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Original Article: Early Anterior Cruciate Ligament Reconstruction Mitigates the Development of Posttraumatic Osteoarthritis in a Murine Anterior Cruciate Ligament Rupture Model

Authors: Retzky JS, Carballo C, Simonian L, Li TM, Suzuki Y, Okazaki Y, Hammad M, Ranga S, Trinh PMP, Aydin E, Covello M, Eliasberg CD, Lu TT, Rodeo SA

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INTRODUCTION / BACKGROUND

Posttraumatic osteoarthritis (PTOA) is one of the most feared sequelae of anterior cruciate ligament (ACL) injury and reconstruction. The literature shows that 23% to 60% of patients develop radiographically detectable degenerative changes 10 to 25 years after ACL reconstruction (ACLR), regardless of technical quality. This places a young and active population at early risk for total knee arthroplasty — a procedure that, in patients under 35, carries substantially higher revision rates.

Several risk factors for PTOA after ACL injury have been identified: concomitant meniscal surgery, elevated body mass index, and chondral injury at the time of ACLR. One question, however, remains actively debated: does the time between injury and reconstruction influence PTOA development? Some studies suggest early ACLR mitigates degenerative progression, while others have found no difference based on surgical timing.

Heterogeneity across published studies — variation in graft types, surgical techniques, definitions of "early" versus "delayed," and osteoarthritis criteria — makes it difficult to derive a definitive answer from clinical data alone. Animal models offer the opportunity to control these variables and isolate specifically the effect of surgical timing on degenerative progression. Prior studies in rats and mice have shown that early knee stabilization mitigates PTOA, but until the present work none used a truly intra-articular ACLR model, relying instead on extra-articular stabilizations that limit clinical relevance.

This study from the Hospital for Special Surgery fills that gap by employing for the first time a murine model with noninvasive ACL rupture followed by clinically representative intra-articular reconstruction, comparing immediate versus delayed ACLR.

OBJECTIVE

To evaluate the effect of ACLR timing on PTOA development using a murine noninvasive (closed) ACL rupture model, and its impact on pain-related gait behaviors, peripheral and central immune and inflammatory response, knee range of motion (ROM), and proximal tibial and distal femoral epiphyseal bone volume.

METHODS

Controlled laboratory study conducted after institutional animal care and use committee approval. Fifty-five male C57BL/6J mice, 11–12 weeks of age (Jackson Laboratory), were randomized to three experimental conditions: isolated ACL rupture (n=16), rupture followed by immediate ACLR (n=16), and rupture followed by delayed ACLR performed 7 days after injury (n=16). Seven uninjured mice served as controls.

Noninvasive ACL rupture was induced with a validated technique: animal prone under anesthesia, right femur in a restrictive holder, knee flexed to 90° and foot in 30° dorsiflexion. An axial load of 5–20 N was applied to the distal tibia at 1.0 mm/s, with rupture confirmed by increased anterior translation on Lachman test. The surgical technique employed a flexor digitorum longus (FDL) autograft, with standardized medial parapatellar arthrotomy. Femoral (retrograde) and tibial (antegrade) tunnels were drilled with a 23-gauge needle at anatomic points. The graft was tensioned to 5N, with femoral fixation by surgical clip and tibial fixation by 4-0 Ethibond suture over a transverse tunnel, with posterior drawer applied at 30° of flexion.

Animals were sacrificed at 28 days postoperatively (ACLR) or postinjury (isolated rupture). Primary histological analysis used safranin O staining and assessment by two blinded reviewers using the Osteoarthritis Research Society International (OARSI) score for medial tibial plateau and medial femoral condyle. Five slides 90 µm apart were analyzed per knee.

Secondary assessments included: range of motion (goniometer on days 14 and 28 postop with two blinded graders); gait analysis via DigiGait (time in swing/stance, frequency, symmetry, paw area at peak stance); flow cytometry of the ipsilateral iliac lymph node (iLN) and spleen with a panel for monocytes, neutrophils, dendritic cells, CD4+/CD8+ T lymphocytes, T regulatory cells, B cells, NK cells, and plasma cells; and micro-CT (µCT) with 12.2 µm voxel for volumetric epiphyseal measurement. An Evans Blue assay confirmed that the iLN is the primary lymph node draining the knee.

MAIN RESULTS

PTOA histological analysis: the isolated rupture and delayed ACLR groups had significantly higher femoral OARSI scores than controls ($p<0.0001$ for both) and immediate ACLR ($p<0.001$ and $p<0.0001$, respectively). No difference between control and immediate ACLR ($p=0.10$) nor

between isolated rupture and delayed ACLR (p=0.39). Identical pattern in tibial scores — isolated rupture and delayed ACLR significantly worse than control (p<0.0001 and p<0.001) and immediate ACLR (p<0.01 for both). Intraclass correlation coefficients were 0.61 (tibia) and 0.82 (femur).

Range of motion: at day 14 postop, both surgical groups (immediate and delayed ACLR) showed significantly lower ROM than control and isolated rupture (p<0.05 for all). At day 28 this profile shifted revealingly — only the delayed ACLR group maintained significant ROM loss versus control (p<0.001), while the immediate ACLR group recovered ROM comparable to controls (p=0.064; no statistical difference).

