ASSOCIATION BETWEEN QUADRICEPS STRENGTH AND TIBIOFEMORAL
CARTILAGE PROTEOGLYCAN DENSITY AT 6 MONTHS FOLLOWING
ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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ABSTRACT

Christian David Hunt: Association between quadriceps strength and tibiofemoral cartilage proteoglycan density at 6 months following Anterior Cruciate ligament reconstruction.
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Anterior Cruciate ligament (ACL) injury is common in the active population. ACL Reconstruction (ACLR) is used to restore stability and allow for return to activity post-ACL injury. A common impairment following ACLR is decreased quadriceps strength in the injured limb, which has been linked to the development of Tibiofemoral Osteoarthritis (OA). Compositional magnetic resonance imaging (MRI) has shown the ability to identify early cartilage changes prior to cartilage structural damage. This preliminary investigation evaluated the association between isometric quadriceps strength and T1rho compositional MRI in weight-bearing regions of tibiofemoral cartilage in 24 subjects at 6 months post-ACLR. We found evidence of compositional changes, measured via T1rho relaxation time, with little change to cartilage volume. There was also a statistically significant association between quadriceps strength and T1rho relaxation times for the three regions of the medial femoral condyle, calling for additional research into the interaction of quadriceps and cartilage composition.

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LIST OF ABBREVIATIONS

ACL	Anterior Cruciate Ligament
ACLR	Anterior Cruciate Ligament Reconstruction
ATT	Anterior Tibial Translation
BB	Bone Bruise
BML	Bone Marrow Lesion
GAG	Glycosaminoglycans
IKDC	International Knee Documentation Committee
JSN	Joint Space Narrowing
KOOS	Knee Injury and Osteoarthritis Score
LFC	Lateral Femoral Condyle
LTC	Lateral Tibia Condyle
LSI	Limb Symmetry Index
MFC	Medial Femoral Condyle
MRI	Magnetic Resonance Imaging
MTC	Lateral Tibia Condyle
MVIC	Maximal Voluntary Isometric Contraction
OA	Osteoarthritis
PG	Proteoglycans
ROI	Region of Interest

CHAPTER I

Introduction

Anterior cruciate ligament (ACL) injury accounts for 50% of all knee injuries in the athletic population[1]. Additionally, ACL injuries occur generally in a younger and more active population, with 18 years of age being the median age of ACL injured patients[2]. Surgical ACL reconstruction (ACLR) is often used to improve static knee stability and return patients to physical activity[3,4]. Treatment of ACL injury accounts for over 1 billion dollars in associated costs in the United States annually[1]. Despite modern advancements in ACLR techniques and improved knowledge and application of rehabilitation and strengthening programs, those who have torn their ACL are still at an increased risk of either tearing the graft in the ACLR limb or the ACL in the contralateral limb[5]. While the re-injury rate is alarming, the long-term consequences of ACL injury and ACLR, specifically the risk of developing tibiofemoral osteoarthritis(OA), add additional cause for concern[6-10]. The development of OA results in increased medical costs annually of over 12,200 dollars[11], and currently does not have a functional cure[12]. Those who have experienced ACLR are both more likely to develop OA[13] and develop it sooner than those who have not[14-16]. In a systematic review of the literature, 36% (286/795) of subjects who experienced ACLR demonstrated evidence of radiographic knee

osteoarthritis within the first decade of ACLR, 48% (702/1468) demonstrated OA in the second decade, and 42% (100/237) demonstrated OA in the third decade[7]. Currently, the pathogenesis related to knee OA onset is unknown[8], yet it has been suggested that a combination of acute and chronic factors contribute to its development post-ACLR[17].

The factors that have been suggested to contribute to the acute development of knee OA are varied: initial damage to the cartilage[18], damage to the meniscus at the initial time of injury[19], and alterations in tissue composition due to the presence of inflammatory mediators[8]. Some chronic contributors to the development of knee OA are altered joint proprioception[20] and reduced strength of the quadriceps musculature[21], both of which combine to alter the kinematics of the knee during walking gait.

Cartilage is influenced by the loads placed upon it[22], and the preservation of functional joint biomechanics following ACLR is paramount to maintaining long-term joint health[23]. Individuals with ACLR demonstrate altered joint kinematics via smaller knee flexion angles[24], as well as greater tibial external rotation during knee flexion[25,26] and greater anterior tibial translation[27] compared to healthy controls in walking gait. There are also alterations in knee motions via changes to joint kinetics such as changes in the knee flexion moment{Hart, 2015 #148}, and knee adduction moment[22,28] during more dynamic motions such as the single leg hop, when compared to uninjured controls. These alterations in joint kinematics result in subsequent alterations in the patterning of load experienced by the tibiofemoral cartilage[25].

One of the most vital components to the preservation of knee kinetics is the strength of the quadriceps muscle group. Quadriceps strength contributes to the balancing of forces acting on the knee[29] by transferring forces through the knee[21]. Quadriceps strength is markedly reduced post-ACL injury and surgical reconstruction[30-33]. These reductions in knee extension strength contribute to the higher mechanical forces experienced by the tibiofemoral joint[34,35] and cartilage degradation within the knee. The presence of a low quadriceps to hamstring ratio (r=0.6) and lower quadriceps strength index (r=0.39) 6 months post-ACLR have been associated with the development of knee OA[36]. Finally, deficits in quadriceps strength are associated with increased joint space narrowing(JSN), an indicator of knee OA, at 4 years post-ACLR[37]. In the case of these studies, the authors called for additional research to evaluate quadriceps strength in conjunction with quantifiable measures of knee tibiofemoral cartilage health in order to better understand the pathogenesis of posttraumatic knee OA.

In the identification and diagnosis of knee OA, the ability to obtain accurate imaging of knee cartilage may allow for the development of appropriate interventions to ensure a higher quality of life in the patient post-surgery[38-40]. Radiographs are currently used as a method to diagnosis knee OA. However, this technique is limited as radiography depends on indirect measures of cartilage via quantification of the joint space width or the presence of osteophyte formation due to its inability to view cartilage directly[41]. Magnetic resonance imaging (MRI) is more sensitive for identifying structural damage to knee cartilage[42]. Structural MRI has been used to identify damage to the cartilage by evaluating cartilage thickness over time through

consecutive imaging sessions. It is important to consider, however, that at the earliest stages of knee OA, there are alterations in cartilage composition prior to changes in the overall thickness of the cartilage[43]. Structural MRI is unable to capture these early cartilage alterations, and thus is limited in its capacity to capture the earliest stages of OA. These limitations in current conventional techniques call for procedures capable of identifying alterations in cartilage at a compositional level[44].

T1rho MRI imaging is emerging as a technique that enables researchers to quantify changes in knee cartilage before structural deformations occur[25]. T1rho evaluates movement of water molecules as they progress through the hyaline cartilage of the knee, measured in milliseconds (ms). Healthy cartilage consists of a high quantity of proteoglycans (PGs) and glycosaminoglycans (GAGs). These cellular constituents of cartilage influence the movement of water molecules through the cartilage tissue. In cartilage that has experienced compositional damage, the densities of PGs and GAGs are reduced, resulting in a more rapid movement of water within the cartilage and consequently an elevated T1rho relaxation time[45]. The ability of T1rho imaging to provide information regarding proteoglycan density permits it to be used to identify cartilage that is in a pre-OA state.

