Musculoskeletal changes following non-invasive knee injury using a novel mouse model of post-traumatic osteoarthritis


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Objective: Post-traumatic osteoarthritis (PTOA) is a common consequence of traumatic joint injury, with 50% of anterior cruciate ligament (ACL) rupture patients developing PTOA within 10–20 years. Currently accepted mouse models of PTOA initiate symptoms using various methods, none of which faithfully mimic clinically-relevant injury conditions. In this study we characterize a novel non-invasive mouse model of PTOA that injures the ACL with a single load of tibial compression overload. We utilize this model to determine the time course of articular cartilage and subchondral bone changes following knee injury.

Design: Mice were euthanized 1, 3, 7, 14, 28, or 56 days after non-invasive knee injury. Knees were scanned using micro-computed tomography (μCT) in order to quantify subchondral trabecular bone, subchondral bone plate, and non-native bone formation (heterotopic ossification). Development of osteoarthritis (OA) was graded using the osteoarthritis research society international (OARSI) scale on histological sections of injured and uninjured knees.

Results: Following injury we observed a rapid loss of trabecular bone in injured knees compared to uninjured knees by 7 days post-injury, followed by a partial recovery of trabecular bone to a new steady state by 28 days post-injury. We also observed considerable non-native bone formation by 56 days post-injury. Grading of histological sections revealed deterioration of articular cartilage by 56 days post-injury, consistent with development of mild OA.

Conclusions: This study establishes a novel mouse model of PTOA, and describes the time course of musculoskeletal changes following knee injury, helping to establish the window of opportunity for preventative treatment.

Introduction

Osteoarthritis (OA) is characterized by degradation of articular cartilage and significant joint pain, often necessitating whole joint replacement. OA is a major health concern, affecting over 27 million Americans and 151 million individuals worldwide. Post-traumatic osteoarthritis (PTOA) is commonly a long-term consequence of traumatic joint injury, with approximately 50% of individuals with anterior cruciate ligament (ACL) rupture or meniscectomy developing PTOA within 10–20 years. While clinically diagnosable PTOA develops on a fairly long time scale, it is likely that structural changes occur much sooner, and cause irreversible changes to cartilage and bone within a short time after injury but before the appearance of painful symptomatic PTOA. If this is the case, the “window of opportunity” for providing treatments aimed at preventing PTOA may be confined to a short time following traumatic joint injury.

Animal models are critical tools for PTOA research, because they can dramatically shorten the time required to develop PTOA (approximately 8–12 weeks in mouse models). Currently accepted mouse models of PTOA initiate symptoms using various methods such as injecting collagenase into the joint, using a needle to induce cruciate transection in the closed knee, applying multiple bouts of mechanical loading, or using surgical techniques to transect or injure the ligaments of the knee or the medial meniscus. These models do not faithfully mimic clinically-relevant injury conditions, due to invasive and non-physiologic injury methods. In addition, methods that utilize invasive surgical procedures may introduce confounding factors associated with the
surgery itself, which may mask the native biological response to injury.

In this study we characterize a novel non-invasive model of knee injury in mice, which is simple to implement, highly reproducible, and closely replicates injury conditions relevant to humans. We utilize this model to determine the time course of articular cartilage and subchondral bone changes following knee injury in mice. We hypothesized that the early structural changes would appear soon after knee injury, and would progressively worsen until “diagnosable” OA is reached by 8 weeks post-injury, similar to other established mouse models of PTOA. Determining the time course of structural changes in musculoskeletal tissues of the knee joint will help establish the window of opportunity for treatments aimed at slowing or preventing PTOA following knee injury.

**Materials and methods**

**Animals**

Forty-eight adult male C57BL/6N mice (age 10 weeks at time of injury) were obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN, USA). Animals were kept in a housing facility for a 1-week acclimation period before injury. All animals were maintained and used in accordance with National Institutes of Health guidelines on the care and use of laboratory animals. This study was approved by our institutional Animal Studies Committee.

