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Impact of ACL Injury on Patellar Cartilage Thickness

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IMPACT OF ACL INJURY ON PATELLAR CARTILAGE THICKNESS

A Thesis Presented

by

Ethan Leveillee

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The Faculty of the Graduate College

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In Partial Fulfillment of the Requirements
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ABSTRACT

ACL injury has been shown to have long-lasting and severe consequences on the different structures of the knee such as the articular cartilage and meniscus. Cartilage thickness changes in particular are indicative of osteoarthritic changes in the tibiofemoral joint. While there has been significant research focused on cartilage changes of the tibia and femur following severe joint trauma, there has been little work focused on patellar cartilage. The following goals were set forth for this study. First, to establish a robust coordinate system to accurately determine the location and orientation of the patella relative to the femur and establish the distribution of articular cartilage thickness on the patella. Second, to determine the effects of ACL injury on patellar cartilage thickness.

Twenty-one individuals (10 males, 11 females) were studied. All individuals had suffered their first ACL injury. MRI data from both the healthy and injured knees were collected an average of 4 ± 0.9 years following the initial injury and ACL reconstruction surgery. Using MRI data, the bone and cartilage surfaces were manually segmented and imported into MATLAB for study. The difference in cartilage thickness between the healthy and injured knees within individuals was the primary measure of analysis. Analysis revealed both decreases and increases in cartilage thickness of the injured knee in comparison to the normal knee. When considering males as a group, four square millimeters of the cartilage of the ACL injured knee underwent significant thinning compared to the normal side, and this occurred in the medial superior aspect of the patellar, (mean thickness difference = -0.381 mm, with SD = 0.084mm). Analysis of the females as a group revealed that five square millimeters of cartilage of the ACL injured knee underwent significant thickening compared to the normal side, and this occurred in the medial inferior aspect of the patella (mean thickness difference = 0.551 mm, SD = 0.015mm).

The findings from this study indicate that directional, regional and sex specific cartilage thickness changes occur following ACL injury, surgery, and 4 year follow-up.
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Chapter 1: Comprehensive Literature Review

1.1. General Anatomy

1.1.1. Femur and Tibia

The knee joint is comprised of several different structures. There are three primary bones: the femur, tibia, fibula, and patella. The tibia, fibula and femur are held together by 4 primary ligaments: the anterior cruciate ligament, posterior cruciate ligament, medial collateral ligament, and lateral collateral ligament. The sphere-like ends of the femur are known as the medial and lateral condyles. They rest and slide/translate on the two concave articular surfaces of the tibia, known as the medial and lateral plateaus. Between the two tibial plateaus is an elevated, narrow piece of bone called the tibial spine. The spine rests between the two femoral condyles in the femoral notch. The surfaces of the femur and tibia are covered by a layer of articular cartilage that provides near-frictionless contact between the femur and tibia during motion and activity. Between the femur and the tibia exists the meniscus. This structure helps distribute contact stresses between the femur and tibia and acts as a shock absorber during loading.
1.1.2. Patella

The patella, which articulates with the trochlea and femoral condyles during flexion and extension of the knee, plays a very important biomechanical role in movement. To promote efficient contact stress transmission, the posterior aspect of the patella is covered with articular cartilage. Due to the high magnitudes of contact stress
produced during flexion and extension of the knee, the patella has the thickest cartilage of any structure in the knee. (Heegaard, Leyvraz et al. 1995) As the knee flexes from full extension, the patella articulates with the femoral condyles, with the posterior ridge riding between the condyles. As the knee is moved into flexion the contact area between the patellar and femur increases. (Heegaard, Leyvraz et al. 1995) Anatomically, the patella is connected to the quadriceps tendon superiorly and attached to the patellar ligament on its inferior side. Without the patella - assuming the quadriceps tendon inserted directly into the tibia - extension of the tibia through contraction of the quadriceps muscle group would be extremely difficult if not impossible. This is due to the fact that the patella moves the force of the quadriceps anterior to the axis of rotation of the tibiofemoral joint, creating a moment arm acting on the tibia to rotate about the condyles. This moment effect is most important when the knee is in flexion. (Yamaguchi and Zajac 1989, Im, Goltzer et al. 2015)
1.2. Cartilage Biochemistry

1.2.1. Composition

The articular cartilage covering the femur, tibia, and patella serves an important role in the knee. Cartilage acts as both a minimal-friction surface for sliding and as a cushion for the underlying subchondral bone. There is no blood or neural supply to the cartilage. It is comprised mainly of collagen and glycosaminoglycan, accounting for roughly 70% of the dry weight of cartilage (60% and 10%, respectively). (McDevitt 1973) Proteoglycans, to which the glycosaminoglycan chains are attached, are able to retain
fairly large amounts of water. Cartilage behaves as a viscoelastic material, as it responds to forces in a non-linear fashion. The properties of cartilage are modeled using biphasic mixture theory. (Lu and Mow 2008) The solid components of the cartilage, such as the glycosaminoglycans, act as an elastic matrix. However, the material itself holds water and is permeable to flow of fluid through its structure. (McDevitt 1973, Lu and Mow 2008) Applying force to cartilage causes both an elastic response in the cartilage matrix, and flow-dependent response related to the force applied and the permeability of the matrix itself. (McDevitt 1973, Lu and Mow 2008)

Several of the types of chains that attach to the glycosaminoglycan backbone contain negatively charged chemical groups, such as sulfate. (Lu and Mow 2008) The negatively charged arms attract positively charged sodium ions into the matrix. (Lu and Mow 2008) This concentration of sodium creates an osmotic gradient, which increases water attraction into the tissue. The resulting pressure from this charge-induced gradient is known as Donnan osmotic pressure. (Lu and Mow 2008) The Donnan osmotic pressure, matrix material properties, and permeability of water flow, has been considered as a triphasic model. (Lu and Mow 2008)

