Intra-articular Femoral Trauma Induces More Severe Contracture in a Mouse Model of Knee Stiffness Compared to Extra-articular Immobilization

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INTRODUCTION: Arthrofibrosis is a complication following primary total knee arthroplasty (TKA) that affects ~4% of patients. Arthrofibrosis is characterized by excessive scar tissue deposition in the joint, resulting in a reduced range of motion of the knee. Pre-clinical modeling of arthrofibrosis in small animal models should reflect both the trauma of TKA and the resulting phenotypic stiffness of this disease. We previously established an extraarticular mouse model of knee stiffness without direct trauma to the joint and were able to reliably induce knee stiffness. To establish a more translational mouse model for arthrofibrosis, here we have now included a direct trauma to the knee joint in addition to extraarticular knee immobilization.

METHODS: Following IACUC approval, 30 mice were randomized into three groups (female, n=10/group): contracture only (C), contracture with arthrotomy (C+A), and contracture with arthrotomy and femoral trauma (C+A+F). In all groups, a 3-0 nonabsorbable suture was passed around the proximal femur and distal tibia using a 21G needle to immobilize the knee in flexion. The C+A group included a lateral parapatellar arthrotomy with exposure of the femoral condyles, mimicking soft tissue dissection during TKA. The C+A+F group included all prior steps with the addition of cortical injury of the non-articular surface of the lateral femoral condyle using a burr to simulate bone trauma typical of femoral cuts during TKA with the corresponding accumulation of hemarthrosis. All limbs were immobilized for 8 weeks, followed by suture removal and 4 weeks of remobilization. Biomechanical stiffness was assessed using a custom load-cell-based device that recorded torque-angle curves. An additional cohort (n=24) underwent identical immobilization and were sacrificed at 3-, 7-, 14- or 21-days post-surgery to collect tissue from the posterior knee capsule for qPCR analysis of the fibrosis markers ACTA2, CTGF, and TAGLN. Kruskal-Wallis test with Dunn's multiple comparisons were used to compare the three experimental groups within the torque range of 0.2-0.6 N·cm and 2-way ANOVA to compare genes expression throughout the time course.

RESULTS SECTION: The C+A+F group was significantly stiffer compared to the C and C+A groups from 0.35-0.6 N·cm of torque. This amounted to the C+A+F group being significantly stiffer by 22.5±6.5 and 24.1±1.6° compared to the C and C+A groups, respectively. The C and C+A groups were not significantly different from each other (p= >0.9). In regard to the expression of fibrosis related genes, ACTA2 was significantly elevated in the C+A+F group at 7 and 14 days, compared to the C and C+A groups. For CTGF, the C+A+F group was significantly elevated at 7 days compared to C and C+A and at 14 and 21 days compared to C. TAGLN showed no significant differences in gene expression between the experimental groups at all timepoints.

DISCUSSION: The addition of non-articular surface intra-articular femoral condyle trauma with formation of hemarthrosis with bone marrow elements significantly increased knee stiffness, indicating that osseous injury contributed to the severity of joint stiffness. This increase in stiffness was accompanied by upregulation of fibrosis-related genes, particularly ACTA2 and CTGF at 7 and 14 days, suggesting sustained activation of fibrotic pathways. These findings reflect clinical observations where surgical trauma, including osseous injury, is associated with postoperative stiffness in arthrofibrosis. By modeling both soft tissue and bony trauma, this approach more closely represents the pathophysiology of arthrofibrosis and provides a translational platform for future studies.

SIGNIFIGANCE/CLINICAL RELEVANCE: Incorporating femoral trauma into this mouse model enhances its clinical relevance by more closely replicating the osseous injury associated with total knee arthroplasty, enabling the study of post-surgical arthrofibrosis and evaluation of targeted therapies.

IMAGES AND TABLES:

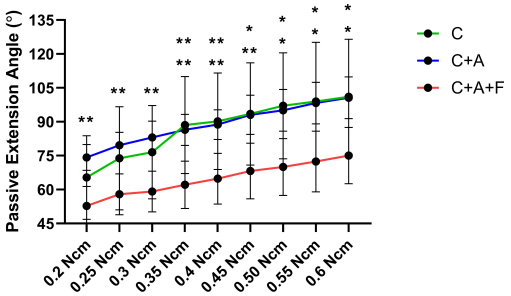

Figure 1. Angles between 0.2-0.6 N·cm torque. C vs. C+A+F (top asterisk) and C+A vs. C+A+F (bottom or individual asterisk). p= 0.05 threshold, where p*= 0.002-0.01 and p**= 0.01-0.03.

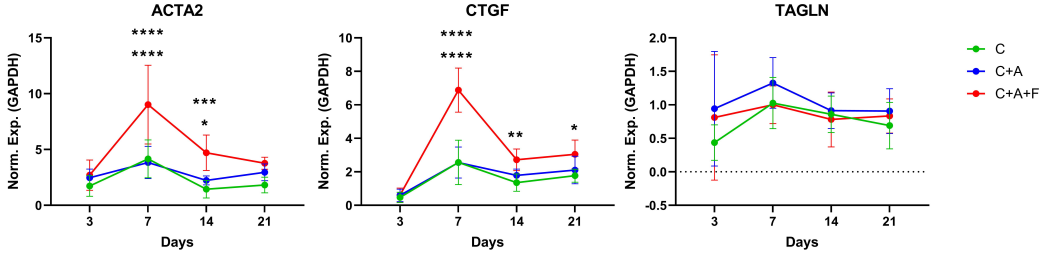

Figure 2. Gene expression time course for 3, 7, 14, and 21 days. C vs. C+A+F (top or individual asterisk) and C+A vs. C+A+F (bottom asterisk). p= 0.05 threshold, where p*= 0.01-0.02, p**= 0.01, p***= 0.001, and p****= <0.0001.