**Tibial compression-induced knee injury**

Knee injury was induced by a single overload cycle of tibial compression, using a system similar to those previously described for studies of bone adaptation. Briefly, the tibial compression system consisted of two custom-built loading platens; the bottom platen that held the flexed knee, and the top platen that positioned the foot, with the ankle flexed at approximately 30° [Fig. 1(b)]. The platens were aligned vertically and positioned within an electromagnetic materials testing machine (Bose ElectroForce 3200, Eden Prairie, MN, USA). Mice were anesthetized using isoflurane inhalation, then the right leg of each mouse was subjected to a single dynamic axial compressive load (1 mm/s loading rate) to a target compressive load of 12 N. This loading method causes a transient anterior subluxation of the tibia relative to the distal femur [Fig. 1(a)]. Knee injury was noted by a release of compressive force during loading [Fig. 1(c)]. Sham injury was performed by...
anesthetizing mice, positioning them into the tibial compression system, and applying a 1–2 N preload.

Assessment of knee injury

Semi-quantitative analysis of injured and uninjured mouse knees was performed to assess the nature and severity of knee injury. One or both knees of mice (n = 6) were injured as described above. Mice were sacrificed 1–4 h after injury, and blinded analysis of knees was performed by two experienced orthopaedic surgeons. Examination included manual manipulation of the knee joint to determine biomechanical joint stability, and dissection analysis. Knee injury was designated as uninjured (grade 0), minor (grade 1), moderate (grade 2), or severe (grade 3). Grading was based on range of motion (anterior/posterior translation, varus/valgus rotation, and internal/external rotation), gross swelling, bleeding in the joint space, visible damage to knee structures, and bone bruising. Knees were then scanned using micro-computed tomography (μCT) as described below, and reconstructed images were used to further diagnose injuries to the knee.

Post-injury activity and time points

Thirty-six mice were unilaterally injured as described above and six mice underwent sham injury, followed by normal cage activity for 1–56 days, after which they were euthanized by CO2 asphyxiation and both knees were extracted for analysis. Mice were euthanized at one of six time points (n = 6 mice/time point): 1, 3, 7, 14, 28, or 56 days after injury. Uninjured control mice (UIC) were euthanized 56 days after sham injury.

μCT analysis of subchondral bone

Bilateral knees were removed post mortem and fixed in 4% paraformaldehyde. Whole knees were scanned using μCT (SCANCO μCT 35, Bassersdorf, Switzerland) according to the guidelines for μCT analysis of rodent bone structure15: energy = 55 kVp, intensity = 114 mA, 15 μm nominal voxel size, integration time = 900 ms. Trabecular bone was analyzed at the distal femoral epiphysis, proximal tibial epiphysis, and proximal tibial metaphysis (Fig. 3). Volumes of interest for the femoral and tibial epiphysis included all trabecular bone enclosed by the growth plate, including both medial and lateral compartments. The tibial metaphysis volume extended 750 μm (50 slices, 15 μm/slice) distal to the metaphyseal growth plate. Trabecular regions were designated on each two-dimensional transverse slice using manually drawn contours that excluded the cortical shell. Trabecular bone volume per total volume (BV/TV), trabecular thickness (Tb.Th), apparent bone mineral density (Apparent BMD; mg HA/cm² TV), and other trabecular bone parameters were directly measured using the manufacturer’s analysis tools. The subchondral bone plate was quantified at the tibial plateau, with a volume of interest extending 600 μm distal to the most proximal point of the tibia, and excluding the underlying trabecular bone (Fig. 3). Cortical thickness and bone tissue mineral density were determined using the manufacturer’s 3D analysis tools. Non-native bone volume (heterotopic ossification) was also quantified, and included all mineralized tissue in and around the joint space excluding the patella, anterior horns of the menisci, fabella, and any mineralized tissue attached to the femur, tibia, or fibula.

Compartment-specific trabecular bone parameters were also quantified for each time point at the femoral epiphysis. For these analyses, trabecular bone of the femoral epiphysis was divided into the medial and lateral compartments (divided along the centerline of the joint); the femoro-patellar compartment was designated by the anterior portion of the epiphyseal growth plate (Fig. 5).