1.2.2. Osteoarthritis

Osteoarthritis involves the progressive degradation of articular cartilage and other components of the joint, such as the bone and ligaments. It is extremely common in the population and has many associated causes including but not limited to: sex, age, weight, and genetics. (Hunter and Felson 2006) The estimated prevalence of OA is 26.9
million in the United States alone.(Initiative 2014) The main presenting symptom of osteoarthritis is a painful joint in which pain is made worse with activity. While rest often makes the pain lessen, severe disease progression can lead to pain even at rest.(Hunter and Felson 2006)

Osteoarthritis that has been caused by injury of a joint is known as post-traumatic osteoarthritis (PTOA). PTOA is a common sequela of ACL injury, with estimates varying between 0%-48% of injuries developing into disease depending on concomitant injuries.(Neuman, Englund et al. 2008) This risk is increased if other structures are damaged in combination with the ACL.(Neuman, Englund et al. 2008, Ichiba and Kishimoto 2009, Oiestad, Engebretsen et al. 2009)

1.3. ACL Injury

1.3.1. ACL Injury and Mechanism

There are two mechanisms of ACL injury: non-contact and contact. It has been estimated that 30% of all ACL injuries are produced by direct contact with the knee, while the remaining 70% of injuries are produced by non-contact mechanisms.(Griffin, Agel et al. 2000) Contact injuries arise from some sort of external trauma applied to the joint. Contact mechanisms of ACL injury are frequently associated with concurrent injuries to the medial collateral ligament, the medial meniscus, or a combination of the two. This combination of three injured structures, known as “O’Donohugh’s triad”, the “terrible triad”, or “unhappy triad”, has been the subject of extensive
Non-contact ACL injury, as the name suggests, occurs in the absence of externally applied loads to the knee. Studies of bone bruises following ACL injury have suggested a pivot-shift motion as the primary non-contact injury mechanism, based on bruises most often occurring on the lateral tibial plateau and the lateral femoral condyle. (Graf, Cook et al. 1993) This motion is a combination of anterior translation and internal rotation of the tibia relative to the femur. Bruises are indicative of the force of impact at the time of injury that were propagated through the cartilage. (Graf, Cook et al. 1993, Sanders, Medynski et al. 2000, Patel, Hageman et al. 2014) As the name pivot-shift suggests, this type of motion in the knee is usually generated when a person attempts to change velocity/direction quickly. Since cutting motions are associated with sports, it follows that the highest rate of ACL injury (roughly 70%) occurs during sports activities. (Griffin, Agel et al. 2000)

1.3.2. ACL Injury Risk Factors

There has been significant research attempting to determine risk factors for ACL injury. This research has revealed a broad spectrum of risk factors. Knee structural risk factors include conformation of the medial and lateral tibial plateaus, (Hashemi, Chandrashekar et al. 2010, Simon, Everhart et al. 2010, Beynnon BD, Hall J et al. 2013, Sturnick DR, VanGorder R et al. 2013) conformation of the tibial spine, (Sturnick DR, Argentieri EC et al. 2013) femoral notch, (Uhorchak, Scoville et al. 2003, Hewett, Lynch et al. 2010, Simon, Everhart et al. 2010, Whitney DC, Sturnick DR et al. 2013) the
meniscus,(Sturnick DR, Argentieri EC et al. 2013) and the structure of the ACL itself.(Simon, Everhart et al. 2010, Whitney DC, Sturnick DR et al. 2013) Increased slope of the lateral tibial plateau has been associated with increased risk of ACL injury, with Beynnon et. al describing an increased risk of 21.7% for every degree of increased slope in females.(Sturnick DR, VanGorder R et al. 2013) Both increased knee laxity and increased BMI have also been shown to be significant ACL injury risk factors.(Uhorchak, Scoville et al. 2003, Kramer, Denegar et al. 2007, Sturnick, Vacek et al. 2015) Sex differences have been found with females experiencing higher rates of ACL injury compared to males.(Arendt and Dick 1995, Anderson, Dome et al. 2001, Beynnon, Johnson et al. 2006) In addition, evidence suggests that certain risk factors may impact injury risk more or less depending on subject sex. (Sturnick DR, Argentieri EC et al. 2013, Whitney DC, Sturnick DR et al. 2013) For example, Sturnick et. al found that a smaller tibial spine had no impact on ACL injury risk for females, but was associated with increased risk in males. Understanding what factors influence risk of ACL injury is important because it provides information to determine who is at increased risk of injury, and gives insight into important features that could be the site of an intervention to reduce the risk of injury.