Gait analysis: no significant differences were detected between groups in swing time, stance time, stride frequency, symmetry, or paw area at peak stance — neither preoperatively nor at the 14- and 28-day timepoints. That is, the observed PTOA differences cannot be attributed to differences in pain-related gait behavior.

Local immune response: the surgical groups (immediate and delayed ACLR) showed increased total ipsilateral iLN cellularity compared with controls and isolated rupture (p<0.05 for all), with elevations in monocytes, neutrophils, resident and migratory dendritic cells, CD4+/CD8+ T lymphocytes, B cells, Foxp3+ T regulatory cells, NK cells, plasma cells, fibroblastic reticular cells, and blood and lymphatic endothelial cells. No differences between immediate and delayed ACLR in this respect, suggesting this expansion is a generic physiological response to surgical intervention. The spleen showed no differences across groups.

Micro-CT: this was a particularly original finding. Proximal tibial epiphyseal bone volume was significantly lower in the delayed ACLR group (median 3.5 mm^3) than in the immediate ACLR group (median 3.9 mm^3; p<0.001). Similar pattern in the distal femoral epiphysis: 6.6 mm^3 (delayed) versus 8.1 mm^3 (immediate; p<0.01). No prior study had quantified epiphyseal bone volume after ACLR.

AUTHORS' CONCLUSION

Immediate ACLR mitigates PTOA development in a murine noninvasive ACL rupture model. Animals undergoing immediate reconstruction showed tibial and femoral OARSI scores indistinguishable from controls, while delayed ACLR (7 days) resulted in degenerative changes comparable to those of untreated rupture. The authors propose two main explanations: (1) persistent joint instability during the first 7 days in the delayed group, and (2) persistent hemarthrosis — well documented as deleterious to cartilage via hemosiderin-mediated chondrocyte apoptosis and macrophage activation with TNF-α release. The preliminary clinical implication is that both early stabilization and possibly hemarthrosis evacuation may help mitigate degenerative progression.

💬 BS DISCUSSION

This is a paper that deserves heightened attention because it touches one of the most sensitive and controversial points of contemporary ACL reconstruction practice: optimal surgical timing. For decades surgeons have operated under the premise that waiting for the "cold phase" of the knee — traditionally 3 to 6 weeks after trauma — would minimize postoperative arthrofibrosis risk. This paradigm, established largely by classic 1990s work, has been progressively challenged, and this study from Scott Rodeo's group (HSS) adds robust experimental evidence to that conceptual revision.

The finding that immediate ACLR produced OARSI scores statistically indistinguishable from healthy controls — and significantly better than ACLR performed just 7 days after trauma — is provocative. Equally interesting is the ROM finding: at 28 days, the immediate ACLR group had recovered mobility comparable to controls, directly contradicting the notion that early surgery predisposes to stiffness. As the authors note, it is plausible that immediate intervention evacuates pro-inflammatory and pro-fibrotic mediators from the articular compartment, mitigating — rather than causing — postoperative fibrosis.

From a mechanistic standpoint, the hemarthrosis-as-villain hypothesis is this work's most original contribution. Immediate ACLR mice underwent arthrotomy right after rupture, with immediate evacuation of intra-articular blood. The delayed ACLR group lived with hemarthrosis for 7 days before surgical clearance. The literature on hemophilic arthropathy is eloquent: blood breakdown products induce chondrocyte apoptosis, hemosiderin deposition in synoviocytes, macrophage release of TNF-α, and accelerated bone resorption. The authors cite Haxaire et al. (Blood 2018) showing that TNF-α pathway blockade in a murine hemophilic arthropathy model mitigates bone loss. The biological coherence is strong.

For BS practice, the message is twofold. First, this work reinforces a growing clinical current — represented by studies like Shelbourne's and more recent European series — that advocates early ACLR in selected patients with good preoperative range of motion, no significant effusion, and rehabilitation motivation. Second, and perhaps more innovative, it surfaces the discussion about acute hemarthrosis management. Joint aspiration after ACL injury — a simple, quick, low-cost gesture — may be underutilized as a potentially chondroprotective measure in patients awaiting reconstruction. Prospective clinical studies specifically evaluating this outcome are warranted.

Limitations are clear and the authors do not omit them: animal model with relevant anatomical differences from humans, open ACLR (arthroscopy impossible in mice), only male animals, and no control over postoperative loading or motion. These points limit direct clinical translation and call for caution in generalization. On the other hand, the experimental design is elegant, the controls adequate, and the multiple outcome validation (histology, ROM, gait, cytometry, μCT) lends robustness to the whole. For BS Papers, the take-home is to systematically discuss, in our acute post-ACL evaluation protocols, three questions: the ideal window for reconstruction, the indication for early joint aspiration, and the communication with the patient about real medium- and long-term PTOA risk. This is exactly the kind of mechanistic evidence that should shape the clinical conversation in coming decades.

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