Early identification of modifiable contributing factors to the development of OA will aid clinicians in the selection of interventions that could prevent OA development. Quadriceps weakness has previously been reported as a contributor to OA development[35], but the relationship between muscle strength and early compositional changes to cartilage has only recently begun to be explored. T1rho

MRI is a current imaging technique that reflects proteoglycan density in tibiofemoral cartilage[46] and proteoglycan depletion is an early sign of OA development. There currently is a lack of research into the relationship between quadriceps strength and proteoglycan density. Therefore, identifying the association between quadriceps strength and cartilage T1rho relaxation values post-ACLR would help build evidence of the role quadriceps strength has on very early compositional changes in a young population at risk for posttraumatic OA following ACLR. The presence of a strong association would contribute to the understanding of the role that quadriceps strength has on early changes to cartilage composition post-ACLR , and drive increased emphasis to the improvement of strength post-ACLR to facilitate long-term joint health.

Specific Aims

o Specific Aim 1: Compare T1rho relaxation times and cartilage volume between the injured and uninjured limbs at 6 months post-ACLR in 6 weight-bearing regions of interest (ROI) of the tibia and femur.

- Hypothesis: ACL injured limbs will demonstrate a higher mean T1rho relaxation time than the uninjured limbs, while exhibiting no difference in cartilage volume.

o Specific Aim 2: Identify the magnitude and direction of the association between quadriceps strength and mean T1rho relaxation times in the injured limb normalized to the uninjured limb (T1rho LSI).

- Hypothesis 1: Lower quadriceps strength of the injured limb will be moderately associated with elevated T1rho LSI in the weight bearing ROI of the femur and the tibia.

- Hypothesis 2: Lower quadriceps strength LSI will be moderately correlated with elevated T1rho LSI.

Clinical significance

Determination of the association between T1rho relaxation times and quadriceps isometric strength will add to the body of evidence highlighting the role of quadriceps muscle strength in cartilage health post-ACLR. If a moderate negative correlation exists between quadriceps strength and the T1rho relaxation times, added emphasis should be placed on regaining quadriceps strength early following ACLR and maintain quadriceps strength following ACLR in order to promote long-term cartilage health and decrease the risk of developing OA.

CHAPTER II

Cartilage Health and Function

Any discussion of tibiofemoral OA must begin with having a prior understanding of cartilage structure. The hyaline cartilage that comprises the tibiofemoral joint is generally between 3 to 4mm thick and covers the regions of the medial and lateral femoral condyles, as well as the medial and lateral tibial plateaus[39]. The tissue composition is 65% to 85% water, with the remaining weight comprising of an extracellular matrix consisting of type II collagen (15-20%), proteoglycans (3-10%)[39], and cartilage-producing chondrocytes (less than 10%)[47].

The structural organization of cartilage consists of various layers of tissue through a complex extracellular matrix[48]. The superficial layer of cartilage is arranged as to create a low friction surface to promote the arthrokinetic motions of roll and glide. This layer consists of thin elongated chondrocytes with fibers resting parallel to the surface and is densely packed with type II collagen[47]. This results in cartilage that is strong, but has a limited capacity to heal itself due to its avascular nature[47]. If damage is sustained by the superficial layer, the chondrocytes will lay down type I cartilage or a fibrocartilaginous scar tissue which lacks the load bearing capacity of the original type II collagen[49].

The second, or transitional layer consists of larger diameter fibers that are randomly dispersed through the tissue matrix. It has chondrocytes which are more metabolically active, which provide an increased capacity for collagen remodeling and healing[50]. The deep zone contains still larger chondrocyte fibers that are oriented vertically relative to the underlying bone and articular surface. This zone's high proteoglycan and water content lend this layer to be better suited to resist compressive forces[47].

Proteoglycans are a vital constituent of cartilage health that are synthesized by the chondrocytes, and consist of glycosaminoglycans attached to a protein core. Proteoglycans are hydrophilic, which enables them to draw water from the extracellular matrix. This generates a "swelling" pressure which serves to counteract the pressure experienced by the cartilage during weight-bearing that drives water out of the extracellular matrix[51]. Due to this interaction, the distribution of proteoglycans in the tibiofemoral cartilage is not homogenous throughout the tissue[48]. Specifically, the portions of the cartilage that are subject to greater compression stress show higher content of proteoglycans, which makes these areas stiffer and better able to resist deformation[52]. The density of proteoglycans is found to be almost 34% higher in the weight-bearing zones of the tibiofemoral cartilage relative to non-weight-bearing sections[53].

With proteoglycans being vital to the healthy structure of cartilage, their damage and subsequent depletion has highly deleterious effects on cartilage integrity and stiffness[49,54]. A study conducted by Saar et al. found that human cartilage deforms at

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significantly lower levels of compression in proteoglycan-depleted cartilage than in healthy cartilage[51].

ACL Injury Role in Knee OA Development

Anterior cruciate ligament (ACL) injury commonly occurs within the athletic population[1]. Oftentimes, reconstructive surgery (ACLR) is used in an attempt to recoup stability in the knee joint in the younger or more physically active patient population[55]. However, a recent review of the literature found that patients who had received ACLR were diagnosed with an increased prevalence of tibiofemoral osteoarthritis (OA): 44% of those who received ACLR as opposed to the 37% of those who did not receive surgery[7]. This indicates that while ACLR is promoted as a procedure to help provide ligamentous stability and help the athlete return to previous activity levels, ACLR does not provide protection against concurrent slow-developing pathologies. The odds ratio for developing OA post-ACL surgery is 4.2 (3.11,5.99)[56] to 7.0 (3.5-13.9)[57]. This means that those who have had an ACL injury and concomitant surgery are 4 to 7 times more likely to develop knee OA than healthy individuals.

With regards to the timing of knee OA, there has traditionally been a noted range of time of 10[16] to 15[57] years between ACLR surgery and the consequent diagnosis of OA. In the research conducted by Nordenvall et al. evidence of radiographic tibiofemoral OA was found in 10% of patients post-ACLR. In a study conducted by Von Porat et al., 78% of patients had noted structural changes evidenced by radiograph in the respective injured knee within 14 years of surgery. Of those with

structural changes, 41% had structural deformities severe enough to qualify them to be diagnosed with OA[58].

The development of cartilage degeneration after ACLR is initiated and driven by a variety of factors[17]. One study evaluated 62 subjects after ACLR surgery and evaluated for 10 different variables to identify characteristics that could be utilized to identify those who are at risk for post-traumatic tibiofemoral OA. Of the 10, the variables that showed the strongest discriminators for developing OA were the presence of meniscus damage/meniscectomy (r= 0.72) receiving chondral damage in the initial injury (r=0.41) and the presence of a weak quadriceps muscle group (r=0.39)[36]. Another strong contributor to the development of post-traumatic OA is the presence and severity of bone marrow lesions[19,59].