1.3.3. ACL Reconstruction

ACL reconstruction is a common procedure that is designed to restore normal function to the knee following an injury. Research has also shown that ACL reconstruction has increased over the past 20 years.(Mall, Chalmers et al. 2014)
Estimates for the number of ACL reconstructions range from 125,000 - 175,000 cases annually.(Dunn, Spindler et al. 2010, Kim, Bosque et al. 2011) However, reconstruction does not restore the knee to its pre-injury state.(Beynnon, Fleming et al. 1995, Frobell 2011, Hosseini, Van de Velde et al. 2012, Tourville, Johnson et al. 2013, Hunter, Lohmander et al. 2014, Kaur, Ribeiro et al. 2016, Mohtadi, Chan et al. 2016, Panos, Hoffman et al. 2016, Wiggins, Grandhi et al. 2016) Differences continue to exist in the knee, such as decreased tibiofemoral joint space,(Tourville, Johnson et al. 2013) changes in gait,(Kaur, Ribeiro et al. 2016) and altered contact biomechanics of the tibiofemoral joint,(Hosseini, Van de Velde et al. 2012) even after successful reconstruction. Two years after ACL injury, cartilage thinning and thickening of different regions of the femur occurred regardless of whether or not the ACL was reconstructed.(Frobell 2011, Harris, Driban et al. 2015) While reconstruction had little impact in the previous study, Hunter et. al demonstrated that those with reconstructed ACLs had greater flattening of the femur compared to those who underwent rehabilitation without surgery.(Hunter, Lohmander et al. 2014) Knee kinematics also remain abnormal in the injured knees after reconstruction, resulting in asymmetrical kinematics.(Beynnon, Fleming et al. 1995, Panos, Hoffman et al. 2016) More importantly, following reconstruction, a second ACL injury is very likely.(Wiggins, Grandhi et al. 2016) A recently published meta-analysis revealed that 15% of people following ACL reconstruction go on to experience a second injury of the same type. Even more alarming, there was a 20% reinjury rate for athletes who following recovery continue to participate in high-level sports activities. This rate increased to 23% when looking at individuals that were 25 and younger.(Wiggins, Grandhi et al. 2016) A
randomized clinical trial reported that using a patellar tendon autograft resulted in less reinjury when compared to reconstruction with quadruple-stranded and double bundled hamstring tendon autograft. (Mohtadi, Chan et al. 2016)

1.4. MRI-Related Topics

1.4.1. MRI and Scoring Systems

MRI has become an important tool for studying the knee. An example of MRI being used to assess joint health is the MRI Osteoarthritis Score (MOAKS). (Hunter, Guermazi et al. 2011) The MOAKS score utilizes 3T MRI to assess the patella, femur, and tibia. Each structure is divided into sub-regions. The patella is divided into medial and lateral regions, while the femur is divided into 6 regions (medial and lateral regions of the trochlea, posterior femur, and central femur). The tibia is divided into 6 regions, with central, anterior, and posterior regions of both the medial and lateral tibia. These regions are evaluated for the presence of osteophytes, bone marrow lesions, cysts, and cartilage loss/thinning. The meniscus is evaluated for damage. The scoring system grades any extrusions of the meniscus while also noting the presence of thinning, missing, and/or torn meniscal tissue. The ACL, PCL, and patellar tendon are evaluated for abnormalities and tears. Finally, the MOAKS system assess the following: abnormal signal level from the iliotibial band, anserine bursa, infrapatellar bursa, and prepatellar bursa, the presence of a ganglion cyst, and any other additional loose bodies. This method of assessing the knee was found to be reliable, both within and between examiners, for most of the measurements listed above. (Hunter, Guermazi et al. 2011)
systems include the Whole-Organ Magnetic Resonance Imaging Score (WORMS) and the Boston Leeds Osteoarthritis Knee Score (BLOKS). (Peterfy, Guermazi et al. 2004, Hunter, Lo et al. 2008) The MOAKS has been shown to be an improvement over these other measurement approaches. (Hunter, Guermazi et al. 2011)

1.4.2. Basic MRI Geometric Measures

MRI has been used to measure a wide variety of different geometric characteristics of the knee structures. MRI is useful for identifying signs of osteoarthritis such as cartilage lesions, bone marrow lesions, and osteophytes. (Culvenor, Collins et al. 2015) For example, reduction in overall cartilage volume was reported in the patella and tibia 2-3 years following injury when compared to control subjects. (Wang, Wang et al. 2015) However, volume may not reflect all of the changes occurring to the cartilage post injury. Both cartilage thickening and thinning have been observed in different regions of the medial tibial plateau following ACL injury in females 27 days following injury, with thickening occurring in the central region and thinning occurred in the posterior region. (Argentieri, Sturnick et al. 2014) For the femur, it has been reported that cartilage thickening occurs in the central region of the medial femur, while thinning occurs in the trochlea 2 years after injury. (Frobell 2011, Eckstein, Wirth et al. 2015) Hunter et. al. have used MRI to measure changes in tibial bone curvature following ACL injury. They demonstrated that after ACL injury, convex structures tended to become more flattened. The opposite was true for concave regions, as they tended to become even more concave. (Hunter, Lohmander et al. 2014)
1.4.3. Advanced MRI Imaging

Specific imaging modalities have been developed to try to discern more specific information about the properties of different knee structures beyond what standard MRI can detect. Recently, research has focused on the use of T1-rho and T2 mapping to evaluate articular cartilage.

As stated by Borthakur et. al. T1-rho is “the spin-lattice relaxation in the rotating frame, during the time of the spin-lock pulse”. (Borthakur, Mellon et al. 2006) It is related to hydration of the cartilage, as well as the macromolecular content of the cartilage. In particular, T1-rho is influenced primarily by collagen and GAG content. (Blumenkrantz and Majumdar 2007, Li, Cheng et al. 2011, Son, Goodman et al. 2013, He, Wu et al. 2014) This imaging technique has been used to measure a wide variety of cartilage and meniscus properties. For example, T1-rho has been shown to change in response to cartilage damage, as well as show significant differences between cartilage lesions when compared to the surrounding healthy cartilage. (Li, Ma et al. 2007, Bolbos, Ma et al. 2008, Li, Pai et al. 2009, Stahl, Luke et al. 2009, Wang, Chang et al. 2012, Souza, Feeley et al. 2013) It has also been demonstrated by Prasad et. al. that prolongation of T1-rho relaxation times are significantly correlated with cartilage damage progression in all compartments of the knee except the medial tibia. (Prasad, Nardo et al. 2013) In the context of ACL injury, T1-rho has been used in several studies. Knee cartilage T1-rho relaxation times have been found to be elevated in those who have suffered a recent ACL injury, suggesting cartilage damage is produced by the forces that occur at the time of the initial trauma. (Pedersen, Martin et al. 2013) T1-rho has also been used to assess the status of cartilage overlaying bone marrow edema-like lesions following ACL injury. (Li, Ma et
This body of evidence suggests that T1-rho may be useful for detecting osteoarthritis, as well as predicting osteoarthritis progression.

