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A study of acute and chronic tissue changes in surgical and traumatically-induced experimental models of knee joint injury using magnetic resonance imaging and micro-computed tomography

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SUMMARY

Objective: The objective of this study was to monitor the progression of joint damage in two animal models of knee joint trauma using two non-invasive, clinically available imaging modalities.
Methods: A 3-T clinical magnet and micro-computed tomography (μCT) was used to document changes immediately following injury (acute) and post-injury (chronic) at time points of 4, 8, or 12 weeks. Joint damage was recorded at dissection and compared to the chronic magnetic resonance imaging (MRI) record. Fifteen Flemish Giant rabbits were subjected to a single tibiofemoral compressive impact (ACLF), and 18 underwent a combination of anterior cruciate ligament (ACL) and meniscal transection (mACLT).
Results: All ACLF animals experienced ACL rupture, and 13 also experienced acute meniscal damage. All ACLF and mACLT animals showed meniscal and articular cartilage damages at dissection. Meniscal damage was documented as early as 4 weeks and worsened in 87% of the ACLF animals and 71% of the mACLT animals. Acute cartilage damage also developed further and increased in occurrence with time in both models. A progressive decrease in bone quantity and quality was documented in both models. The MRI data closely aligned with dissection notes suggesting this clinical tool may be a non-invasive method for documenting joint damage in lapine models of knee joint trauma.
Conclusions: The study investigates the acute to chronic progression of meniscal and cartilage damage at various time points, and chronic changes to the underlying bone in two models of posttraumatic osteoarthritis (PTOA), and highlights the dependency of the model on the location, type, and progression of damage over time.

Introduction

Posttraumatic osteoarthritis (PTOA) is a form of secondary osteoarthritis that can result from joint trauma. Tearing of the anterior cruciate ligament (ACL) due to jump landings is a common sports related knee injury[1–3]. The current literature indicates the occurrence of PTOA does not depend on whether or not the ACL is reconstructed following injury[4]. Magnetic resonance imaging (MRI) of the knee is a common method for diagnosing damage to knee joint structures. This non-invasive method is often used clinically by surgeons to determine the severity of damage[5,6]. In experimental studies, micro-computed tomography (μCT) is frequently used in addition to MR imaging to monitor OA development[7,8]. The use of MR imaging in lapine models is less studied[9,10], but could be a useful tool for monitoring soft tissue damage throughout a traumatized joint.

Previous models have been used to recapitulate PTOA for the purpose of investigating the pathogenesis of OA. One of the most widely used models is an ACL transection (ACLT) model, where the

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ACL is transected and degradation of the joint is monitored over time. However, ACLT models so not take into account acute meniscal damage that is often documented in conjunction with ACL tears[11,12] following large compressive tibiofemoral forces through the joint at the time of injury[1–3,13–16]. For this reason, two new lapine models have been developed: a modified ACLT (mACLT) model[17] and a traumatic impact (ACLF) model[18]. Similar to the ACLT model, the mACLT model destabilizes the knee by transecting the ACL; however, in the mACLT model partial meniscal transections are also introduced. The ACLF model induces ACL rupture and damage to the surrounding structures, including the meniscus, via a single blunt force impact to the tibiofemoral joint.

The objective of the current study was to use conventional MR and μCT imaging to document joint damage immediately following trauma and longitudinally in both the mACLT and ACLF models. It was hypothesized that (1) untreated acute soft tissue damage will be progressive, (2) the MR images will provide a description of damage documented at dissection in the lapine model and (3) differences will be evident between the two experimental models. If successful, we could be assured that conventional MRI techniques can be used confidently in longitudinal studies of PTOA in these lapine models, and understand how differences in experimental models may translate to differences in soft tissue and bone damage.

Methods

Animal care

All animals were housed in individual cages (60 × 60 × 14 in) for the duration of this study, which was approved by Michigan State University and Colorado State University All-University Committees on Animal Use and Care. Thirty-three skeletally mature (5–8 months of age) Flemish Giant rabbits (5.4 ± 0.6 kg, 13 females and 20 males) were used in the study. Animals were placed under anesthesia (2% isoflurane and oxygen) and the right limb was subjected to trauma with the contralateral limb unaffected to serve as an internal control. All animals received buprenorphine for post-trauma pain every 8 h for 3 days. For the duration of the study animals were monitored by a licensed veterinary technician. Animals were randomly placed into two experimental groups and three time points as described below.

