Medial femoral condyle defect drives degeneration in compartment-matched meniscus and tibial plateau

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INTRODUCTION: Initiating injury to soft tissues of the joint leads to osteoarthritis (OA) development but little is known about joint tissue crosstalk and how an initiating injury to either cartilage or meniscus drives joint deterioration as a whole. There is clinical evidence that untreated cartilage defects lead to meniscus degeneration,[1] but to our knowledge no studies have investigated how unilateral condylar defects affect the surrounding tissues in the medial and lateral joint compartments. The New Zealand white male rabbit osteochondral defect model is well-characterized and widely used to study articular cartilage repair.[2,3] Clinically, it is well established that the structure and organization of the extracellular matrix (ECM) of the meniscus is changed in OA.[4] However, no studies in preclinical models have identified structural and organizational changes in the meniscus or tibial plateau following a focal femoral condylar cartilage defect. Therefore, the objectives of this study were to 1) assess the gross, surface morphological changes in the tibial plateau in joints with or without a condylar osteochondral defect and 2) examine the structural and compositional changes in the menisci ECM adjacent to cartilage defects compared to healthy controls.

METHODS: Medial and lateral menisci were harvested from an *in vivo* osteochondral defect model in New Zealand white male rabbits (Fig 1A). Animal studies were performed in accordance with approval from the New York University Institutional Animal Care and Use Committee (IACUC: 2017-0025). Rabbits underwent surgery to create osteochondral defects on the medial condyle, were injected with saline at 4 weeks, and were sacrificed 12 weeks post-surgery (Fig 1B). Four groups of menisci and tibial plateaus were studied: (1) medial defect (in contact with defected condyle), (2) lateral defect (adjacent compartment to defected condyle), (3) medial no defect (control with no defect in condyle), and (4) lateral no defect (control with no defect in condyle). The osteochondral defect model positions the medial meniscus to be in contact with the injured cartilage, under which lies the medial tibial plateau (Fig 1A). The lateral meniscus remains in contact with the uninjured condyle and the lateral tibial plateau beneath. Tibial plateaus (n=4 per group) were stained with India ink and analyzed using ImageJ to obtain percentage of area covered by ink. Meniscus (control n=4, defect n=2) tissues were fixed in 10% formalin buffered solution, switched to 70% ethanol, embedded in paraffin wax, and sectioned for histological processing. Histological slides were stained with Safranin-o and picrosirius red, followed by imaging under brightfield (saf-O) and polarized light (picro). Percentage of India ink coverage was compared between control and defected joints within each compartment (medial and lateral) using t-tests.

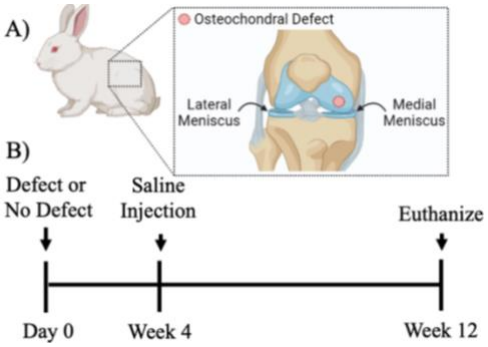

Figure 1: A) New Zealand white rabbit depicted with an osteochondral defect on the medial condyle. B) Surgical timeline depicting surgery (day 0), saline injection (week 4), and euthanasia (week 12).

RESULTS: India ink was used to highlight fibrillation and surface damage to the tibial plateau (Fig 2A). ImageJ analysis showed a significant increase in the area percentage covered by India ink in the medial side of the defect joint compared to the medial side of the control joint ($p<0.05$, Fig 2B). There was no difference in the India ink coverage on the lateral side of the defect joint compared to the control joint ($p=0.71$). Safranin-O staining of the menisci showed increased GAG content in the medial menisci of the defect joint compared to the lateral menisci (Fig 3A). However, there was little to no difference in staining of GAGs between the menisci in the control joint. The medial menisci of the defect joint displayed an increase in GAG in the inner and middle zones compared to the medial meniscus of the control joint (Fig 3A). Polarized light micrographs of these menisci stained with picrosirius red showed increased fiber thickness in the medial meniscus compared to the lateral menisci of both defect and no defect joints. However, the medial meniscus of the defect joint had regions with increased fiber thickness (Fig 3B, white arrows) and a higher prevalence of red instead of green coloring compared to the menisci from other groups, indicating more tightly packed or thicker fibrils (Fig 3B).