Damage to Cartilage

Injuries to the ACL are generally classified as pertaining to one of two categories due to their mechanism, contact or noncontact, with almost 70% of the injuries seen being attributed to a noncontact mechanism[55]. During noncontact injury, the patient is generally cutting, jumping, or pivoting on one leg. The vertical loading from the jump results in a force of approximately 6 times the patient's bodyweight that is experienced by the tibiofemoral joint[60]. At impact, the tibiofemoral cartilage is subjected to a high degree of stress by the compressive and shear loads placed upon it, resulting in damage to the cartilage as well as the ACL[9]. Injuries to the tibial plateau have been found to be significantly dependent on the loading position of the knee at time of injury. Levine et al., while observing cadaveric knees

placed under load, found that that while no relationship existed between stabilizing

structures of the knee joint and loading patterns for ACL injury, tibial plateau injury

patterns were significantly dependent on their respective loading condition for

cartilage damage[61]. This finding was corroborated by an observational analysis

completed by Potter et al. This study observed the damage sustained by the

cartilage in a ACL injury over the course of 11 years using a cohort of 40 subjects

who had experienced an isolated ACL tear. 2 subjects suffered a subsequent ACL

tear in the course of the study, bringing the total knees observed to 42 knees. Of the

42 knees injured in the course of the study, all of the patients had visible damage to

the cartilage along the lateral tibial plateau at the time of initial injury as visualized by

MRI[9]. An arthroscopic study done by Hirose et al., found that in 23 subjects who had

a traumatic ACL tear, 15 of them experienced damage to the articular cartilage. Of

those who experienced damage, 8 had damage isolated to the medial femoral

condyle (MFC), 5 had damage to both medial and lateral femoral condyles(LFC),

and 2 had damage to the MFC, LFC and lateral tibial plateaus (LTP)[62].

Cartilage is a dynamic structure whose thickness[63] and composition[64] are

subject to change. In a study by Frobell et al., 61 subjects had MRI measurements

of their tibiofemoral cartilage over the course of 2 years at the 3, 6, 12, and 12 month

post-ACL injury time points. Frobell found that cartilage thickened over central

medial aspect of femur (+2.7% percentage change) and significantly thinned in

posterior femur in the medial (-2.6% change) lateral zones (-2.6% change)[65]. This

change in cartilage thickness profile is due to the altered loads placed upon the knee

and associated up or down regulation of chondrocyte metabolism[23,66].

Bone Marrow Lesion

In an ACL injury, not only is the cartilage acutely damaged but there is the damage to the underlying subchondral bone[61]. This is associated with a pattern of bruising which extends from the cortical layer of bone into the deeper tissue, described in the literature as a bone bruise (BB) or bone marrow lesion (BML). BML are found in conjunction with an ACL injury in 30-70% of the instances[67]. BML will appear on an MRI as increased signal intensity in the subchondral bone near the osteochondral junction[68]. BMLs are more often found on the lateral side of the knee due to the increased abduction moment experienced by the knee in noncontact ACL injuries[69-71]. The presence of BML have been seen at the time of injury[43,59,63,65,72,73] and will generally decrease in size over time[43]. In a study by Frobell in 2011, at diagnosis of ACL tear, 95% of the subject's knees presented with posttraumatic BML in the lateral aspect of the tibial plateau with a mean volume 12.9 mL. Additionally, 77% of the subjects demonstrated the presence of BML on lateral aspect of femoral condyle with a mean volume of 6.9 mL. At 2 years post-injury, there was a complete resolution of BML for 54 of the knees in the lateral compartment of tibia and for 44 of the knees in the lateral portion of the femur. During this time however, 21 knees developed new lesions post-surgery over the lateral portion of the femur and the tibia[65].

The presence of BML is relevant because the size of bone marrow edema pattern at baseline has been found to be significantly associated with increased cartilage loss at year 1 ($p=0.001$), year 2 ($p=0.008$) and year 3 ($p=0.039$) post-injury[9].

The Meniscus

The meniscus contributes to filling the joint space between the femur and the tibia. This structure consists of a C-shaped medial meniscus and an O-shaped lateral meniscus, each consisting of an anterior, central, and posterior horn. They are split into 2 zones: with the larger inner zone comprised primarily of type II collagen and being unvascularized, with the outer zone being smaller, vascularized, and comprised of type I collagen[74]. The menisci serve two roles in relationship to a healthy knee joint: they serve to provide stability to the tibiofemoral joint by increasing surface congruity between the convex femur and the flat tibia and they also serve to help distribute forces in the knee to help protect the articular cartilage. The force distribution of the meniscus ranges between 44% and 78% of the vertical compression load. Additionally, 61% to 81% of posterior shear force is attenuated by the meniscus as the knee moves through flexion[75].

Damage to the meniscus is often found in conjunction with an acute ACL tear[2]. This happens due to the mechanism of injury that damaged the ACL ligament and articular cartilage[76-79]. Damage to the meniscus, regardless if it occurs in the medial or lateral portions; results in increased compression of the tibiofemoral joint space, as well increase in the anterior/posterior shear forces experienced by the knee joint[78,79]. After damage to the meniscus has been sustained, the likelihood of damaging the hyaline cartilage rises to as high as 80% in the section of the knee associated with the meniscus tear[76,80] or an odds ratio of 6.9[81].

Traditionally, knee osteoarthritis has been viewed as a mechanically driven pathology[82]. After ACL injury, mechanical changes to the loads placed upon the knee cartilage do not completely explain the variability in time from injury to diagnosis of knee OA. Damage to the cruciate ligaments, joint capsule, and other synovial tissue cause a metabolic cascade of inflammatory mediators. This has led to research of looking at chemical biomarkers in an attempt to identify possible factors that contribute to the increased damage of cartilage and incidence of OA[72].

The cartilage building block of proteoglycans are structured with a protein core with glycosaminoglycan (GAG) side chains. These have been found to be sensitive to inflammatory cytokines which accelerate the degradation of PGs and GAG's in cartilage to a significant extent[83,84]. One particular inflammatory mediator that has been shown to cause cartilage degradation is the presence of Intra-articular Interleukin (IL)-1[85]. This cytokine triggers the release of release of matrix metalloproteinases (MMP)[86]. This collection of cytokines affect the cartilage in two manners; primarily by breaking the GAG chains[87], and secondarily by activating procolleganase which functions to catabolize the cartilaginous matrix[88].

Quadriceps Muscle Group and OA development Post-ACLR

In order to maintain a healthy joint, there needs to be a balance between the internal and external forces that the joint experiences at any given point in the sagittal and frontal plane movements[89]. The quadriceps muscle group achieves this

balance by co-contracting with the hamstrings during closed kinetic chain tasks in order to help promote joint congruency and stability[90].

Quadriceps Strength Post-ACLR

While there has been some argument regarding the role of the of the quadriceps in the initial noncontact ACL injury[91], there is widespread recognition that the strength of the quadriceps muscle is drastically reduced post-ACL injury and subsequent surgery[92]. These deficits are present as soon as at 1 month post-ACLR[30]. In the study previously mentioned, isometric quadriceps strength was compared between injured and uninjured control groups at various time-points after ACLR. In this study, the average torque produced by injured knees was 83 Nm, while the corresponding limb in uninjured control subjects generated 210 Nm[30]. This lack of strength is not isolated to being found shortly after injury, with deficits being observed at 3-4 years or more post-surgery[32,93].

Deficits in quadriceps strength have been found to be predictive of limitations in self-reported function post-ACLR[31]. One study viewed the relationship between quadriceps strength and different functional tests at 6 months post-surgery. The authors found ACLR patients who reported low levels of knee function, measured by having a mean IKDC (International Knee Documentation Committee) survey score of 74.7, also presented with a diminished quadriceps strength LSI of 0.80 between the injured and healthy knees. This is a noted difference from those reported higher levels of function via a mean IKDC score of 92, who demonstrated a LSI of 0.94[94].