T2 is the measure of the spin-spin relaxation time. T2 is a useful measure for looking at the cohesion of the collagen matrix, and the movement of water within the matrix. (Blumenkrantz and Majumdar 2007, Braun and Gold 2011, He, Wu et al. 2014) Similar to T1-rho, T2 values have been shown to be elevated in cartilage that shows osteoarthritic damage. (Li, Ma et al. 2007, Stahl, Luke et al. 2009, Baum, Joseph et al. 2013, Son, Goodman et al. 2013) This is thought to be produced by the increased permeability of the cartilage matrix and the associated increase in water flow through the damaged matrix. (Braun and Gold 2011) Evidence suggests elevated T2 values are also predictive of osteoarthritic progression. Prasad et al. found that elevated T2 in all compartments, except the lateral tibia, were predictive of cartilage degeneration. (Prasad, Nardo et al. 2013) Similar results were found by Liebl et al. who demonstrated that there was significant T2 elevation in knees that progressed to develop OA compared to controls in all compartments of the knee except the medial tibia. They suggested that T2 imaging may be useful for predicting the development of osteoarthritis before any radiographic evidence is present. (Liebl, Joseph et al. 2014) Elevated T2 relaxation times in certain regions of the femur and tibia have been seen at an average of 45 ± 14 days following initial injury. (Palmieri-Smith, Wojtys et al. 2016). At one year follow-up the regions that were initially elevated had returned to normal, while other regions that had initially been normal had decreased significantly. (Palmieri-Smith, Wojtys et al. 2016) The relationship between T2 and weight loss has also been explored by Serebrakin et al.
They found that, in an at-risk group for developing OA, those who lost greater than 10% of their body weight had a significantly smaller increase in T2 values over the course of two years when compared to those whose weight remained with +/- 3% of their initial weight. (Serebrakian, Poulos et al. 2015) However, it has been shown that T2 may only be useful as a predictive tool of arthritic degeneration in the earlier stages of the disease. As the severity of cartilage damage increases, T2 becomes less useful for predicting further degeneration. (Jungmann, Kraus et al. 2013)

Injury to the meniscus in combination with ACL injury leads to an increased risk of developing osteoarthritis. Therefore, investigation of the meniscus has also been the focus of T1-rho, and T2 imaging. Rauscher et. al. found that T1-rho and T2 signals were significantly elevated in the meniscus in the presence of mild osteoarthritis about the knee when compared to a healthy knee. T1-rho and T2 signals were also significantly elevated in severe osteoarthritis when compared to mild osteoarthritis. (Rauscher, Stahl et al. 2008) Similar results were found by Wang et. al. who found elevated T1-rho in the meniscus when comparing moderate-severe OA with doubtful-minimal OA. (Wang, Chang et al. 2012) Similar to articular cartilage, it appears that elevated T1-rho and T2 values are indicative of damage and/or more likely to progress to a diseased state.

Exercise causes increased joint loads and modified joint biomechanics compared to activities of daily living. As such, it induces measurable changes in the articular cartilage. It has been shown that, after extended exercise, cartilage volume is reduced by a significant amount, 5.1% in the tibial cartilage, and 7.0% in the patellar cartilage. However, this volume appears to mostly restore after only an hour of rest. (Kessler, Glaser
et al. 2008) Another study found that cartilage required roughly 90 minutes of unloading to fully restore volume following 100 knee bends. It was also demonstrated that successive 50 knee-bends every 15 minutes after the initial 100 knee bends maintained a relatively constant amount of deformation, instead of a progressively increasing amount of deformation. (Eckstein, Tieschky et al. 1999) The use of more advanced MRI techniques, such as T1-rho, have revealed that the underlying structure of the cartilage may not recover as rapidly as the volume of the cartilage. Marathon runners were shown by Luke et. al. to have elevated T1-rho and T2 values post marathon in all compartments except the lateral tibia and lateral femur. Following three months of limited training (no longer exercising at a marathon training level), T1-rho relaxation times continued to remain elevated, while T2 values did not. (Luke, Stehling et al. 2010) Similar results were found by Stehling et. al. in relation to the meniscus. After running a marathon, the medial and lateral meniscus demonstrated significantly elevated T1-rho and T2 values compared to controls. A three month follow up MRI of the marathon runners revealed that, similar to knee cartilage, T2 values had returned to near normal while T1-rho values continued to remain significantly elevated. (Stehling, Luke et al. 2011) This suggests that not only are gross conformational changes occurring after exercise, but that there may be long-term compositional changes/damage that follow extended periods of exercise.
1.5. Literature Review References


