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


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ARTICLE INFO

Article history:
Accepted 10 February 2015

Keywords:
MRI
Cartilage deformation
Mechanobiology
COMP
Aggrecan
Biomarker

ABSTRACT

Meniscal tears are common injuries, and while partial meniscectomy is a frequent treatment option, general meniscal 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 E2, and the collagen type II cleavage biomarker C2 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.

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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 degenerative 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; Hosher 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
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., 2010; Lee et al., 2006). 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 E2 (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 plateau 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 (Rhino3D, 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.
(Coleman et al., 2013), corresponding to a difference in cartilage thickness of 1% (Coleman et al., 2013; Widmer et al., 2013).

2.3. Fluoroscopic imaging

Each subject’s injured and contralateral uninjured control knee were imaged using biplanar fluoroscopy (Pulsera, Philips, The Netherlands) (Abebe et al., 2011a, b). Digital radiographs were captured while the subject was standing with a single knee positioned between the crossing beams of the fluoroscopes. To evaluate a wide range of motion, each subject performed a quasi-static lunge from full extension to 90° in increments of 30°. To capture even deeper flexion, we also included a 105° knee flexion position. Subjects were positioned at each flexion angle using a goniometer. The radiographic images were imported into the solid modeling software to reproduce the position and orientation of the fluoroscopes at the time of testing. For each flexion angle, the MR-based 3D models of the femur and tibia were imported into this system and manually positioned in 6 degrees of freedom until their projections matched their respective silhouette on each of the fluoroscopic images simultaneously (Fig. 1) (DeFrate et al., 2006). Thus, the 3D models were used to reproduce the position of the knee during the lunge sequence (Abebe et al., 2011b; DeFrate et al., 2006). Previous studies have shown that this methodology can reproduce joint motion to within less than 0.1 mm and 0.3° (Caputo et al., 2009; DeFrate et al., 2006; Utturkar et al., 2013).

2.4. Measurement of cartilage strain

Knowing the relationship of the cartilage surfaces relative to the bones from MRI, areas of overlap of the undeformed tibial and femoral cartilage mesh surfaces were used to calculate tibiofemoral cartilage contact strains in each knee position. Cartilage-to-cartilage contact strains were calculated by taking the ratio of the distance of penetration to the thickness of the two cartilage layers at each point on the tibial cartilage surface (Bischof et al., 2010; Van de Velde et al., 2009) (Fig. 2). Peak strains were calculated on both the injured and uninjured knee in both the medial and lateral compartments (Bischof et al., 2010). To capture even deeper flexion, a 105° knee flexion position was included with a meniscus tear (bottom right), the cartilage contact strain increased 7% in the injured knee. No statistically significant interactions between flexion angle and meniscal injury were observed (Fig. 4, p=0.038). In the normal knee, contact strain ranged from 15±3% at 0° of flexion to 17±3% at 105° of flexion. In the injured knee, contact strain was 12±3% at 0° of flexion and increased to 23±7% at 105° of flexion. There was a statistically significant increase in the medial compartment, as compared to the uninjured knee (bottom left).

3. Results

Peak contact strains in the medial compartment of the injured knee were significantly greater than those of the uninjured knee (Fig. 3, p=0.008). Across all flexion angles, peak medial compartment strain averaged 17±5% (mean ± standard deviation) in the intact knee, compared to 23±7% in the injured knee. No statistically significant effects of flexion angle (p=0.59) or significant interactions between flexion angle and the presence or absence of meniscal injury (p=0.21) were detected.

In the lateral compartment, a statistically significant interaction between flexion angle and meniscal injury was observed (Fig. 4, p=0.038). In the normal knee, the contact strain ranged from 15±3% at 0° of flexion to 17±3% at 105° of flexion. In the injured knee, contact strain was 12±3% at 0° of flexion and increased to 23±7% at 105° of flexion. There was a statistically significant increase in the medial compartment, as compared to the uninjured knee (bottom left).

**Fig. 2.** Strain (ε) across the tibiofemoral joint was approximated from the overlap in cartilage surfaces. The penetration distance (d) was divided by the combined thickness of the undeformed tibial (t1) and femoral (t2) cartilage surfaces at each point within the joint to create a strain map (top). Contact strain maps were created for all angles of both the injured and uninjured knees. The strain maps are shown for one subject at 60° of flexion. With a meniscus tear (bottom right), the cartilage contact strain increased in the medial compartment, as compared to the uninjured knee (bottom left).