Histological evaluation of cartilage

After μCT analysis, knees were decalcified for 4 days in 10% buffered formic acid and processed for standard paraffin embedding. Sagittal 6 μm sections of individual knees were cut across the entire joint separated by 250 microns (approximately 10–12 levels per joint). Three slides were cut at each level, and were stained with Safranin-O and Fast-Green, Masson’s Trichrome, or hematoxylin and eosin (H&E). All slides were identified as medial, lateral, notch or other. Medial and lateral locations were identified by the presence of anterior and posterior horns of the meniscus. For these slides, the articular surfaces of the tibia and femur were graded. Notch locations were identified by the presence of cruciate ligaments and patella. For these slides, the cartilage of the femoro-

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**Fig. 2. Injury characterization.** (a) Semi-quantitative analysis of injured and uninjured knees indicated severe and easily identifiable knee injuries. All injured knees were correctly identified (n = 7), with an average grading of 2.6 (2.3–3.0), indicating moderate to severe injury. All but one uninjured knees (4/5) were correctly identified as uninjured (grade 0), while one was false positively identified as injured. The most common indicators of injury were increased anterior/posterior translation and external rotation of the knee, with minor swelling and hemarthrosis. Based on these analyses, readers diagnosed injured knees with disruption of the ACL. (b) μCT indicated avulsion fractures present in all injured knees, identifiable by bone fragments suspended in the joint space, consistent with disruption of the ACL.
The patellar joint was graded. Slides that could not be identified as medial, lateral, or notch were not graded. Blinded slides were graded independently by three readers using the osteoarthritis research society international (OARSI) scale. Briefly, grade 0 corresponded to normal articular cartilage; grade 0.5: loss of Safranin-O and/or cellular changes without structural changes to the articular surface; grade 1: small fibrillations without loss of cartilage; grade 2: vertical clefts down to the layer immediately below the superficial layer and some loss of surface lamina; grade 3: vertical clefts/erosion to the calcified cartilage extending to <25% of the articular surface; grade 4: vertical clefts/erosion to the calcified cartilage extending to 25–50% of the articular surface; grade 5: vertical clefts/erosion to the calcified cartilage extending to 50–75% of the articular surface; grade 6: vertical clefts/erosion to the calcified cartilage extending >75% of the articular surface. Grades for all slides from each location of each sample were averaged, and grades from the three readers were averaged for each location.

A board-certified veterinary pathologist also examined H&E stained slides from each knee to quantify synovial hyperplasia, inflammation, and fibrosis. These pathological conditions were graded as: 0 = normal, 1 = minor, 2 = minimal, 3 = moderate and 4 = severe.

Serum biomarkers of OA

OA progression was monitored using a serum biomarker of OA, cartilage oligomeric matrix protein (COMP). COMP is a non-collagenous component of cartilage matrix that is released from damaged cartilage into synovial fluid and serum, and has increased production during the repair-response of chondrocytes after joint injury. Serum was collected at days 1, 3, 7, 14, 28 and 56 in injured mice, and at days 14, 28 and 56 for uninjured mice. Serum levels of COMP were measured using a commercially available animal assay (MD Bioproducts, St Paul MN, USA).

Statistical analysis

μCT and histology results for injured and uninjured knees were compared at each time point using a two-tailed paired t-test. Differences between time points and UIC were determined using a one-way analysis of variance (ANOVA), with post hoc analysis by Fisher’s Protected Least Significant Difference (PLSD) test. Significance was defined as P < 0.05 for all tests. Mean (95% confidence interval) are presented for all data.

Results

Tibial compression-induced knee injury

In all 36 injured mice, knee injury was induced using a single 12 N compressive load. Mean compressive force at knee injury was 10.19 (9.83–10.54) N.

Assessment of knee injury

Analysis of injured and uninjured knees indicated severe and easily identifiable knee injury. Readers successfully identified knee injury status in 11/12 mouse knees. All injured knees were correctly identified (n = 7), with an average grading of 2.6 (2.3–3.0), indicating moderate to severe injury. All but one uninjured knees (4/5) were correctly identified as uninjured (grade 0), while one was false positively identified as injured [Fig. 2(a)]. The most common indicators of injury were increased anterior/posterior translation...
and external rotation of the knee, minor swelling and hemarthrosis. Medial and lateral collateral ligaments remained intact for all knees. Based on these findings, readers diagnosed injured knees with disruption of the ACL.