While knee extensor strength has been recognized for its role in the function of healthy knees, recent reviews of the literature found that there is no universal standard for identifying when an athlete is cleared to return to play post-ACLR[95,96]. In a review conducted by Lynch et al., the authors suggested that ACLR limbs need to demonstrate quadriceps strength between 85% and 95% of the uninjured limb in order to be termed a successful outcome. In more recent years, more functional and quantifiable measures of quadriceps strength have been used to evaluate quadriceps strength post-ACLR. In a study by Kuenze et al., 22 ACLR subjects at 31 months post-surgery were matched with 24 uninjured controls. The variable of interest was the maximal voluntary isometric contraction (MVIC) of the quadriceps muscle group normalized to body mass (Nm/Kg) as well as the quadriceps strength limb symmetry index (LSI) (injured/uninjured). Those who had experienced ACLR were found to have a MVIC of 2.46(Nm/kg) with an LSI of 0.85 between the injured and uninjured knees, as opposed to a 2.72(Nm/kg) and LSI of 0.97 for the control group. Using a receiver-operator characteristic (ROC) curve, a clinical threshold was suggested to maximize patient reported outcomes of increased functionality and decreased pain and limitation post-ACLR. The identified threshold was an MVIC of 3.0(Nm/kg) and a LSI strength index of 0.94[97].

Quadriceps Strength Reduction and Biomechanics

The quadriceps muscle group is one of the largest and strongest muscle groups in the leg[98]. This being the case, quadriceps strength is invaluable to healthy knee joint mechanics by contributing to the control of forces acting on the knee[99]. In

the study previously mentioned[99], quadriceps strength was significantly correlated with the peak knee flexion angle during the first 50% of stance phase in walking gait. Greater knee flexion angles place higher demand on quadriceps, noted by the correlation between knee flexion angle and flexion moment (r=0.66)[99].

Strength losses post-ACLR surgery have a net result of changing the kinematics of the knee joint[100]. In the afore-mentioned study, subjects who were at minimum 12 weeks post-ALR were divided into operationally "weak" and "strong" groups dependent on the quadriceps LSI, 0.80 and 0.90 respectively. Subjects in the "weak" group demonstrated showed diminished knee angle (20.99 degrees) at peak flexion in walking gait when compared to uninjured controls (26.54). Subjects classified as "strong" demonstrated no significant difference from uninjured controls[100]. Decreased knee flexion angles result in decreased surface area of the tibiofemoral cartilage which experience weight-bearing, resulting in higher loads placed upon the weight-bearing cartilage[101]. Diminished quadriceps strength is also associated with increased variance in knee angle[24], resulting in changes of the portions of the cartilage that experience the higher degrees of load[23]. These changes in forces experienced by the knee contribute to the continued development of knee OA post-ACLR[34,35].

Quadriceps Strength and OA

Quadriceps strength deficits are a common development post-ACLR[92] as well as being found in conjunction with knee OA[102,103]. This results in questions regarding the nature of the relationship between quadriceps strength and the role that it plays

in OA pathogenesis and development. Currently the literature is conflicting regarding the presence and nature of this relationship. Previous studies viewing the association between radiographic OA and quadriceps strength have found results ranging from there being no relationship between the two[104], no protective effect of strength to incidence of OA- but there being a reported decrease in pain (p<0.002) and increased function as strength improved (p<0.0001)[105], to there being a protective effect for increased quadriceps strength against patellofemoral cartilage loss[106], to increased strength protecting against the progression of tibiofemoral OA[35]. This spectrum is due to the fact that many previous studies defined OA as being able to be seen and captured by radiograph. In the review by Segal et al., it was noted that while research which viewed the relationship between strength of the quadriceps muscle group and radiographic changes to cartilage found no association between the two; research which evaluated quadriceps strength in conjunction with the developmental stages of OA found the inverse to be true[34], suggesting that quadriceps strength could be more impactful on cartilage health than previous research would have suggested. In all cases, authors called for more research using techniques more sensitive then radiography in order to better identify the relationship and role of quadriceps strength and the early development of knee OA[21,34,107].

Imaging of Knee OA

Diagnosis of the entity of post-traumatic osteoarthritis can be very difficult due to the lack of readily available and simple orthopedic testing aside from monitoring a patient's history and pain[108]. The use of diagnostic imaging in this case is therefore

vital to identify the scope and severity of cartilage damage[109]. Due to the long-term implications of being diagnosed with OA, the more rapid diagnosis and location of degenerative changes in the hyaline cartilage allows for more rapid treatment and improved strategies to maximize patient outcomes by preventing the development of knee OA.

Radiography

Radiography is a classic staple for the development of knee OA due its ease of use and cost-effective nature. It is important to note however, that when viewing cartilaginous structures that radiography is limited. Due to a lack of ability to capture cartilage directly, radiography relies on tracking cartilage health through indirect measures- namely the presence and development of osteophytes and the narrowing of the tibiofemoral joint space, using systems such as the Kellgren-Lawrence Grading Scale[110].

The presence of marginal osteophytes in the tibiofemoral joint space has been demonstrated to be a measure used to identify knee OA. A meta-analysis demonstrated that 20% of those who have sustained an ACL injury demonstrate "moderate to severe" changes in the cartilage as measured by radiography as opposed to 4.9% in the control group- representing a 4x increase in risk[111] to the cartilage post-ACL injury. The use of radiography however has been shown to be not particularly sensitive to evaluating early changes in cartilage degeneration. In a study by Kijowski et al., 125 patients with tibiofemoral OA were evaluated via radiography and had their OA scores compared with values gained by arthroscopy.

The sensitivity of measuring osteophytes and OA progression in the medial compartment of the knee was 67% in identifying a true positive, and a specificity of 73% in identifying a true negative. The values of the lateral compartment were less sensitive, 49%, however it was more specific, 81%. This study also reviewed the sensitivity and specificity of measuring for the presence of joint space narrowing (JSN) in the medial and lateral compartments of the tibiofemoral joint. While the specificity, or true positive, of JSN was low for the medial (46%) and lateral (7%) compartments, the specificity was very high for both compartments (95%) and (100%) respectively. This means that by the time that JSN is found on radiography, OA has already developed in the evaluated limb[112].

It is important to note that in the time that there is sufficient change in osteophyte formation and JSN to be indicative for knee OA, there has been a loss of 11%-13% in cartilage volume as measured by MRI[113]. As a result, more sensitive means of imaging are needed to identify early changes to cartilage structure and health than are offered via radiography.

Magnetic Resonance Imaging

The use of magnetic resonance imaging has been increasing in recent years as related to knee OA identification and tracking due to its multiplanar imaging, tissue contract, and lack of invasiveness. It is used clinically when attempting to visualize tissue that is not readily visible on radiographs; such as the cruciate ligaments, meniscus, and knee hyaline cartilage[43]. Clinical magnetic resonance imaging (MRI) will oftentimes use a "fat-suppressed" model to the increase contrast

between tissues to be better able to identify defects in the cartilage[38]. It is important to note that the use of MRI serves to provide a snapshot of the body segment of interest at any given moment and serial images need to be taken to track changes over time, particularly in the case of knee OA where changes can be insidious[9,43,65,114].