Please cite this article as: Carter, T.E., et al., *In vivo* cartilage strain increases following medial meniscal tear and correlates with synovial fluid matrix metalloproteinase activity. Journal of Biomechanics (2015), http://dx.doi.org/10.1016/j.jbiomech.2015.02.030
Fig. 3. In the medial compartment, meniscus injury increased peak contact strains. There were no statistically significant effects of flexion or interactions between flexion and injury. Data is presented as the mean peak contact strain ± standard deviation.

Fig. 4. In the lateral compartment, a statistically significant interaction between flexion angle and meniscal injury was observed. At the maximum flexion angle of 105°, peak contact strains were increased in the injured knee as compared to the contralateral control. Data is presented as the mean peak contact strain ± standard deviation.

increase in contact strain between the normal and injured knee at 105° of flexion ($p = 0.029$).

All of the catabolic biomarkers were detectable in the synovial fluid from the injured knee at the time of joint surgery. The median total MMP activity was 906 × 10³ fluorescent units/mL in the synovial fluid of the meniscal tear patients (Fig. 5A). The median concentration of each of the other biomarkers in the synovial fluid was 78 µg/mL sGAG (Fig. 5B), 15 µg/mL COMP (Fig. 5C), 25 ng/mL PGE2 (Fig. 5D), and 69 ng/mL C2C (Fig. 5E).

Given the significant increases in cartilage strain in both the medial and lateral compartments at 105° of flexion, we averaged the strain across both compartments to give an average total strain across the tibiofemoral joint. This average strain was then correlated to the concentrations of the biomarkers in the synovial fluid (Table 1). There was a positive correlation between the total MMP activity and average cartilage strain ($R = 0.79$, $p < 0.05$). However, there were no significant correlations between sGAG, COMP, PGE2, or C2C levels and cartilage strain in these subjects.

4. Discussion

This study investigated in vivo cartilage contact strain patterns in knees with injured meniscal tears through the use of MRI, biplanar fluoroscopy, and 3D modeling and correlated cartilage strain with biomarkers of cartilage metabolism in the synovial fluid, which have previously been associated with the development of osteoarthritis. Based on the established link of increased risk for early onset osteoarthritis following meniscal tear (Lohmander et al., 2007), our hypothesis was that there would be increased contact strain in the injured knees and that the catabolic biomarkers would correlate with cartilage strain. In general, our results confirm the hypothesis, demonstrating that medial compartment strains increased significantly across all flexion angles and that lateral compartment strains increased at 105° of flexion. Overall, the average increase in contact strain following injury was approximately 6% in the medial compartment. Because peak strains were elevated in both compartments at maximum flexion, correlations were performed between average strain and biomarker levels in this knee position. As a result, we found that average cartilage strain at 105° of flexion correlated with the total MMP activity in the synovial fluid.

Several previous studies have examined tibiofemoral cartilage contact strains in healthy knees (Bingham et al., 2008) and knees with cruciate ligament deficiencies (Van de Velde et al., 2009). The magnitudes and trends in contact strains reported in this study are consistent with these previous studies (Bingham et al., 2008; Van de Velde et al., 2009). Specifically, these previous studies have shown that strains from the uninjured knee of subjects with ACL injuries and in subjects with healthy knees ranged from 10–30%, with higher values typically occurring in the medial compartment (Bingham et al., 2008; Van de Velde et al., 2009).

The effects of the medial meniscus injury were most evident in the medial compartment, which experienced significantly elevated contact strains compared to the uninjured control knee at all flexion angles. Other studies have investigated the mechanical effects of meniscal injuries and treatment on various knee functions in both computational (Bae et al., 2012; Peña et al., 2005; Zielinska and Donahue, 2006) and in vitro (Allaire et al., 2008; Bedi et al., 2010; Lee et al., 2006; Seitz et al., 2012) models. However, these data are typically reported in the form of contact pressures or stresses. While it is not possible to infer contact stresses directly in the current study, the data trends are similar in both model modalities, indicating that loss of medial meniscus integrity results in increases in medial compartment loading. Interestingly, the results of the present study also found increased contact strains in the lateral compartment at 105° of flexion. Since the medial meniscus is believed to have an important role in transmitting load in higher flexion angles (Lee et al., 2006; Pinkerova et al., 2009; Seitz et al., 2012; Yao et al., 2008), it is likely that disruptions in the position of the knee due to a medial meniscus tear alter load transmission through the lateral compartment as well, as observed in this study.

