

Delayed anterior cruciate ligament reconstruction exacerbates post-traumatic osteoarthritis and impairs knee motion in a murine model of anterior cruciate ligament reconstruction

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INTRODUCTION:

Post-traumatic osteoarthritis (PTOA) develops in up to two-thirds of patients after anterior cruciate ligament reconstruction (ACLR). Although some studies suggest that early ACLR may reduce the risk of PTOA, others have reported no clear association between surgical timing and disease progression. PTOA development is influenced by persistent preoperative knee instability, concomitant meniscal or chondral injury, and inflammatory responses to injury and surgery. Clinically, early reconstruction is often delayed to avoid arthrofibrosis, yet the optimal length of this waiting period remains undefined.

Furthermore, while meniscal injury is recognized as a risk factor for PTOA, the specific impact of pre-reconstruction delay on PTOA progression has not been fully understood. The primary aim of the present study is to evaluate the impact of timing of ACLR on the development of PTOA using a murine model of ACLR. We hypothesized that prolonged delay before ACLR would accelerate postoperative osteoarthritic progression and reduces knee motion.

METHODS: All experiments were approved by the Institutional Animal Care and Use Committee. Thirty-six 12-week-old male C57BL/6J mice (average weight: 26 g) were used in this study, and underwent open ACL transection followed by ACLR surgery using ipsilateral flexor digitorum longus tendon autograft as previously described [1]. The mice were randomly assigned to one of the three groups: 1) immediate ACLR group, 2) ACLR at 2 weeks after transection (ACLR@2w group), 3) ACLR at 4 weeks after ACL transection (ACLR@4w group). All mice were euthanized at 8 weeks post injury.

The primary outcome measure was histologic evaluation of osteoarthritis. Secondary outcomes measures included radiographic osteoarthritis evaluation using Kellgren-Lawrence (K-L) classification, micro-computed tomography analysis of the subchondral bone, knee range of motion (ROM) testing, and evaluation of anterior tibial translation (ATT) on lateral view radiographs. Radiographic data were obtained at 4 weeks and 8 weeks after injury and the rest of the outcomes were at 8 weeks only. Statistical analysis was carried out using one-way ANOVA followed by multiple comparisons using the Bonferroni test, with statistical significance set at $p < 0.05$.

RESULTS: The delayed ACLR groups had higher femoral and tibial OARS scores (more OA) compared to the immediate ACLR groups ($p < 0.05$) (Fig 1A). There were no significant differences in radiographic PTOA grading among groups at 4w post injury. The immediate ACLR group showed significantly lower K-L grade than delayed ACLR groups at 8 weeks after injury ($p < 0.001$), although there was no significant difference between delayed ACLR groups (Fig 1B). The immediate ACLR group exhibited higher bone volume fraction, trabecular thickness, and bone mineral density, while the delayed ACLR@4w group showed higher cortical thickness in both femur and tibia (Fig 2). All groups exhibited restricted ROM compared to the contralateral knee. However, the delayed ACLR groups had significantly restricted knee extension and ROM compared to the immediate ACLR group (Fig 3). There was no significant difference in ATT among groups.

DISCUSSION: Delayed ACLR, performed two or four weeks after ACL injury, resulted in cartilage degeneration, cortical bone thickening, and loss of knee motion compared with immediate reconstruction, indicating that delayed ACLR exacerbates the development of PTOA in this murine model. Interestingly, no significant differences were observed between the two delayed ACLR groups in terms of osteoarthritic progression or other outcome measures. This suggests that early intra-articular pathological changes occurring immediately after ACL injury - such as synovial inflammation and hemarthrosis may drive PTOA progression before ACLR as noted in previous studies [2]. However, the present study performed open ACL transection with later delayed ACLR timepoints, and with a longer observation period to assess PTOA development and functional outcome. These findings indicate that minimizing the delay before ACLR may help reduce PTOA development and better preserve joint function. Ongoing investigations in our laboratory will use this model to evaluate treatment with pharmacologic mediators of inflammation, and we will also incorporate gait analysis to further assess functional and pain-related outcomes in this model.

SIGNIFICANCE/CLINICAL RELEVANCE: This study demonstrates that delayed anterior cruciate ligament reconstruction exacerbates post-traumatic osteoarthritis in a murine model of anterior cruciate ligament reconstruction

REFERENCES: [1] Lebaschi A et al. J Knee Surg. 2017. [2] Retzky SJ et al. ORS 2025.

Figure 1: (A) Histological evaluation: femoral and tibial OARS scores. (B) Radiographic osteoarthritis evaluation using Kellgren-Lawrence classification.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

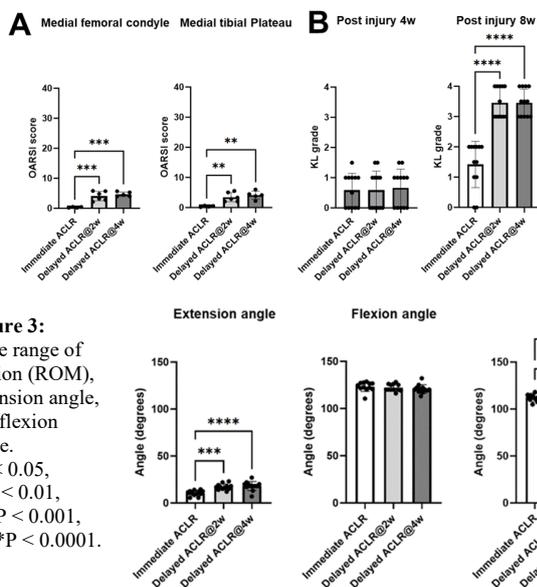


Figure 2: Micro-computed tomography analysis.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

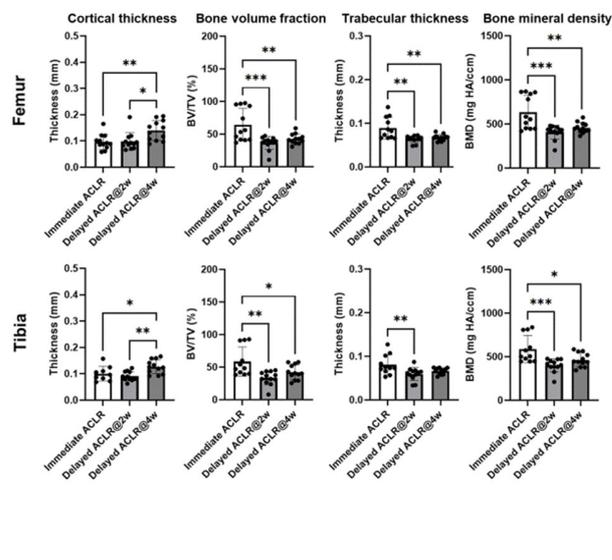


Figure 3:

Knee range of motion (ROM), extension angle, and flexion angle.

* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$.