While tracking changes to the knee cartilage in OA, it is important to have a grading system in order to classify and the levels of damage. One of the best has shown to be the whole organ magnetic resonance imaging score (WORMS). A given knee is classified by the thickness of the cartilage and its corresponding signal. Healthy, undamaged cartilage is scored as a 0, signifying normal thickness and signal. Early chondral defects of 1 signify normal cartilage thickness but with an increased signal. The score of 2 identifies a partial thickness focal defect that is less than 1 cm in width. A score of 3 signifies the presence of either multiple areas of partial thickness defects mixed with areas of normal thickness or a grade 2 defect wider than 1 cm but less than 75% of the region. For a knee to be scored as a 4, there needs to be diffuse regional partial thickness loss that extends for more than 75% of the cartilage. To score a 5 identifies multiple areas of full thickness loss or a grade 2.5 lesion wider than 1 cm but less then 75% of the region. Finally, scoring 6 signals the presence of full thickness loss of the cartilage. The normal WORMS paradigm has been shown to be a reliable measure for grading cartilage health[115].

T1rho

Recent developments in imaging have brought about the creation of quantitative MRI techniques[39,40]. These allow the clinician to quantifiably measure components of the tissue of interest[45]. Regarding the study of OA, the technique of T1rho has been found to be able to accurately measure proteoglycan density via measuring the motion interaction between water and the local macromolecule environment[116,117]. This provides the clinician the capability to identify the breakdown of cartilage by measuring proteoglycan (PG) depletion in the cartilage[38]. PG depletion is identified when the values for a particular region of interest are elevated as the lack of PGs result in a decrease of free water and a resulting increase in T1rho mean relaxation time[118].

The use of T1rho to identify cartilage health post-ACLR has been shown to be effective. T1rho imaging has able to identify PG health at injury baseline and reductions of PG density as recently as 6 to 12 months post-ACLR[46,119]. This was evidenced in a study completed by Theologis et al., in which 18 subjects had T1rho imaging done in order to evaluate the health of the tibiofemoral cartilage at the 12 and 16 months post-ACLR. Each patients' knee was divided sagittally into medial and lateral portions, each of which was further divided into 8 different regions of interest (ROI); 5 on the femur, 3 on the tibia. The results showed evidence of changes to the T1rho relaxation times in the weight-bearing zone of the medial tibial plateau and femoral condyle at 12-16 months post-ACLR, with no notable difference in cartilage thickness between injured and healthy knees. The opposite was found to be true in the lateral compartment, with the T1rho was unchanged, but the thickness

profiles for the lateral femoral condyle and tibial plateau were significantly thinner. Sub-compartment analysis of the medial tibia revealed the weight-bearing region had greater T1rho and thinner cartilage compared to the uninjured knee. The medial femoral cartilage's most anterior compartment and weight-bearing regions demonstrated greater T1rho relaxation times in the injured knee when compared to the same region in the uninjured knee[80].

The sensitivity of T1ro to identifying pre-osteoarthritic changes has been well documented[120]. Research done by Gubta et al., found T1rho presented with elevated values for the whole knee when compared with what was quantified as normal cartilage via arthroscopy and traditional magnetic resonance imaging at time of ACLR surgery. Statistically significant elevations were seen in the lateral tibia at the superficial (p=0.03), deep (p=0.04), and full thickness (p=0.02) cartilage defects. T1rho relaxation times were also seen to increase as severity of arthroscopic lesion increased in the superficial and deep regions of the knee. This leads to the conclusion being drawn that T1rho is more sensitive than arthroscopy when viewing small cartilage lesions at time of ACLR[121]. The increase in lesions experienced by the lateral compartment is not surprising when bearing in mind the shear and rotational component that is experienced at the time of ACL injury and the resulting apoptosis of chondrocytes[9].

The use of T1rho has also been helpful in illustrating the damage to the cartilage in relationship to the presence of bone marrow lesions (BML). In research conducted by Bolbos et al., the knee joint of 16 patients with concurrent ACL tear and 15 healthy controls was compared via use of T1rho. BMLs were present in all of

the subjects. The lesions experienced were distributed so 81% of patients had BML present on the lateral tibia, 56% had BML present on the lateral femoral condyle, and 44% had BML to both regions. After T1rho imaging, the results were that cartilage values in the cartilage overlaying the BML was significantly increased over the lateral tibia, (47.15ms ±12.96ms (p=0.002) when compared to the control of uninjured cartilage[122].

Abnormal tibiofemoral kinematics following ACLR have been associated with increased cartilage degradation[25,123]. In the study by Haughom et al., 11 subjects had MRI images acquired at 18 months post-ACLR surgery. T1rho relaxation times were significantly increased in the general medial femoral cartilage with injured knees having a mean T1rho relaxation time of 42.6±3.7ms and with healthy knees demonstrating a mean relaxation time of 39.8±3.3ms and a p value of 0.04. This difference was more pronounced when investigators looked specifically at the weight-bearing portion of the medial femoral cartilage, with the cartilage-injured knees demonstrating a mean T1rho relaxation time of 42.2±5.9ms, while healthy knees presented with a mean T1rho relaxation time of 38.5±4.0ms, with the resulting p being equal to 0.01[25]. In measuring anterior tibial translation(ATT), there was a statistically significant increase in the T1rho relaxation times for those patients categorized as having abnormal ATT, suggesting that there is a possible link between altered kinematics after ACLR and early damage to the cartilage.

Chapter III

METHODS

Participants

All participants were between 18-35 years of age and were recruited to the study within 14 days of sustaining an ACL injury. Recruitment occurred upon initial presentation at an orthopedic clinic. Prior to inclusion into the study, an orthopedic physician confirmed ACL rupture via clinical exam and anatomical MRI. Measurements of the variables of interest were completed at 6 months post-ACLR.

We excluded females who were currently pregnant or planning on becoming pregnant within the course of the study, patients who had a prior diagnosis of inflammatory arthritis, surgery consisting of the reconstruction of multiple structures within the injured knee, or those declining to undergo ACLR. Subjects who exhibited the presence of a cardiac pacemaker, cochlear implant, clinical hypertension, claustrophobia, hepatic diseases or seizures were also excluded.

Contact and scheduling of participants was completed via phone and email correspondence by study personnel. Follow up visits were completed at the Sports Medicine Research Lab (SMRL) on the campus of the University of North Carolina at Chapel Hill. All participating subjects signed the appropriate informed consent form

that was approved by the Institutional Review Board at the University of North Carolina at Chapel Hill.

ACLR and Therapeutic Rehabilitation

All participants received a patellar tendon autograft performed by one of the three orthopedic surgeons participating in the study. Following the completed ACLR surgery, study participants were referred to either a licensed physical therapist or athletic trainer for a supervised rehabilitation program. This program began during the first week post-ACLR and was deemed complete when the patient was able to return to activity.

Procedures

Quadriceps Strength Measurement

Isometric quadriceps strength was tested at 6 months post-ACLR using a HUMAC Norm dynamometer (Computer Sports Medicine Inc., Stoughton, MA). The variable of interest was quadriceps MVIC in both the ACLR limb and contralateral limb. The order of limbs being tested was selected randomly (ACLR vs. contralateral). The subject was seated in the HUMAC and positioned in 85 degrees of hip flexion and 90 degrees of knee flexion[31]. The adjustable straps on the dynamometer were then used to secure the pelvis and torso of the test subject. This, coupled with the instruction for the subject to maintain the position of arms crossed in front of the chest, helped isolate the generation of force to the quadriceps musculature[124]. After confirming that the axis of rotation for the lever arm would pass

through the middle of the tibiofemoral joint, the lever arm was secured to the leg at 3 cm above the ankle mortise.