CT imaging of injured and uninjured knees indicated avulsion fractures present in all injured knees, identifiable by bone fragments in the joint space [Fig. 2(b)], consistent with disruption of the ACL.

CT analysis of bone structure

At the femoral and tibial epiphysis we observed a rapid and considerable loss of trabecular bone volume (BV/TV) in injured knees compared to uninjured knees following injury, reaching a minimum at the 7-day time point (−44% at the femoral epiphysis, −40% at the tibial epiphysis), followed by a partial recovery of trabecular bone tissue to a new steady state (−80% of day 1 value) by the 28-day time point. Tb.Th and Apparent BMD also decreased from day 1 to day 7 at the femoral epiphysis (−24% [c] and −25% [e], respectively) and tibial epiphysis (−15% [d] and −20% [f], respectively). A similar, but lower magnitude trend was also observed in the contralateral uninjured limb. All data points are individually plotted on graphs; lines connect the group means for injured and uninjured animals harvested at different time points post-injury.

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μCT analysis of bone structure

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Compartment-specific analysis of femoral epiphysis trabecular bone indicated similar magnitudes of bone loss for the medial, lateral, and femoro-patellar compartments (Fig. 5). From day 1 to day 7, the medial compartment BV/TV decreased 43%, the lateral compartment decreased 42%, and the femoro-patellar compartment BV/TV decreased 48%.

We observed minor changes in cortical bone parameters at the subchondral bone plate of the tibial plateau following knee injury. Cortical thickness was significantly lower in the injured knee compared to the uninjured knee at day 7 only (−6.6%, P = 0.0022), while tissue BMD was significantly decreased (−2.9
to −4.5%) in the injured knee for all time points except day 1 (P = 0.00006–0.0138).

Considerable non-native bone formation (heterotopic ossification) was observed at 4 and 8 weeks post-injury (Fig. 6). Non-native bone volume was 4-fold and 31-fold greater in the injured knee than the uninjured knee at day 28 and 56, respectively (P-values indicate injured vs uninjured comparison for each time point).

Histological evaluation of cartilage

Grading of histological sections revealed deterioration of articular cartilage in injured knees by 56 days post-injury, consistent with the development of OA. Specifically, we observed focal loss of Safranin-O staining indicating decreased proteoglycan concentration, minor fissuring of articular cartilage, frequent loss of the surface zone and the flattened elongated chondrocytes of the upper zone, cell death in the articular cartilage superficial zone, and atrophy of articular chondrocytes (Fig. 7). Blinded grading of histological sections revealed statistically significant differences in OARSI score at the medial tibia (P = 0.0001), medial femur (P = 0.0043), and lateral femur (P = 0.0007) at 56 days post-injury. No statistically significant differences in OARSI score were observed at earlier time points. At the femoro-patellar joint we observed very little degeneration of either the patella or the underlying surface of the femur in injured knees, although we did occasionally observe “bumps” forming on the articular surface of the patella (Fig. 7). Grading by a veterinary pathologist indicated significant synovial hyperplasia, inflammation, and fibrosis following knee injury, even at early time points [Fig. 8(b–d)].

OA biomarker quantification

Serum levels of COMP were significantly elevated in injured mice compared to uninjured mice at all time points except day 28 [Fig. 8(a)]. In uninjured mice there was no significant difference in serum COMP levels between day 14, 28 and 56, therefore these data were pooled.

