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In vivo cartilage strain increases following medial meniscal tear and correlates with synovial fluid matrix metalloproteinase activity

Teralyn E. Carter [a], Kevin A. Taylor [a], Charles E. Spritzer [b], Gangadhar M. Utturkar [a], Dean C. Taylor [a], Claude T. Moorman III[a], William E. Garrett [a], Farshid Guilak [a], Amy L. McNulty [a], Louis E. DeFrate [a,*]

[a] Department of Orthopaedic Surgery, Duke University Medical Center, Durham, NC, United States
[b] Department of Radiology, Duke University Medical Center, Durham, NC, United States

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ABSTRACT

Meniscal tears are common injuries, and while partial meniscectomy is a frequent treatment option, general meniscus loss is a risk factor for the development of osteoarthritis. The goal of this study was to measure the *in vivo* tibiofemoral cartilage contact patterns in patients with meniscus tears in relation to biomarkers of cartilage catabolism in the synovial fluid of these joints. A combination of magnetic resonance imaging and biplanar fluoroscopy was used to determine the *in vivo* motion and cartilage contact mechanics of the knee. Subjects with isolated medial meniscus tears were analyzed while performing a quasi-static lunge, and the contralateral uninjured knee was used as a control. Synovial fluid was collected from the injured knee and matrix metalloproteinase (MMP) activity, sulfated glycosaminoglycan, cartilage oligomeric matrix protein, prostaglandin E_2, and the collagen type II cleavage biomarker C2C were measured. Contact strain in the medial compartment increased significantly in the injured knees compared to contralateral control knees. In the lateral compartment, the contact strain in the injured knee was significantly increased only at the maximum flexion angle (105°). The average cartilage strain at maximum flexion positively correlated with total MMP activity in the synovial fluid. These findings show that meniscal injury leads to loss of normal joint function and increased strain of the articular cartilage, which correlated to elevated total MMP activity in the synovial fluid. The increased strain and total MMP activity may reflect, or potentially contribute to, the early development of osteoarthritis that is observed following meniscal injury.

1. Introduction

Meniscal tears are a common injury, with more than 850,000 meniscal surgeries performed each year in the United States and nearly twice as many worldwide (Arendt et al., 1999; Baker and Lubowitz, 2006). The menisci play a critical role in normal knee function by providing important load bearing capabilities, lubrication, proprioception, joint congruity, and joint stability (Ahmed and Burke, 1983; Haut Donahue et al., 2004; Markolf et al., 1981; Wojtys and Chan, 2005). Meniscal injury is associated with pain and degradative changes in the knee joint that may ultimately lead to osteoarthritis (Badlani et al., 2013; Berthiaume et al., 2005; Christoforakis et al., 2005; Hunter et al., 2006; Majewski et al., 2006; Roos et al., 1998; Sharma et al., 2008; Wyland et al., 2002). Furthermore, the surgical treatment of a meniscal tear by partial or total meniscectomy is strongly associated with articular cartilage degradation and the progression of osteoarthritis (Lohmander et al., 2007, 1994; Roos et al., 1998; Wyland et al., 2002). In fact, more than half of people with meniscectomy develop knee osteoarthritis within 5–15 years after joint injury (Lohmander et al., 2007, 1994). Therefore, surgeons attempt to preserve and repair the native meniscal tissue following injury (Abrams et al., 2013; Hutchinson et al., 2014; Lee et al., 2006; Maffulli et al., 2010). However, when repair is not feasible, partial meniscectomy is frequently implemented to treat meniscal tears. While these patients report improvements in pain and function, the ability of this surgery to mitigate the risk of premature development of osteoarthritis may be limited (Andersson-Molina et al., 2002; Fauno and Nielsen, 1992; Hall et al., 2014; Hoser et al., 2001; Katz et al., 2006; Rangger et al., 1995).

In order to better understand the mechanisms by which meniscal injury or meniscectomy predisposes the joint to

* Correspondence to: Orthopaedic Research Laboratories, Department of Orthopaedic Surgery, Box 3093, Duke University Medical Center, Durham, NC 27710, United States.

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osteoarthritis, changes in joint loading have been assessed using a variety of approaches, including finite element models (Peña et al., 2006; Peña et al., 2005; Wilson et al., 2003; Zielinska and Donahue, 2006), animal models (Cook et al., 2006; Elliott et al., 1999), and cadaveric studies (Bedi et al., 2010; Lee et al., 2006; Seitz et al., 2012). For example, finite element modeling of the joint has shown that partial meniscectomy, similar to total meniscectomy, results in decreased contact areas and increased peak stresses in articular cartilage (Peña et al., 2006; Peña et al., 2005; Zielinska and Donahue, 2006). Furthermore, in human cadaveric knees, radial tears or partial meniscectomy significantly increased contact pressures, and surgical repair of the meniscus failed to restore the normal pressure distribution in the knee (Bedi et al., 2012, 2010). However, available *in vivo* data detailing the changes in tibiofemoral contact mechanics following meniscal tears is limited.

In addition to the altered mechanical environment following a meniscal tear, the biochemical environment may also be affected by joint injury (Brophy et al., 2012; Lindhorst et al., 2000; Lohmander et al., 1999). A variety of biomarkers of cartilage metabolism in the synovial fluid have been associated with the development of osteoarthritis, including matrix metalloproteinases (MMPs) (Baragi et al., 2009; Janusz et al., 2002; Pozgan et al., 2010), sulfated glycosaminoglycans (sGAGs) (Lindhorst et al., 2000; Lohmander et al., 1999), cartilage oligomeric matrix protein (COMP) (Carlson et al., 2002; Wu et al., 2014), prostaglandin E_2 (PGE2) (Nishimura et al., 2002), and C2C (Fraser et al., 2003), which is a type II collagen neoepitope released upon collagenase cleavage. However, the relationship between catabolic biomarkers in the synovial fluid and cartilage strains following meniscal injury has yet to be studied. Such information could provide insights into the link between biomechanical and biochemical changes in injured joints that may promote the early development of osteoarthritis.

