500 people suffer ACL injuries every year in the United States. After injury, most patients will receive ACL reconstruction, in which surgeons replace the injured ACL with autograft or allograft tissue to restore the biomechanical stability of the injured joint. However, in 10 – 20 years, this type of injury still commonly leads to post-traumatic osteoarthritis (PTOA), which can significantly affect patients' quality of life. In our previous study, we found that surgical restabilization of the knee immediately after non-invasive ACL injury in mice slowed PTOA progression. In addition, our follow up study found that one week of hindlimb unloading (HLU) between ACL injury and restabilization surgery also effectively mitigated PTOA at later time points. However, it is still unclear if exercise after knee surgery is beneficial or harmful to the progression of PTOA and OA-related pain. Therefore, the goal of this study was to determine if different intensity of exercise after knee restabilization surgery would affect PTOA progression and pain compared to unexercised mice. We hypothesized that low intensity exercise would be beneficial in slowing PTOA progression and diminishing joint pain compared to unexercised mice, while moderate intensity exercise would be less effective. We further hypothesized that mice with low intensity or moderate intensity exercise would recover from injury-induced muscle loss faster than unexercised mice.

METHODS: 84 female C57BL/6J mice (12-weeks-old at the time of injury) were used in this study. All mice were subjected to non-invasive ACL injury followed by 1 week of HLU and then had knee restabilization surgery or sham surgery. During the restabilization surgery, a bone tunnel was drilled in the anterior side of the proximal tibia and a suture was passed through the tunnel and around the posterior site of the distal femur beneath the fabellofemoral ligaments, then the suture was tightly tied on the lateral side of the joint. For sham surgery, the suture was tied loosely. All mice had one week of post-operative recovery after surgery and were then randomly assigned to 6 experimental groups: 28 mice that underwent no exercise after surgery, 28 mice that were subjected to low intensity exercise (6 m/min, 30 min/day, 5 days/week), and 28 mice that were subjected to moderate intensity exercise (12 m/min, 30 min/day, 5 days/week). Half of the mice in each group completed 1 week of exercise and were euthanized 3 weeks after injury (2 weeks after surgery) and the remaining mice completed 4 weeks of exercise and were euthanized 6 weeks after injury (5 weeks after surgery) for analysis of OA progression and muscle (soleus and gastrocnemius) changes. All mice were measured weekly with a dynamic weight bearing system to determine pain in the joint. Knee joints were analyzed with micro-computed tomography to measure epiphyseal trabecular bone microstructure and osteophyte volume, and with whole-joint histology to grade OA progression and synovitis. Muscles were analyzed for muscle mass and muscle fiber types using immunohistochemistry (IHC). All procedures were approved by the UC Davis Institutional Animal Care and Use Committee.

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RESULTS: At week 3, low intensity exercise was able to mitigate epiphyseal trabecular bone loss caused by the ACL rupture (-18% BV/TV compared to -28% in mice without exercise; Figure A). No significant difference was observed in osteophyte formation between these groups at week 3, but less osteophyte volume was formed in the low intensity exercise group compared to the other groups at week 6 (Figure B & C). Based on the histological images of knee joints, more chondrophytes/osteophytes were observed in the moderate intensity exercise group (Figure D). With OA scoring on histological images, we observed that restabilization surgery slowed OA progression, especially in exercise groups (Figure E). We further found that exercise was able to restore the gastrocnemius muscle loss from injury and surgery which is commonly observed in patients (Figure F).

DISCUSSION: This study found that low intensity exercise following knee restabilization surgery was an effective intervention for mitigating short-term bone loss and slowing long-term PTOA progression after ACL injury. These results are consistent with other studies investigating low intensity exercise or voluntary running wheel after ACL injury that showed some reduction in OA progression. We also found that 4 weeks of exercise in mice was able to effectively restore muscle loss caused by injury and surgery, which might have some correlation with OA progression. Altogether, these data suggest that low-level exercise can help maintain both bone and muscle health in joints following ACL injury and reconstruction surgery that contribute to PTOA progression after the joint stability is restored. However, further studies are needed to investigate the biological and mechanical effects of exercise that can delay PTOA progression or diminish the severity of PTOA.

SIGNIFICANCE/CLINICAL RELEVANCE: This study established that low-intensity exercise after knee restabilization surgery was an effective biomechanical intervention for preserving bone volume after surgery and did not exacerbate osteophyte formation. The results of this study will help inform rehabilitation strategies or recommended activities for human subjects after ACL reconstruction.

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