Participants were acclimatized to the testing procedure through the use of a progressive "warm-up" of isometric contractions[31]. The subjects were instructed to "kick out" into the lever arm while attempting to reach a given percentage of their perceived maximum effort[124]. Participants maintained each contraction for 2 seconds at 25%, 50%, and 75% of maximal effort[125]. Following the warm-up, the participants performed 3 to 5 maximal voluntary isometric contractions, spaced 60 seconds apart until the peak torque in the limb being tested was within 10% of the previous trial in two consecutive trials[31]. The torque produced during the three highest trials was averaged and used to set a target torque threshold for test trials.

Two maximal effort tests were completed in which the torque met or surpassed the torque threshold. The torque signal was sampled at 2000Hz and low pass filtered at 50 Hz (zero-phase shift, fourth-order Butterworth)[31]. The maximum torque produced in these two trials was normalized to body mass and averaged as the variable of interest for quadriceps strength. The limb symmetry index (LSI) for quadriceps strength was calculated by dividing the injured limb by the uninjured limb.

Magnetic Resonance Imaging of the Articular Cartilage

Magnetic Resonance Acquisition

T1rho MRI images were sampled using a Siemens Magnetom TIM Trio 3T scanner with a 4-channel Siemens large flex coil (516 mm × 224 mm, Siemens,

Munich, Germany). Participants arrived at our biomedical-imaging center 30 minutes prior to the scan and remained seated to unload the knee cartilage prior to the scan. The injured knee was scanned prior to the contralateral knee. For imaging, we used a T1rho prepared three-dimensional Fast Low Angle Shot (FLASH) with a spin lock power at 500 Hz, five different spin lock durations (40, 30, 20,10, 0 ms) and a voxel size of 0.8 mm x 0.4 mm x 3 mm (field of view =288 mm, slice thickness = 3.0 mm, TR = 9.2 ms, 160 × 320 matrix, gap = 0 mm, flip angle = 10 degrees, echo train duration time = 443 ms, phase encode direction of anterior/posterior).

Articular Cartilage Segmentation

A single investigator manually segmented the tibiofemoral articular cartilage on the 0ms spin lock duration T1rho image using the ITK Snap software. A musculoskeletal radiologist confirmed anatomical accuracy of segmentations. The weight-bearing regions of medial and lateral femoral condyles and medial and lateral tibial plateaus were each identified and sub-sectioned into 3 regions of interest (ROI) based on the representation of the meniscus in the sagittal plane.

The femoral condyles were segmented anterior to posterior by identifying the weight-bearing portions of the cartilage via their contact and positioning relative to the meniscus. The first ROI (MFC 1/LFC 1) comprised of the portion of the cartilage superior to the region demarcated by the borders of the anterior horn of the meniscus. The second ROI (MFC 2/LFC 2) comprised of the cartilage superior to the zone between the anterior horn of the meniscus and the posterior horn of the

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meniscus. The third ROI (MFC 3/LFC 3) comprised the cartilage superior to the posterior horn of the meniscus[80].

The tibial plateaus were segmented anterior to posterior by identifying the cartilage in relationship to the position of the meniscus. The first region of interest (MTC 1/LTC 1) comprised of the portion of the cartilage inferior to the region demarcated by the anterior horn of the meniscus. The second region of interest (MTC 2/LTC 2) comprised of the cartilage inferior to the zone between the anterior horn of the meniscus and the posterior horn of the meniscus. The third region of interest (MFC 3/LFC3) comprised the cartilage inferior posterior horn of the meniscus[80].

T1rho Relaxation Time Quantification

Voxel by voxel T1rho relaxation times were calculated from a five-image sequence created with a MatLab program (MatLab R2014b [8.4.0] MathWorks, Natick, MA, USA) using the following equation: $S(TSL) = S_0 \exp(-TSL/T1rho)$. In this equation S corresponds to signal, TSL is the length of the spin-lock time, S_0 is signal intensity when TSL equals zero, and T1rho is the T1 relaxation time in the rotating frame. The segmented T1-weighted MRI image was overlaid onto the calculated T1rho image to determine T1rho relaxation times for the above ROIs. Mean T1rho relaxation times were extracted for each ROI and used for analyses. Greater T1rho relaxation times were interpreted as being associated with lesser proteoglycan density.

Based on previous studies which looked at the strength of the association between isometric measures of quadriceps strength and quantitative MRI (T2 mapping), we estimated that there would be moderate correlations between mean T1rho relaxation times and isometric quadriceps strength[126]. We determined that at α=0.05, with a power analysis of 1-β=0.8, to find a moderate correlation of 0.45, 29 subjects would be needed in order to determine statistical significance.

Statistics

Statistical analyses were completed using SPSS Statistical Software (SPSS, Version 23.0, IBM Corp., Somers, NY).

The mean T1rho relaxation times and measure of cartilage volume were generated for the 6 weight-bearing regions of interest of the tibiofemoral cartilage in each subject's injured and uninjured knees using the ITK-Snap software[127]. After having gathered the mean relaxation times for each compartment, a LSI was then calculated (injured/uninjured) to evaluate the symmetry between the injured and uninjured knees in each respective region of interest (Table 6). An LSI was not calculated for cartilage volume.

To establish reliability of imaging segmentations, inter- and intra-rater reliability was calculated using intra-class correlation coefficients (ICC). Levels of reliability were previously established, with (ICC $_{2,1}$ <0.49) demonstrating a low level of agreement, (ICC $_{2,1}$=0.5-0.75) demonstrating moderate agreement, and (ICC $_{2,1}$ > 0.76) being a high level of agreement. Inter-rater reliability was completed by re-segmenting a subset of 10 randomly selected knees previously segmented by a separate trained investigator. The investigator being evaluated was blinded to the

scores and segmentations of the previously segmented knees (Table 2). Intra-rater

reliability was completed by re-segmenting a subset 10 randomly segmented knee

that had been segmented more than 6 months previously by the same investigator

(Table 3). Standard error of the measurement(SEM) was calculated for both the

inter- and intra-rater reliability measures to establish the precision of the

measurements. SEM was calculated as $SD\sqrt{1 - ICC}$.

Intra-rater reliability was also assessed for the cartilage volume of each ROI

(Table 3). Cartilage volume was used to determine if there were differences in the

volume of each ROI between the injured and uninjured limb.

To identify differences between injured and uninjured knees at 6 months

post-ACLR separate paired t-tests were used to compare the mean T1rho relaxation

time and cartilage volume for each sub region of cartilage (MFC 1/LFC 1, MFC

2/LFC 2, MFC 3/LFC 3, MTC 1/LTC 1, MTC 2/LTC 2, MTC 3/LTC 3) between limbs.

The statistical significance was set *a priori* at α=0.05 for all comparisons.

Our second aim was to identify the presence of an association between

quadriceps strength and mean T1rho relaxation times. When assessing for normality

using Shapiro Wilks (p<0.05), the data for some of the ROIs were non-normally

distributed (LFC 1 injured, LTC 3 injured, LTC 2 injured, MTC 1 injured, LFC 1

uninjured, LTC 3 uninjured, LTC 2 uninjured, LTC 1 uninjured, MFC 2 uninjured).

Pearson Product Moment correlations were used to determine the association

between quadriceps strength and T1rho LSI when the data was normally distributed.