Altered joint loading is believed to play an important role in the development of osteoarthritis (Guilak, 2011). While the multifactorial origin of mechanically-induced joint degeneration remains to be elucidated, the connection between traumatic knee injury and early osteoarthritis is well established, especially given the high rates of disease progression in those who have ligamentous or meniscal injuries (Lohmander et al., 2007). Because these injuries have been shown to invoke joint kinematic changes during a variety of functions (Ahn et al., 2011; Andriacchi et al., 2004; Bedi et al., 2010, 2012; Chen et al., 2012; Tashman et al., 2004), it has been suggested that these ensuing changes alter cartilage loading detrimentally. Several studies, including our present findings, provide support for this hypothesis by demonstrating alterations in cartilage stress and strain patterns after joint injury (Bedi et al., 2013, 2010; Bischof et al., 2010; Peña et al., 2005; Van de Velde et al., 2009). However, despite the increasing evidence of altered stress and strain distributions in the joint following injury, how these changes relate to mechanical and other physical factors experienced at the cellular and molecular compositional level is less clear (Halloran et al., 2012). In this regard, in vivo strain data, in combination with experimental measures of contact stress (Bedi et al., 2010) and computational...
Synovial fluid metalloproteinase (MMP) activity, sulfated glycosaminoglycan (sGAG) concentrations, cartilage oligomeric matrix protein (COMP) concentrations, prostaglandin E2 (PGE2) levels, and C2C concentrations in the synovial fluid. Each point indicates the concentration for an individual and the median for each biomarker is indicated by the line.

Table 1
Correlation of average cartilage strain to biomarkers.

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Spearman R</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMP</td>
<td>0.79</td>
<td>0.04</td>
</tr>
<tr>
<td>sGAG</td>
<td>-0.64</td>
<td>0.12</td>
</tr>
<tr>
<td>COMP</td>
<td>-0.57</td>
<td>0.18</td>
</tr>
<tr>
<td>PGE2</td>
<td>0.50</td>
<td>0.25</td>
</tr>
<tr>
<td>C2C</td>
<td>0.14</td>
<td>0.70</td>
</tr>
</tbody>
</table>

models of the knee (Peña et al., 2006; Wilson et al., 2003; Zelinski and Donahue, 2006) may provide important insights into the mechanobiologic response of cartilage to altered loading (Sanchez-Adams et al., 2014). In this study, we have shown the effects of a meniscal tear on cartilage strain but it is also important to note that the altered mechanical loading in the joint following a meniscal injury likely affects other joint tissues including the meniscus, bone, ligaments, and synovium. In particular, the meniscus, bone, and synovium have been shown to be involved in the production of catabolic biomarkers as well (Brophy et al., 2012; Galliera et al., 2010; Heard et al., 2011).

Cartilage strain following meniscal injury correlated positively with total MMP activity in the synovial fluid. MMPs are a family of enzymes capable of degrading all components of the extracellular matrix, and in particular the collagenases MMP-1, MMP-8, and MMP-13, and membrane type 1 MMP (MT1-MMP) are the only enzymes capable of breaking down the intact triple helical collagen (Billinghurst et al., 1997). MMPs have previously been shown to be upregulated following meniscal injury (Brophy et al., 2012; Killian et al., 2011) and to be mechanically regulated (Blain, 2007). In addition, specific inhibition of MMP-13 or broad spectrum MMP inhibition protects against the development of osteoarthritis following medial meniscus tear in a rat model (Baragi et al., 2009; Janusz et al., 2002). Broad spectrum MMP inhibition can also promote integrative meniscal repair in the presence of IL-1 (McNulty et al., 2009). In this study, the total MMP activity measured is a combination of the activity of both the pro-MMPs and active MMPs secreted into the synovial fluid. Very few of the synovial fluid samples contained active MMPs and thus the majority of the MMPs were in the proenzyme form. Therefore, it is possible that active MMPs may be bound in the tissue extracellular matrix or may have degraded during sample processing. Alternatively, the MMPs in the joint are not yet activated. A variety of factors in the joint can activate the pro-MMPs, including plasmin and MT-MMPs (Milner et al., 2001) and also activated protein C (APC), which is elevated in the synovial fluid of osteoarthritic patients (Jackson et al., 2014). Therefore, the measured total MMP activity is a good surrogate for the potential MMP activity in the joint that may contribute to extracellular matrix component breakdown and ultimately osteoarthritis.