Discussion

In this study we described a novel, non-invasive method for inducing ACL rupture in mouse knees in vivo. Using this model, we investigated the magnitude and time course of articular cartilage and subchondral bone changes that occur following ACL injury. After 8 weeks post-injury we observed degeneration of the articular cartilage in injured knees, indicating the development of mild OA. Surprisingly, we also observed a rapid and considerable loss of trabecular bone within 1 week of injury, followed by a partial recovery of bone tissue back to a new (but lower) steady state by 4 weeks post-injury. These rapid and substantial changes to the trabecular bone...
were unanticipated and contrary to our initial assumption of slow, progressive structural changes following knee injury. The novel mouse injury model utilized in this study is an important step forward for mouse models of PTOA. This model is the first to non-invasively induce ACL injury with a single mechanical loading cycle. In this way, our model faithfully mimics injury conditions relevant to human injury. Importantly, this model is also fast (<5 min) and easy to perform, and highly reproducible. As stated previously, many mouse models of PTOA use invasive methods such as collagenase injection or surgical transection of musculoskeletal structures to induce knee injury, which complicate outcomes due to confounding factors associated with the invasive injury methods themselves, especially at the early time points. In this way, non-invasive models are much more desirable for studies of early time points. Poulet et al. have described a non-invasive model that used tibial compression (single or multiple loading sessions) similar to the methods used in the current study to initiate OA symptoms. However, their model does not utilize an injury that is relevant to humans, and in order to induce more severe symptoms this model requires multiple loading sessions. Furman et al. described a mouse model of PTOA in which closed intraarticular fractures were created in the tibial plateau of mice. This non-invasive model is useful for investigations of high impact joint injuries involving bone fracture, but does not as accurately replicate conditions that would be relevant to low-impact injuries such as ACL ruptures.

The rapid loss of trabecular bone observed following knee injury may be due to several contributing factors including injury-induced inflammation. ACL rupture in humans causes an immediate flare of inflammatory cytokines, including elevated levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, IL-8, IL-1 receptor antagonist, and IL-10. Several of these inflammatory cytokines cause changes in both bone and cartilage. Bone formation and resorption rates are abnormal in altered inflammatory states such as chronic infection and rheumatic disease. A number of cytokines associated with inflammation, including TNF-α, IL-1, and IL-6 promote bone resorption by directly or indirectly promoting osteoclastogenesis. However, the role of acute injury-induced inflammation in the development of PTOA remains unclear. It is possible that this acute inflammation may act as a stressor event, triggering bone resorption by osteoclasts, followed by subsequent bone formation, as previously described for bone remodeling. In fact, the time course of the loss and reformation of trabecular bone observed in our study nearly

Fig. 7. Histological assessment of OA. (a–b, d–f) Sagittal histological sections of the medial aspect of uninjured (a–b) and injured (d–f) knees 56 days post-injury stained with Safranin-O/Fast-Green. By day 56 we observed minor fissuring of articular cartilage surface, frequent loss of the surface zone and the flattened elongated chondrocytes of the upper zone, cell death in the articular cartilage superficial zone, and atrophy of articular chondrocytes (d–e). By day 56 there was also considerable non-native bone formation (heterotopic ossification) in injured knees (f). Grading of OA using the OARSI scale showed statistically significant progression of OA at the medial and lateral femur, and the medial tibia compared to uninjured knees, while the lateral tibia showed OA progression in both injured and uninjured knees (c). No statistically significant changes in OA status were observed at earlier time points. In some injured knees we observed “bumps” on the articular surface of the patella (h) compared to the smooth articular surface typically observed (g, stained with Masson’s Trichrome). Grading of slides by a veterinary pathologist showed significant inflammation, synovial hyperplasia, and fibrosis in injured knees compared to uninjured knees, even at early time points (i, figure from day 3 post-injury, stained with Hematoxylin and Eosin).
identically mimics the time course of osteoclast and osteoblast activity following extraction of maxillary molars in rats\(^1\). Inflammation associated with knee injury may play an important role in the early structural changes observed in subchondral bone following injury.

Another potential factor contributing to the observed bone changes is altered mechanical loading of the limb due to altered joint biomechanics, decreased cage activity of injured animals, or favoring the injured limb. We did not quantify animal movement following injury, although we qualitatively noted that animals appeared to ambulate normally. The magnitude of the bone loss observed in this study also makes it unlikely that decreased mechanical loading would fully explain the observed loss of trabecular bone. We observed a 40–44% decrease in BV/TV at the tibial and femoral epiphysis from day 1 to day 7 post-injury. In contrast, Judex et al.\(^2\) observed a 20.6% loss of trabecular BV/TV from the femoral epiphysis of C57BL/6 mice after 15 days of total hindlimb unloading. This suggests a mechanism of bone loss that is not driven exclusively by mechanical unloading.