Spearman's Rank Order coefficient was calculated when data was non-normally

distributed. We determined the associations between 1) quadriceps strength of the

injured limb and the T1rho LSI of the following ROIs: (MFC 1/LFC 1, MFC 2/LFC 2, MFC 3/LFC 3, MTC 1/LTC 1, MTC 2/LTC 2, MTC 3/LTC 3), 2) quadriceps strength LSI and the T1rho LSI of the ROIs listed above. For post hoc analysis, partial correlations were used to evaluate the effect of patient-reported pain during activity, measured by the KOOS pain subscale[128] at 6 months post injury, on significant associations between quadriceps strength and T1rho values.

Results

Thirty subjects participated in the study. Two subjects were unable to complete strength testing for the injured knee at 6 months post-ACLR due to pain and were excluded from statistical analysis. Four additional subjects were excluded due to a history of ACL injury prior to the injury which qualified them for the study. Bilateral T1rho MRI and strength outcomes were collected for the remaining 24 subjects, and their demographics are presented in Table 1.

T1rho Segmentation

Inter-Rater Reliability

There was a high level of inter-rater absolute agreement (ICC $_{2,1}$ ≥ 0.80 for all ROI) between the novice and trained investigator for the T1rho mean relaxation times for each ROI. Additionally, there was high inter-rater consistency (ICC $_{2,1}$ ≥ 0.84) for all ROI. Inter-rater reliability for cartilage volume demonstrated a range of agreement, with the majority of the ROI demonstrating moderate to high absolute

agreement and consistency (ICC $_{2,1}$ ≥ 0.60), with one region of interest (MFC 1) showing a low level of agreement for both absolute agreement (ICC $_{2,1}$ = 0.202) and consistency (ICC $_{2,1}$ = 0.210) (Table 2).

Intra-Rater Reliability

The intra-rater reliability for T1rho relaxation times was high (ICC $_{2,1}$ ≥ 0.70) for absolute agreement, as well as for consistency (ICC $_{2,1}$ ≥ 0.70). Intra-rater reliability of the cartilage volume measure was also evaluated (Table 5, Intra-rater reliability of cartilage volume). High reliability was found in both the absolute agreement (ICC $_{2,1}$ ≥ 0.82) and the consistency measures (ICC $_{2,1}$ ≥ 0.84) (Table 3).

Differences in T1rho Relaxation Times

Significantly greater T1rho relaxation times were found in the ACLR limb compared to the contralateral limb for the region of LFC 3 (t_{23}=2.866, p=0.009), LFC 2 (t_{23}=2.793, p=0.01), LFC 1 (t_{23}=4.358, p<0.001), LTC 3 (t_{23}=2.513, p=0.019), MFC 2 (t_{23}=3.157, p=0.004), and MFC 3 (t_{23}=2.866, p=0.001) (Table 5).

Cartilage Volume

A statistically significant increase in cartilage volume between the injured and uninjured limbs was found in MTC 3 ($t_{23=}$-2.428, p=0.022). No other significant differences in cartilage volume were noted (Table 6).

Quadriceps Strength and T1rho Values

A statistically significant negative association was found between the MVIC of the injured limb with T1rho values for MFC 3 (ρ=-0.40, p=0.049; Figure 3), MFC 2 (r=-0.45, p=0.027; Figure 2), and MFC 1 (ρ=-0.46, p=0.022; Figure 1). No statistically significant associations were found between injured limb quadriceps strength for the ROI in the lateral femoral condyle or the tibia. Additionally, there were no statistically significant associations between the quadriceps strength LSI and the mean t1rho relaxation times in any of the femoral or tibial ROI.

Post Hoc Analysis

In post-hoc analysis, we controlled for the KOOS pain scale at 6-months following ACLR for the significant associations previously found between MVIC of the injured limb and the T1rho LSI. At time of analysis, only 18 subjects had completed the KOOS survey. As a result, we conducted the partial correlations using the available 18 subjects as a subset. We found that after accounting for pain the associations between MVIC and T1rho LSI for MFC 3 (r_{15}= -0.33, p=0.2), MFC 2 (r_{15}= -0.32, p=0.21), MFC 1 (r_{15}= -0.26, p=0.32) were not statistically significant.

Discussion

The most important finding of the current study was the significant negative association between injured knee quadriceps strength and T1rho LSI for the weight bearing regions of the medial femoral condyle at 6 months post-reconstruction. The significant negative association indicates that those with weaker quadriceps

demonstrated greater T1rho relaxation times in the injured knee compared to the contralateral knee. There were significantly greater T1rho relaxation times in the injured knee compared to the contralateral knee in 50% of the weight bearing ROIs, particularly in the femoral condyles. This supports our hypothesis that ACLR limbs would demonstrate a higher mean T1rho relaxation time than the contralateral limb. This indicates that there are compositional changes occurring in the cartilage in the injured limb as early as 6 months post-ACLR. This early change in cartilage composition, and evident association with quadriceps strength, illustrates the impact of muscle strength on the compositional health of cartilage and its role in post-traumatic knee osteoarthritis.

T1rho Relaxation Times

Greater T1rho relaxation times were noted in the ACLR limb in the regions of MFC 1, MFC 2, LFC 1, and LFC 2, while the remaining regions in the femur and tibia in the injured limb did not display as high of relaxation times. The greater T1rho relaxation times in the injured knees are similar to previous studies that demonstrated greater relaxation times in the medial compartment of the femur post-ACLR compared with contralateral control subjects[118] or the contralateral limb[46,80]. In a study by Osaki et al., those who underwent ACLR exhibited significantly greater T1rho relaxation times in the anterior and middle weight-bearing compartments of the medial femoral condyle at 2 years post-ACLR when compared with contralateral controls[118]. Theologis et al. identified a significantly greater relaxation time in the medial femoral condyle at the time point of 12–16 months post-ACLR when

compared to the contralateral knee[80]. The present study contributes to the current literature by noting these same elevated levels in T1rho relaxation times, but at the much earlier time point of 6 months, indicating that compositional changes to cartilage can occur much sooner than previously identified.

It is relevant that the increase in T1rho relaxation times was found when there was little difference in cartilage volume between injured and uninjured knees, with a difference in cartilage volume only being noted in MTC 3. This suggests compositional change can occur with little to no change in the cartilage volume. This concurs with the understanding that changes in the proteoglycan density can begin as early as 6 months after ACLR, which has been noted in the recent literature[62,129,130] and without visible changes to cartilage volume[131]. This is relevant to the understanding of the etiology of post-traumatic OA, since changes in cartilage composition may not be easily addressed by traditional rehabilitation techniques. Therefore, early identification of individuals at risk for developing OA could contribute to the implementation of strategies to mitigate OA development.

It is important to note that there are likely a variety of factors that result in an uneven distribution of stresses and loads on the cartilage, explaining the varied change in T1rho relaxation times. One of these proposed factors is the presence of damage to the cartilage sustained at initial injury[132]. As a result of the traumatic nature of an ACL rupture, some damage to the cartilage has been found in almost all ACL injuries when initially evaluated[9]. Due to the cross-sectional nature of the current study at 6 months post-injury, the role of initial damage to cartilage on mean T1rho relaxation time was not evaluated. This could be addressed through the

usage of serial MRI sessions, evaluating the cartilage at multiple time points and evaluating the changes in T1rho relaxation times over time.