The primary goals of this study were to quantify the effects of meniscal tears on *in vivo* cartilage strains over a full range of weight bearing flexion angles and to determine the relationship of cartilage strain with biomarkers of cartilage degradation in the synovial fluid. We hypothesize that following a medial meniscus tear, the contact strain in the medial compartment will be increased as compared to the uninjured knee and that cartilage strain magnitudes will positively correlate with catabolic biomarkers in the synovial fluid.

2. Methods

2.1. Patient recruitment and inclusion criteria

Eight subjects (5 male, 3 female, mean age: 54, range: 48–62) with an isolated unilateral medial meniscus injury were recruited and provided informed consent for this study with approval by the Duke University Medical Center Institutional Review Board (IRB). All subjects reported an identifiable, traumatic injury that occurred prior to their study visit. Subjects had full range of motion in the injured knee at the time of study participation. In addition to a clinical examination and patient history, the diagnosis of meniscal tear was confirmed by clinical MRI. From the scans, the range of tears were classified as follows: body/posterior horn tear with a flipped fragment (4 subjects) and complex tear of the posterior horn (4 subjects). Subjects were excluded if they had MRI evidence of arthritis, previous knee surgery, or chronic knee pain. In all subjects, the contralateral knee was normal with no history of trauma, chronic pain, or surgery and served as a control. MR images were reviewed by a board certified musculoskeletal radiologist with more than 25 years of experience. Cartilage of the femoral condyles and tibial plateaus was assessed in both knees. Six of the subjects had normal cartilage. Minimal surface irregularity was present on one surface of each of the two remaining subjects (one medial tibial plateau and one posterior medial femoral condyle).

2.2. MR-based modeling

Cartilage contact strains were measured using a previously established technique combining MR-based 3D models of the knee and biplanar fluoroscopy (Bischof et al., 2010; Van de Velde et al., 2009). Both the injured and uninjured control knees were imaged using a 3T MR scanner (Trio Tim, Siemens, Germany). Sagittal plane images were captured using a fat-suppressed 3D double-echo steady state (DESS) sequence (flip angle: 25°, TE: 6 ms; TR: 17 ms) with a 16 cm × 16 cm field of view. The matrix was 512 × 512 pixels and slice thickness was 1 mm. Next, the MR images were imported into solid modeling software (Rhinoceros, Robert McNeel and Associates, Seattle, WA) so that outlines of the bony cortices and articular cartilage surfaces could be traced. These line models were converted into point clouds and 3D meshes of the femur, tibia, and articular cartilage were created with Geomagic Studio software (3D Systems, Rock Hill, SC) (Fig. 1) (Coleman et al., 2013). This method has been previously validated for measuring tibiofemoral cartilage thickness (Van de Velde et al., 2009). Additionally, a recent study from our laboratory demonstrated a coefficient of repeatability of 0.03 mm in measuring tibial, femoral, and patellar cartilage thickness

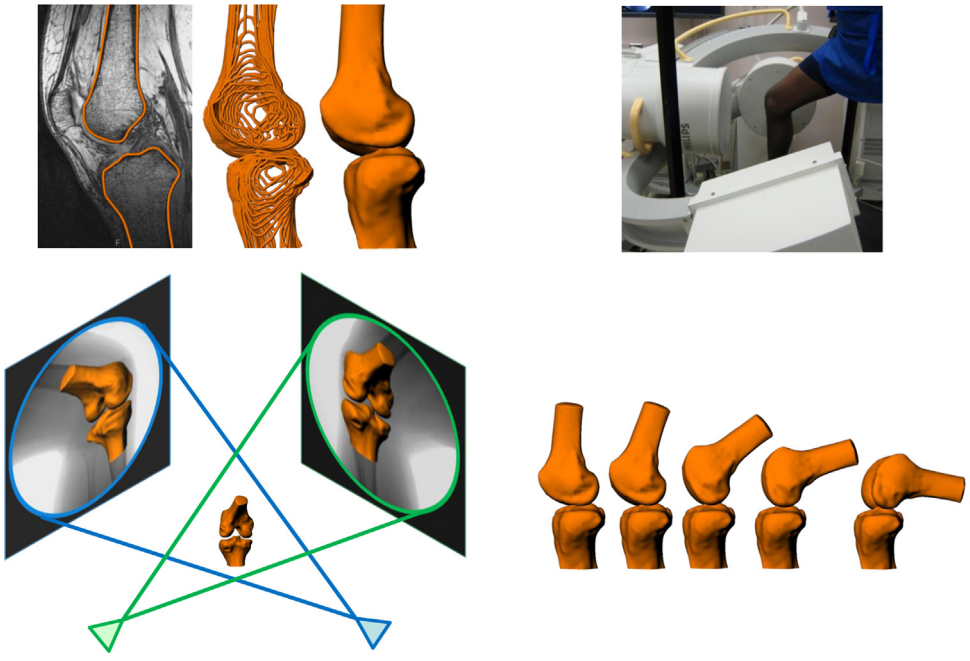

Fig. 1. High resolution MR images were segmented to create 3D models of the knee (top left). Next, the patients were imaged using biplanar fluoroscopy while performing a quasi-static lunge (top right). The fluoroscopic images and 3D models were used to reproduce the motion of each knee during the lunge (bottom).