2.0. Title Page and Authors

Impact of ACL Injury on Patellar Cartilage Thickness

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2.1. Abstract

ACL injury has been shown to have long-lasting and severe consequences on the different structures of the knee such as the articular cartilage and meniscus. Cartilage thickness changes in particular are indicative of osteoarthritic changes in the tibiofemoral joint. While there has been significant research focused on cartilage changes of the tibia and femur following severe joint trauma, there has been little work focused on patellar cartilage. The following goals were set forth for this study. First, to establish a robust coordinate system to accurately determine the location and orientation of the patella relative to the femur and establish the distribution of articular cartilage thickness on the patella. Second, to determine the effects of ACL injury on patellar cartilage thickness. Twenty-one individuals (10 males, 11 females) were studied. All individuals had suffered a first time ACL injuries to one of their knees. MRI data from both the healthy and injured knees were collected an average of 4 ± 0.9 years following the initial injury and ACL reconstruction surgery. Using MRI data, the bone and cartilage surfaces were manually segmented and imported into MATLAB for study. The differences in cartilage
thickness values between the healthy and injured knees within individuals was the primary measure of analysis. Analysis revealed both decreases and increases in cartilage thickness of the injured knee in comparison to the normal knee. When considering males as a group, four square millimeters of the cartilage of the ACL injured knee underwent significant thinning compared to the normal side, and this occurred in the medial superior aspect of the patellar, (mean thickness difference = -0.381 mm, with SD = 0.084mm). Analysis of the females as a group revealed that five square millimeters of cartilage of the ACL injured knee underwent significant thickening compared to the normal side, and this occurred in the medial inferior aspect of the patella (mean thickness difference = 0.551 mm, SD = 0.015mm). The findings from this study indicate that directional, regional and sex specific cartilage thickness changes occur following ACL injury, surgery, and 4 year follow-up.

2.2. Introduction

ACL injury is a serious medical concern that can have severe long-term consequences. It is estimated that 70% of these injuries result from non-contact mechanisms, while the remaining 30% are produced by collision trauma.(Griffin, Agel et al. 2000) One of the major sequelae of ACL injury is the development of post-traumatic osteoarthritis (PTOA). The estimated risk for developing osteoarthritis following an ACL-only injury has been reported to range between 0%-13% 15 years following ACL injury.(Neuman, Englund et al. 2008) The risk is further increased if the meniscus is injured in combination with the ACL, with estimated rates of developing osteoarthritis rising to 21%-48%.(Neuman, Englund et al. 2008, Ichiba and Kishimoto 2009, Oiestad,
Engebretsen et al. 2009) The cost burden to society has been estimated to be between $38,121 - $88,538 per injury, depending on treatment method following the injury. (Mather, Koenig et al. 2013)


Given all the research done with the femur and tibia, we are beginning to get a picture of what happens to these knee structures following ACL injury. Studies such as those conducted by Frobel and Eckstein have revealed how cartilage responds after ACL injury. (Frobell 2011, Eckstein, Wirth et al. 2015) Frobel described how regional cartilage thickness changes occurred following ACL injury, with thickening occurring in the medial central femur, while thinning occurred in the femoral trochlea. (Frobell 2011) By collecting data at 4 weeks, 2 years, and 5 years following ACL injury, Eckstein was able
to demonstrate overall cartilage thickening of the tibiofemoral joint over time, and this occurred at an increase of 0.4% per year. Interestingly, sub-regions within the joint experienced greater rates of change within the first 2 years following ACL injury compared to the following 3 year time interval (years 2 to 5 following the injury). This suggests that, while overall thickness changes may occur at a constant rate, regional differences in the rate of change exist that are related to time after injury. (Eckstein, Wirth et al. 2015) However, far less research has focused on the impact of ACL injury on patellar cartilage. It has been demonstrated that patellofemoral cartilage lesions 1 year post-reconstruction predicts worse quality of life scores 3 years following reconstruction compared to those without lesions. (Culvenor, Collins et al. 2015) Hunter et. al demonstrated that larger changes in bone area of knee structures, including the patella, is associated with more severe progression of OA, both radiographically and in terms of pain. (Hunter, Nevitt et al. 2015) Wang et. al demonstrated that 2-3 years following ACL injury, overall cartilage volume is decreased compared to control subjects, including patellar cartilage. (Wang, Wang et al. 2015)

The goals of this study are first to establish a reliable coordinate system for determining the position and orientation of the patella relative to the other structures of the knee. Second, we determined the effect that ACL injury, reconstruction with a bone-patellar tendon-bone autograft and 4-year follow-up, has on the thickness of patellar cartilage. By comparing cartilage thickness within an individual, we can explore the impact injury, surgery, and time on the injured knee.
2.3. **Methods**

2.3.1. **General**

Twenty-one subjects (10 males, 11 females, mean age: 29.4 years, ranging from 15 – 53.7 years) were evaluated within this study (Table 1). This data set is a subset of the larger data set reported in the cohort study by Tourville et. al. (Tourville, Johnson et al. 2013). The MRI data that were analyzed in this study were collected at an average of 4 ± 0.9 years after subjects suffered a first time ACL injury and underwent subsequent ACL-reconstruction with a bone-patellar tendon-bone autograft. None of the individuals in this study had a history of knee trauma or injury prior to their ACL injury.

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.3</td>
<td>17.3 – 43.1</td>
</tr>
<tr>
<td>BMI</td>
<td>24.9</td>
<td>21.1 – 28.7</td>
</tr>
</tbody>
</table>

The geometries of the patellar bone and cartilage were characterized via data collected from manual segmentation of MRI images acquired at Fletcher Allen Health Care with a 3T research MRI (manufacturer: Philips, model: Achieva). Subject’s knees
were placed in extension, while laying supine in the scanner. An 8-channel SENSE knee coil was used. Acquired MRI sequences that were used for segmentation were T1-weighted, fast field echo (FFE) scans with a slice thickness of 1.2 mm and a within plane resolution of 0.3 mm x 0.3 mm. The outline of the patellar bone and patellar cartilage surfaces were manually segmented in the axial and sagittal planes. Segmenting was carried out using a Cintiq 21 UK Digitizing tablet (Wacom Tech Corp, Vancouver, WA, USA). The MRI data were viewed using OsiriX. (Pixmeo, Geneva, Switzerland, Version 5.6, open source)