We observed a similar (but lower magnitude) pattern of trabecular bone loss in the contralateral limb following injury. This pattern of bone loss is meaningful, since it indicates a possible systemic effect of knee injury on bone structure. This finding supports previous clinical studies, which showed elevated concentrations of aggrecan, COMP, and matrix metalloproteinase-3 (MMP-3) in the uninjured knee of ACL rupture patients\(^3\).\(^4\)

This study has several strengths that represent important steps forward for studies of PTOA. First and foremost, we have described a novel mouse model of PTOA that uses a single cycle of non-invasive mechanical loading to rupture the ACL. This model creates biological and biomechanical conditions that are relevant to traumatic joint injuries in humans, allowing us to more confidently investigate clinically-relevant processes that occur early after injury. Second, we investigate structural and biological changes that occur shortly after injury. Most investigations of PTOA using animal models have not investigated these early time points, ignoring the changes that occur in the first few days after injury. Third, we describe novel changes that occur in subchondral bone after joint injury. These changes have not been previously described, and may be vital in establishing the window of opportunity for treatments aimed at slowing or preventing PTOA.

While our mouse model is able to rapidly and reproducibly disrupt the ACL, the clinical relevance of this injury is still not ideal, since it produces avulsion fractures rather than pure mid-substance tears in the ligament. Clinically, most ACL failures are primarily due to mid-substance tears alone, with avulsion fractures occurring in less than 10% of adult patients\(^5\).\(^6\). In contrast, avulsion fractures are commonly present in ACL ruptures in pediatric patients\(^7\).\(^8\). It is possible that the mice used in this study (10 weeks old at the time of injury) are not fully skeletally mature, predisposing them to avulsion fractures with ACL rupture. It is also possible that the mechanical loading methods utilized in this study are more likely to induce avulsion fractures, while alternative methods may be able to induce mid-substance tears without avulsion.

Another limitation of this study is that our mouse model produced only mild OA within 8 weeks following knee injury, as opposed to other PTOA models that produce more severe cartilage degeneration within the same time period. This is not altogether surprising, since our model uses a single cycle of non-invasive mechanical loading to induce knee injury, which is likely a more mild injury than surgical transection of knee structures or other similar invasive models. It is also possible that the change in joint biomechanics induced by our model is less severe than in other models that disrupt the ACL or medial meniscus, although this was not quantified. In order to observe more substantial degeneration of articular cartilage, future investigations using our model could investigate time points beyond 8 weeks post-injury, or utilize secondary methods such as exercise to shorten the time for development of PTOA.

This study also has other minor limitations that must be acknowledged. First, we do not present longitudinal changes that occur in single animals, but rather describe groups with different end points. Future studies will investigate uninjured control (UIC) mice at earlier time points, but provides less reliable longitudinal outcomes and less statistical power. Future studies will use in vivo...
Another limitation is that we did not quantify uninjured control processes to more accurately determine longitudinal changes. Additionally, we did not anticipate the contralateral response to injury at early time points. Future studies will investigate UIC at earlier time points.

Conclusions

We have characterized a novel knee injury mouse model for studies of PTOA. This model is a significant improvement over other mouse models of PTOA, since it induces an injury that is translatable to humans, is easy to implement, and highly reproducible. Using this model, we characterized the time course of articular cartilage and subchondral bone changes following injury. Along with degeneration of the articular cartilage and mild OA, we observed novel results of rapid subchondral bone loss following injury, followed by rapid recovery of trabecular bone and malformation of bone in the joint space. These data help establish the window of opportunity for treatments aimed at preventing or slowing PTOA following injury, and suggest that current clinical practice may miss this window, leaving injured joints vulnerable to early structural changes.

Author contributions

All authors have made substantial contributions to the conception and design of the study, or acquisition of data, or analysis and interpretation of data. All authors have been involved in drafting the article or revising it critically for important intellectual content. All authors have given final approval of the version to be submitted.

Dr. Blaine A. Christiansen and Dr. Dominik R. Haudenschild take responsibility for the integrity of the work as a whole, from inception to finished article.

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None of the authors have any financial or personal relationships with other people or organizations that could potentially influence (bias) their work and conclusions.

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