The synovial fluid concentrations of sGAG, COMP, PGE2, and C2C in our study were not correlated with average cartilage strain. Aggrecan turnover is increased following meniscal tears (Lohmander et al., 1999) and with high strain of cartilage and meniscal explants (Killian et al., 2011; Waters et al., 2014). COMP synthesis and release by chondrocytes is mechanically regulated (Piscoya et al., 2005; Wong et al., 1999) and has been shown to be elevated following canine meniscectomy, with peaks around 4–8 weeks after injury (Lindhorst et al., 2000). Previous studies have shown that 30 min of one-legged knee extension exercise decreases synovial fluid COMP in osteoarthritic knees (Helmark et al., 2012). Furthermore, the knee state and type of exercise impact alterations in COMP levels, as in healthy knees serum COMP levels correlate with cartilage volume changes after drop landing but not after running (Nielhoff et al., 2011). PGE2 is also increased in osteoarthritic synovial fluid (Nishimura et al., 2002) and is mechanically regulated in cartilage, as well as meniscus (Fermor et al., 2002; Hennerbichler et al., 2007; Waters et al., 2014). Finally, a trend towards increased C2C was reported at 30 days following a single 8 MPa stress on cartilage explants (Barr et al., 2014). However, in the meniscal tear subjects, longer times following joint injury may be necessary to detect the breakdown of the collagenous matrix.

Since the type of meniscus injury varied between patients and the extent of tissue removed during a meniscectomy varies, future studies may wish to examine changes in joint biomechanics with the loss of different proportions of the meniscus. In cadaveric studies, joint contact stresses increase with the extent of meniscus removal (Baratz et al., 1986; Bedi et al., 2010; Lee et al., 2006). While we did not group our population according to type or severity of medial meniscus tear, the results of our study show that load transmission changes occur after meniscus injury and prior to meniscectomy. Surgical protocols now emphasize minimizing the preservation of the meniscal peripheral rim, in order to minimize changes in contact area and joint stability (Englund, 2008; Lee et al., 2006). Future studies measuring in vivo strain in patients following surgical treatment should provide key information to further revise guidelines on the acceptable limits of...
resection to maintain normal cartilage contact patterns, with the goal of ultimately reducing the risk of osteoarthritis development. A potential limitation of this study is the relatively small sample size, which was sufficient to determine biomechanical differences and also the strong correlation between strain and MMP activity but is likely limited for the detection of small to modest correlations of other biomarkers. Additionally, the single timepoint of synovial fluid collection at surgery and the wide range of time from injury to collection across the patients may have made correlations difficult to detect. Furthermore, synovial fluid from the contralateral, uninjured knee could provide information on the baseline biomarker profiles of each individual in relation to those of the injured knee. The measured synovial fluid concentrations in the meniscal tear subjects are slightly lower than previously reported for patients following an ACL tear; however, the collection of synovial fluid occurred much closer to the time of injury in the ACL study (average 15 days versus median 13 weeks) (Catterall et al., 2010).

It is important to note that meniscal injuries can occur as a result of an acute trauma or due to tissue degeneration. In general, degenerative tears are associated with increased age and osteoarthritic changes (Berthiaume et al., 2005; Englund, 2008; Greis et al., 2002). Additionally, degenerative tears often have an insidious onset of symptoms without a specific traumatic event initiating injury (Englund, 2008; Howell et al., 2014; Silvonen et al., 2013). Therefore, to minimize the effects that existing joint degeneration may be playing in the measurements of the present study, patient inclusion criteria were enforced to recruit individuals with an identifiable, traumatic injury and no MRI evidence of cartilage degeneration on the femoral condyles or tibial plateaus of both knees.

In conclusion, this study investigated in vivo tibiofemoral contact strain patterns in patients with an isolated medial meniscus tear and levels of biomarkers of cartilage metabolism in the synovial fluid. Cartilage contact strains increased after meniscal tear when compared to the contralateral control knee, especially at higher flexion angles. In addition, total MMP activity positively correlated with the average cartilage strain across the joint at maximum flexion. These findings suggest that the ability of the meniscus to distribute load is compromised after the injury, thus overloading the cartilage and upregulating mechanically sensitive mediators like the MMPs. These changes likely contribute to the development of osteoarthritis following meniscal injury and support the need to improve surgical treatment options to restore normal cartilage loading.

Conflict of interest statement

The authors of this manuscript have no conflicts of interest related to the content of the study.

Acknowledgments

This work was supported in part by the National Institutes of Health grants AR63325, AR65527, AR48182, AR48852, AG15768, AR50245, and AG46927. The technical assistance provided by Dr. Virginia Kraus and Janet Hubner through the Biomarkers Shared Resource at Duke University Medical Center is also gratefully acknowledged.

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Ahmed, A.M., Burke, D.L., 1983. In vitro measurement of static pressure distribution in porcine medial meniscal tear when compared to the contralateral control knee, especially at higher flexion angles. These changes likely contribute to the development of osteoarthritis following meniscal injury and support the need to improve surgical treatment options to restore normal cartilage loading.

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