2.3.2. Coordinate System

The technique used to establish the coordinate system in the patella was based on the method developed by Rainbow et al. (Rainbow, Miranda et al. 2013) Using a 3-dimensional surface meshing method, the center of gravity and the moments of inertia of the patellar bone were calculated. The center of gravity of the patellar bone served as the origin of the coordinate system. The axes of the coordinate system were determined using a multi-step approach. As described by Rainbow, the disk-shaped geometry of the patella lends itself to consistently producing a principal axis of inertia that is oriented in an anterior-posterior direction. This direction served as the y-axis (Figure 3). Next, a best fit line was fit to the posterior ridge of the patellar bone surface. This line was projected onto the plane that was defined to be perpendicular to the previously calculated y-axis (Figure 4). The z-axis was then defined as being parallel to the posterior ridge best-fit line, with positive being in the superior anatomical direction. With the y and z axes thus defined, the x-axis orientation was found simply by the cross-product of the y and z axes.
The positive direction was defined as lateral with respect to patella and as such left and right knees had x-axes that pointed in opposite directions.

Figure 3: Example Patellar Point Cloud w/ Anterior-Posterior Moment of Inertia. The blue dots are raw data points of segmented patellar bone. The red line represents the anterior-posterior directed principal axis of inertia. This axis defines the y-axis.
Figure 4: Finding Posterior Ridge and Fit Line. A line is fitted to the series of points indicated by the red circles. The orientation of this line, in the plane defined as normal to the anterior-posterior (y) axis, defines the z-axis.
2.3.3. Cartilage thickness

Thickness of the cartilage was determined by projecting a vector normal to the surface of the cartilage at each grid point location and measuring the distance between the surfaces of the articular cartilage and bone. Thickness was calculated for both the MRI...
data segmented in the axial and sagittal planes and then averaged (Figure 6). The
cartilage surface was then divided into medial and lateral regions using the posterior
ridge best fit line as the dividing border (see Figure 7 for an example). The patella was
then further divided into superior and inferior regions. The dividing line was centered in
the middle of the patella between the minimal and maximum z-values of the average
patellar cartilage height. Thus, we established: medial superior, medial inferior, lateral
superior, and lateral inferior regions of interest (see Figure 7 for an example). To make
comparisons between knees a 1 mm x 1 mm grid was overlaid across the cartilage
surface, with each point of this grid becoming one point of measure (Figure 11). The grid
was scaled in width and height based on the cube root of the volume of the patellar bone.
2.3.4. Reliability Analysis

A subset of 16 knees (8 injured, 8 healthy) was used to measure the within examiner measurement reliability of the cartilage thickness measurements, and the location and orientation of the coordinate system. Segmentation of the 16 knees was conducted by the same examiner at two measurement sessions that were separated by 3 weeks. Intraclass correlation coefficients (ICC’s) were calculated to assess the reliability of the cartilage thickness measurements (Table 1). This was done separately for the
sagittal and axial data. The mean and standard deviation of the bone volume, location of the origin (x-deviation, y-deviation, z-deviation, total deviation), and orientation of the three axes, were also measured (Table 2).

2.3.5. Outcome Measure and statistical analysis
The effect of ACL injury, surgery, and reconstruction was analyzed by measuring the differences in cartilage thickness between the healthy and injured knee of the study participants. A paired t-test was used to compare the thicknesses at each point. Due to the large number of points being compared, the Benjamini-Hochberg false discovery rate (FDR) correction was used to control for multiple comparisons.

2.4. Results
2.4.1. Reliability Outcome
The cartilage thickness reliability study demonstrated a high intra-rater reliability, with the lowest ICC value > 0.95 (see Table 2). The location of the origin (mean = 0.133 mm, SD = 0.051 mm) of the coordinate system, as well as the orientation of the Y-axis (mean = 0.366 degrees, SD = 0.224 degrees) were reliable. The X and Z axes were not as reliable, but still fairly consistent (mean = 1.225 degrees, 1.223 degrees, SD = 0.917, 0.933, respectively).

The average patellar bone volume was 16,799.6 cubic millimeters. The volume of the patellar bone on average was 214.9 cubic millimeters less at the second measurement time point in comparison to the first. A 214.9 cubic millimeters difference represents a change of 1.28 % between the measurement time intervals.
Table 2: Cartilage Thickness ICC Values. ICC’s were calculated independently for MR imaging plane and side of the patella.

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Medial</th>
<th>Lateral</th>
</tr>
</thead>
<tbody>
<tr>
<td>View</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sagittal</td>
<td>0.985</td>
<td>0.981</td>
</tr>
<tr>
<td>Axial</td>
<td>0.958</td>
<td>0.967</td>
</tr>
<tr>
<td>Averaged</td>
<td>0.978</td>
<td>0.978</td>
</tr>
</tbody>
</table>

Table 3: Mean and Standard Deviation Between The Two measurement Time Points. Each of these values represent comparing the second time point measurements to the first time point. Volume is a measure of the volume of the bone. dX, dY, and dZ is the offset distance of the origins in the x, y, and z axes, respectively. Distance is the average total distance separating the origins. dX-angle, dY-angle, and dZ-angle measure the degree offset, on average, of the calculated axes.