ACLF model

Fifteen animals received a closed-joint impact to the tibiofemoral joint (ACLF), similar to previous studies[19,20,18]. In brief, the impacting force was applied using a gravity accelerated mass of 1.75 kg dropped from a height of 70 cm and attached to a pre-crushed aluminum honeycomb head (Hexweb Rigicell, Hexcel Corp. Stamford, Conn.). To ensure a single insult, the impact sled was arrested following impact. ACL rupture was confirmed with an anterior drawer test. ACL tearing and acute meniscal damages were documented with a post impact MRI. Three animals were euthanized at 4 weeks, six at 8 weeks, and six at 12 weeks.

mACLT model

The remaining 18 animals received an ACL transection as well as a radial transection in the white zone of the central region of the medial meniscus with a longitudinal transection extending though the main body and a radial transection of the lateral meniscus in the white zone of the central region with a longitudinal tear extending anteriorly (mACLT)[17]. Limited lateral joint access prevented the longitudinal tear from extending into the posterior lateral region. Six animals were euthanized at each time point (4, 8, 12 weeks).

MRI

MRI was used to document tissue damages in each joint following initial trauma (acute damage), as well as just prior to euthanasia (4, 8, or 12 weeks post-trauma, chronic damage). Meniscal damage was identified as being in the anterior horn, anterior junction, body, posterior junction, or posterior horn. Cartilage damage on the tibial plateau was characterized as anterior, central, or posterior as well as sub-meniscal and peripheral when appropriate. Femoral cartilage damage was characterized in the weight bearing, non-weight bearing, or peripheral regions. Imaging was performed with a GE (Waukesha, WI) HD × t 3.0 T magnet using an 8 channel HD wrist coil. Sagittal and coronal proton density sequences were performed with 3000–5000 ms repetition time, 32–34 ms time to echo, ±62.5 kHz receiver bandwidth, 2 excitations, 1.5 mm slice thickness with 0 interslice gap, 512 × 384 matrix size, and an 8 cm field of view. Sagittal and coronal fat suppressed proton density sequences were also performed with 3000–5000 ms repetition time, 32–34 ms time to echo, ±50 kHz receiver bandwidth, 2 excitations, 1.5 mm slice thickness with 0 interslice gap, 416 × 256 matrix size, and an 8 cm field of view. The images were interpreted by a fellowship-trained musculoskeletal radiologist with 8 years of clinical experience (RF).

μCT

Bones from each animal were scanned via μCT (Scanco μCT 80, Scanco Medical AG, Brüttisellen, Switzerland) with an isotropic voxel size of 25 μm. Four spatially distributed cylindrical volumes of interest (VOI) were identified for each tibia and femur based on anatomical markers[21]. The following measurements were obtained: volumetric trabecular material bone mineral density (mgHA/cm^3) (Tb.BMD), trabecular bone volume fraction (bone volume/total volume, Tb.BV/TV), trabecular number (Tb.N), trabecular thickness (mm) (Tb.Th), trabecular separation (mm) (Tb.Sp), cortical material bone mineral density (mgHA/cm^3) (Ct.BMD), cortical bone porosity (Ct.Po), and volume of osteophytes (mm^3)[21].

Cartilage morphology

Following euthanasia, India ink was lightly applied to the articular cartilage surfaces to highlight surface fissures, cartilage degradation, and other irregularities. The surfaces were digitally photographed (Polaroid DMC2, Polaroid Corp., Waltham, MA) under a dissecting microscope at 12X and 25X (Wild TYP 374590, Heerbrugg, Switzerland). Two blinded graders assessed the tissues for morphological damage using a semi-quantitative grading scheme, as previously described[22]. Grades ranged from 1 indicating normal appearing cartilage to 4 representing full thickness erosion and exposed underlying bone. Grades were averaged between the two blinded graders with an ICC value of 0.84.

Statistical analysis

For trabecular and cortical bone parameters obtained from μCT, a mixed model analysis of variance (ANOVA) with Tukey post-hoc tests were performed using Minitab software (Minitab, Inc., State College, PA) to compare injured limbs to uninjured limbs with significance corresponding to a *P*-value less than 0.05.

Results

Rabbits in the ACLF groups favored the contralateral limb for the first 3–5 days, while mACLT animals favored the contralateral limb for 1–3 days post-surgery. All ACLF animals experienced ACL tears,