DISCUSSION: Joints with a medial femoral condylar defect had increased surface damage on the medial tibial plateau compared to control joints. The osteochondral defect in the medial femoral condyle leads to higher contact pressures and aberrant loading conditions, leaving the joint vulnerable to degenerative processes and the progression of OA.[5] This increased damage suggests that the altered loading environment on the medial side of defected joints affects the underlying tissues. Additionally, Safranin-O staining indicated increased GAG content of the medial menisci of joints with defects. This is consistent with other studies that found that the menisci of patients with late-stage OA or traumatic meniscal tears displayed increases in proteoglycan deposition.[6] Finally, picrosirius red staining showed increased collagen fiber thickness in the meniscus adjacent to the condylar defect. Although we would expect to see more prevalent decrease in collagen organization in menisci in contact with defected condyles, as usually found in OA menisci,[6] it has been shown that regions of menisci exposed to increased mechanical stress in had increased collagen fiber thickness in OA mice.[6] This study demonstrated that altered loading environment on the medial side of the joint due to the femoral defect can have cascading effects on adjacent and sub-adjacent tissues, as demonstrated by the increase in surface damage in the tibial plateau and altered meniscal ECM. While the medial condylar defect affected the underlying compartment-matched tissues, the lateral menisci in joints with defects were unaffected at this time point (12 weeks post-injury).

SIGNIFICANCE: Osteochondral defects in the femoral condyle drive compartment-specific degradation of the underlying meniscus and tibial plateau. This degradation highlights cartilage-meniscus tissue crosstalk and its effect on tibial plateau morphology and meniscus ECM turnover and maintenance.

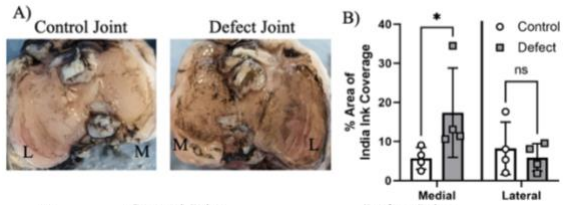

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Figure 2: A) Tibial plateau from control joint (left) and defect joint (right) stained with India ink to highlight surface damage. M: Medial; L: Lateral. B) Quantitative analysis of the percentage of area covered by India ink staining.

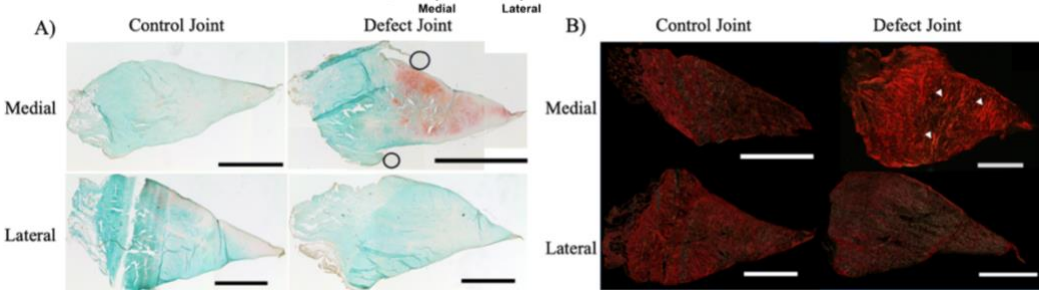

Figure 3: A) Representative brightfield micrographs of meniscus sections stained with Safranin-O and B) Picrosirius red of representative medial and lateral menisci (joint-matched). Picrosirius red images were taken under polarized light and show increased fiber diameter (white arrows). Scale bars: 1 mm.