<table>
<thead>
<tr>
<th>Measures (Time point 2 vs. Time point 1)</th>
<th>Volume (mm^3)</th>
<th>dX (mm)</th>
<th>dY (mm)</th>
<th>dZ (mm)</th>
<th>Distance (mm)</th>
<th>dX-Angle (degrees)</th>
<th>dY-Angle (degrees)</th>
<th>dZ-Angle (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-214.9</td>
<td>0.029</td>
<td>0.099</td>
<td>0.027</td>
<td>0.133</td>
<td>1.225</td>
<td>0.366</td>
<td>1.223</td>
</tr>
<tr>
<td>SD</td>
<td>121.9</td>
<td>0.047</td>
<td>0.075</td>
<td>0.037</td>
<td>0.051</td>
<td>0.917</td>
<td>0.224</td>
<td>0.933</td>
</tr>
</tbody>
</table>

2.4.2. Cartilage Thickness Outcomes

Average cartilage thickness values for the 4 groups (injured and uninjured males and females) were calculated and plotted (Figures 7 – 10). For males and females, cartilage thickness values were thinner around the outside border of the posterior articular surface of the patellar, and became thicker when moving towards the center of the articular surface (Figures 7 -10). The injured and uninjured knees of the males and females had a thick region of cartilage that covered approximately 60% of the medial-lateral directed width and 30% of the superior-inferior directed height of the cartilage, with this region centered near the center of the articular surface of the cartilage.

The differences in cartilage thickness were calculated for females and males (Figure 11 and Figure 12, respectively). This was determined with the convention of subtracting the average cartilage thickness values of the uninjured knees (Figure 8, Figure
10) from the average cartilage thickness values of the injured knees (Figure 7, Figure 9). These results demonstrate the magnitude of difference in cartilage thickness, on average, between the injured and the uninjured knees (Figure 11, Figure 12). Note that differences less than 0.1 mm are greyed out as the magnitude of this difference is less than the minimum resolution that we can measure. Looking at the graphs of the males and females, it is apparent that, while some similarities exist in the injured to normal side thickness values, there are differences. While both males and females showed thinning in the medial superior aspect of the patella, males showed much greater thickening in the superior lateral region of the patella while females demonstrated thickening in the medial inferior region.

After analyzing the differences between the healthy and injured knees, there were a total of 9 data points that were statistically significant after correction for multiple comparisons (Figure 13, Figure 14). Four significant points (4 square millimeters) of difference were found in males (Figure 14). These points were in the medial superior region of the patella (mean thickness difference = -0.381 mm (thinning), with SD = 0.084mm). Five significant points (5 square millimeters) of difference were found in the medial inferior compartment of the female knees (Figure 13) (mean thickness difference = 0.551 mm (thickening), SD = 0.015mm).
Figure 7: Average Cartilage Thickness, Injured Females (mm). The black dots represent the 1 mm x 1 mm grid, while the colors represent the overlaying cartilage thickness. Blue represents region of thin cartilage, while red shows areas of thicker cartilage. The black lines represent the divisions between the four quadrants (medial superior, medial inferior, lateral superior, lateral inferior).
Figure 8: Average Cartilage Thickness, Uninjured Females (mm). The black dots represent the 1 mm x 1 mm grid, while the colors represent the overlaying cartilage thickness.
Figure 9: Average Cartilage Thickness, Injured Males (mm). The black dots represent the 1 mm x 1 mm grid, while the colors represent the overlaying cartilage thickness.
Figure 10: Average Cartilage Thickness, Uninjured Males (mm). The black dots represent the 1 mm x 1 mm grid, while the colors represent the overlaying cartilage thickness.
Figure 11: Average Differences (Females, mm). This graph is generated by taking the values of average cartilage thickness in the female injured knees, and subtracting the values of the cartilage thickness of the uninjured female knees. Blue regions represent areas where the injured cartilage was thinning with respect to the uninjured knee, while red represents thickening.
Figure 12: Average Differences (Males, mm). This graph is generated by taking the values of average cartilage thickness in the male injured knees, and subtracting the values of the cartilage thickness of the uninjured male knees. Blue regions represent areas where the injured cartilage was thinning with respect to the uninjured knee, while red represents thickening.
Figure 13: Location of Significantly Different Points (Females). Green represents all the points that were not significant after statistical analysis and correction. The red points show the location of the significant points, and the magnitude of the thickness difference (mm).
Figure 14: Location of Significantly Different Points (Males). Green represents all the points that were not significant after statistical analysis and correction. The blue points show the location of the significant points, and the magnitude of the thickness difference (mm).

2.5. Discussion

This study established that a coordinate system could be located in the patella in a reliable manner by the same investigator. The cartilage thickness (all measures), location of the coordinate system origin, and orientation of the axes of the coordinate system were found to be consistent between the two measurement time points. Our findings suggest that the discoid geometry of the patella allows placement of an anterior-posterior axis such that it is located at the principal axis of inertia of the patella in reproducible manner.(Rainbow, Miranda et al. 2013) The mean error and standard deviation of the X and Z axes were found to be nearly identical. This is not surprising, given the consistency of the Y-axis. Once the Y-axis is established, this determines the
plane within which the others axes are located. Since the X and Z axes are by definition always 90 degrees apart, and given that location of the Y-axis was found to be very consistent, it would make sense that the deviation of X axis would be identical to the deviation of the Z axis.

Significant side-to-side differences in patellar cartilage thickness were found within male and female subjects; however the response was different between the sexes: significant thinning occurring in the males while significant thickening occurring in the females. Specifically, the injured knee of the male subjects had 4 significant points (4 square millimeters) that had cartilage thickness values that were less than the normal side. These differences were located in the medial superior region of the patella, (mean thickness difference: -0.38 mm, with SD = 0.08mm). In contrast, the injured knee of the female subjects had 5 significant points (5 square millimeters) that had cartilage thickness values that were greater than the normal side, and these differences were located in the medial inferior region of the patella (mean thickness difference; 0.55 mm, with SD = 0.02mm). While these differences were located over small areas they represent differences that are significant from both biomechanical and biological perspectives.

In both males and females there were many points that, while not statistically significantly different, demonstrated a strong trend toward statistical significance. Many of these points were located within the medial regions of the patella, with points having p-values that ranged from 0.07-0.09. The statistical approach that we used corrected for false detection rate using the Benjimini-Hochberg FDR correction and this is may have over corrected for multiple comparisons. Fundamentally, Benjimini-Hochberg should
only be used in cases where each comparison is independent of each other. While comparison of cartilage thickness values may be independent when considering opposite sides of the patella (for example, the medial versus lateral regions, or superior versus inferior regions), it could be argued that adjacent measurements that are only separated by one square of the the 1mm by 1mm grid may not be completely independent. It is possible that we were overly aggressive in correcting for multiple comparisons, which may explain why there are large regions of differences in cartilage thickness (Figure 11, Figure 12), but only a few select points that were statistically significantly different (Figure 13, Figure 14).

It is not possible for us to determine what caused the specific patterns of thickening and thinning in the articular cartilage as this report represents secondary analysis of a descriptive study. (Tourville, Johnson et al. 2013) In Lu’s et al. biphasic model of articular cartilage, he describes that the material properties of cartilage are determined by the interaction between the elastic structure of the cartilage matrix, and the permeability of the matrix to fluid flow. (Lu and Mow 2008) If the cartilage matrix is damaged, and loses some of its stiffness, it would have a propensity to compress more under identical loads. In addition to simple cartilage loss, this could explain why certain regions of the patella cartilage appear to undergo thinning. It may be that excess compression in one region of patella cartilage causes water trapped within that region to flow to other regions of patella cartilage, and this could explain the swelling/thickening. Secondly, it may be that damage to the cartilage matrix has a direct effect on the cartilage permeability leading to an increase in the rate of water flow through the cartilage which
may explain both thickening and thinning due to increased water movement. Lu et. al also described the triphasic model of articular cartilage, in which negatively charged glycosaminoglycan chains have negatively charged chemical groups that attract positively charged sodium ions, creating the Donnan osmotic pressure gradient. (Lu and Mow 2008) If a region of cartilage were to be damaged and lose some of its negatively charged chains, that region would no longer attract as many sodium ions. This would create an osmotic gradient within the cartilage itself, with water tending to flow towards the regions where the ions exist in greater concentration, and away from the damaged areas. This is another potential mechanism that may help provide insight into why we observed regions of thickening and thinning of the articular cartilage.

This study was focused on establishing within subject differences in cartilage thickness between the healthy and injured knees following severe joint trauma. Unfortunately, we were unable to collect data from control subjects and consequently a potential weakness of this study is that the differences we observed may be explained by the naturally-occurring side-to-side differences in patellar morphometry that exists within subjects with normal knees that have not suffered injury. At the current point in time we do not know what the magnitude and distribution of this difference is for subjects with normal knees that have not suffered prior injury. Additionally, there have been no studies that have focused on the role that patellar geometry has on influencing the risk of ACL injury. It is possible that part of the reason why the subjects in the current study suffered ACL injury is due to the geometry of the patella itself, and that the differences that we observed are not produced by the injury, but could actually contribute to the risk of
suffering an injury. Studies have demonstrated that in healthy, uninjured individuals there are no significant side-to-side differences in cartilage thickness in the tibia. (Sturnick, Van Gorder et al. 2014); however, the patellar cartilage thickness differences in healthy individuals should be established.

Wang et. al. showed that patellar cartilage volume is significantly decreased 2-3 years following ACL injury and reconstruction compared to uninjured knees. (Wang, Wang et al. 2015) However, they focused on changes in the overall volume of the patellar cartilage, and did not determine changes in specific regions. Our data suggest that the structure of patellar cartilage is impacted by the injury, surgery and recovery in a complex manner: some regions of the injured patellar cartilage increase in thickness while other regions undergo a decrease in thickness following the injury, surgery and recovery. In addition, it appears as if the patellar cartilage of males and females are impacted differently. Knowing that regional differences exist within the patella suggests that we may be missing important information by simply looking at the change in patellar cartilage volume as a single outcome because increases in cartilage thickness in one region of the patella may be offset by decreases in cartilage thickness in another region. It may be that the biological mechanisms that are responsible for change are very different between different regions of the patella.

Despite some of the shortcomings of this study, there are positive conclusions that can be drawn from the results. We determine that the placement and orientation of the coordinate system was highly reliable. Being able to accurately and consistently determine the position of the patella relative to other bone structures is important for
future work that requires accurate and reliable tracking of the location and orientation of the patella relative to the femur. This finding is in agreement with Rainbow et. al, whose paper served as the foundation for establishing the coordinate system described in the current report. (Rainbow, Miranda et al. 2013)

Li et. al found that only the central region of patellar cartilage demonstrated a significant changes in T1-rho relaxation time after ACL injury (there was no difference for the T2 signal), while the medial and lateral aspects of the patella showed no difference for either T1-rho or T2. (Li, Pai et al. 2009) This is in contrast to where we observed changes in cartilage thickness: All of the significant thickness changes we observed were located on the medial aspect of the patella. However, Li et al. included a central region and we did not. Direct comparisons between our work and that of Li et al. is difficult as the authors did not define how the regions of the patella cartilage were defined. Inspection of their figures suggests that the patella was divided into equal thirds medially to laterally. Our significant data locations appear to lie outside of the “middle third”. Our observations are supported by the average thickness differences graphs (figures 11,12), which show greater differences in the medial and lateral sides of the patella but not about the central region of the patella cartilage.

This study, though limited in size, has shown that there are significant differences in the thickness of cartilage following ACL injury, surgery, and 4 year follow-up. Coupled with the prior studies that have shown changes in all the structures about the knee, we are beginning to develop an understanding of the global changes to the knee following ACL injury. With further data collection using the methods described
in this paper, it should be possible to obtain an improved understanding of cartilage changes in the patella following severe knee trauma.
2.6. Article References


Chapter 3: Comprehensive Bibliography