Another mechanism for greater T1rho relaxation times is the occurrence of a meniscal tear[133]. The presence of meniscal injury results in an increased amount of compressive and shear force experienced by the underlying cartilage because of the loss of structural integrity in the meniscus[134]. The presence of meniscal tear is associated with a greater T1rho relaxation time for both the tibial and femoral cartilage [135]. While the presence of a meniscus tear was not a formal part of the investigation and analysis, we observed that the majority of the 24 subjects presented with some form of meniscal tear. Of the 24 subjects, there were 17 lateral meniscus and 2 medial meniscus tears present.

The role of functional biomechanics has been proposed as a mechanism for the development of knee OA post-ACLR[8]. Alterations in joint kinetics would bring about changes in loading experienced by knee cartilage[136] and therefore influence proteoglycan density and T1rho relaxation times. Van Rossom et al., found that T1rho relaxation times were significantly correlated with the type of tibiofemoral contact forces experienced by the knee[137]. In this study, the walking gait kinematics and T1rho relaxation times were evaluated in 15 healthy subjects. The researchers found that greater T1rho relaxation times were associated with the presence of anterior-posterior shear loading in the regions of both the medial ($r=0.69$, $p=0.008$) and lateral condyle ($r=0.7$, $p=0.007$) of the femur. Analysis of the association of compressive loading of the femoral condyles found a negative association for the lateral femoral condyle ($p=-0.59$, $p=0.03$), while no significant association was found

in the region of the medial femoral condyle[137]. Zaid et al. found that that those who had experienced ACLR demonstrated a more anterior tibial position compared to the contralateral control limb during weight-bearing MRI The anterior tibial position post-ACLR was found to be associated with greater T1rho relaxation time in the medial femoral compartment of the injured knee at 1 year post-reconstruction ($\rho=0.66$, $p=0.01$)[138], demonstrating the relationship between kinematics and relaxation times in injured subjects.

In summary, the proteoglycan content of cartilage is integral to its structural integrity. Alterations to joint kinematics post ACLR[139-142] expose the cartilage to altered wear patterns and contribute to its breakdown, exhibited by elevated T1rho relaxation times as the proteoglycan content is depleted.

Quadriceps Strength Post-ACLR

It is well documented in the current literature that there are decreases in quadriceps strength post-ACL injury immediately post-injury[143], at return to activity[144], and even as long as 20 years post-injury{Tengman, 2014 #689} compared to healthy controls. In the current study, the injured limb was found to produce just 62% of the torque generated by the contralateral limb at 6 months post-ACLR (injured=1.91nm/kg, contralateral=3.09nm/kg). The importance of regaining muscular strength post-ACL injury is readily recognized as an important part of a successful outcome[96]. In the clinical setting, in order for the patient to return to pre-injury activity, he or she is required to achieve at minimum an 80% symmetry between the injured and contralateral limb [145]. Alternatively, he or she must generate

more than 3.00Nm/Kg in knee extension [97] as part of a battery of tests[144]. The presence of a significant deficiency in injured knee quadriceps strength illustrated by a weak ($MVIC_{inj}$=1.91Nm/Kg) and a decreased MVIC LSI (0.64) in the current study raises serious concerns, due to the importance of the quadriceps muscle group not only in functional and patient-reported outcomes post-ACLR but also for its role in maintaining healthy knee function.

Quadriceps Strength Post-ACLR and Knee Function

Quadriceps strength post-ACLR has been associated with patient reported outcomes for knee health and function[31,146,147]. Pietrosimone et al. found that isometric quadriceps strength normalized to body weight displayed great accuracy (AUC=0.76; 95%, CI 0.6-0.86) for identifying a subject's high self-reported function as reported by the IKDC survey, and that subjects who demonstrated a quadriceps torque normalized to body weight of > 3.10 Nm/kg were 6 times more likely to report a high level of knee function as compared to those with lower levels of quadriceps strength[31].

Deficiencies in strength post-ACLR result in changing the kinetics of the knee joint[100,148], thus understanding the role of a weaker quadriceps group in relationship to knee joint function is critical. Weakness in the quadriceps muscle group results in asymmetries in knee movement during drop landing tasks[149] and during walking gait [24,100]. Schmidtt et al. found that 8 months from ACLR, those who were classified as "low strength" (isometric quadriceps LSI <85%) demonstrated greater asymmetries in knee flexion moment, peak vertical ground reaction force, and knee loading rates

(peak vertical reaction force divided by time to reach peak) compared to the strong

(isometric LSI >90%) and uninjured control group when completing a drop landing

task[149].

Lewek et al., evaluated kinematics of walking gait at 12 weeks post-ACLR.

Subjects were divided into two groups dependent on the isokinetic quadriceps LSI,

those demonstrating an LSI of <0.80 were classified as weak, and those with an LSI

of >0.90 were classified as strong[100]. Subjects in the "weak" group demonstrated

lower peak knee flexion angle (20.99 degrees) during a walking task compared to

contralateral controls (26.54 degrees)[100]. Asymmetries in walking gait as a result of

quadriceps weakness have been noted at the time of return to sport as well. Di Stasi

et al. found that those who failed return to sport testing (90% or greater on isometric

quadriceps LSI) demonstrated statistically significant decrease in knee flexion angle

at initial contact (p=0.027) as well as at peak knee flexion angle (p<0.001) in the

injured knee compared to the uninjured knee during walking gait[24]. This decrease in

knee flexion angles during walking gait in ACLR subjects has been identified in other

research as well[150,151]. The decrease in knee flexion angle results in a reduced joint

contact area of the tibiofemoral cartilage, resulting in an increased load on the

portions of the cartilage that experience weight bearing[66]. Therefore, deficiencies in

muscle strength bring about changes to kinematics which impact joint health.

Quadriceps Strength and Cartilage Health

Quadriceps muscle strength has been identified as a factor in cartilage

health[34]. Quadriceps strength has also been listed as a possible protector against

OA development[35], and the reductions in quadriceps strength post-injury have been suggested as a possible factor in the development of knee OA[21,107]. Palmieri-Smith et al. found that in a sample of 348 women, those who displayed higher values of isometric quadriceps strength displayed less evidence of radiographic knee OA than those who were relatively weaker[152]. Quadriceps strength has also been linked with early onset of knee OA. Tourville et al. noted that deficits in quadriceps strength were correlated with increased narrowing of the space between the tibia and femur in the ACLR knee over a 4-year period compared to the contralateral limb[37]. Isometric quadriceps strength has been related to radiographical changes to knee cartilage prior to clinical diagnosis[153]. Measurements of quadriceps strength and the understanding of the specific interaction of quadriceps strength and early markers of cartilage health is invaluable to the early identification and care of those at risk of developing early onset OA. In the present study, we found statistically significant associations between normalized decreased quadriceps MVIC in the ACLR limb and the T1rho relaxation time LSI for the medial femoral cartilage in the ACLR limb, suggesting that the strength of the ACLR limb directly influenced the difference in T1rho relaxation times in the ACLR limb. We did not find evidence of a similar association when evaluating the MVIC LSI and the T1rho LSI, suggesting that the strength asymmetry between limbs did not play as large of a role in elevated T1rho relaxation times as we initially hypothesized.

The presence of pain has been indicated in the inhibition of the quadriceps muscle group[125] post-ACLR[32,154,155] and could therefore have an effect on proteoglycan density. In our study, we evaluated the subject's reported pain at 6

months post-ACLR using the KOOS (Knee Injury and Osteoarthritis Score) and its effect as a covariate on the association between the MVIC of the injured limb and the T1rho LSI as a post hoc analysis. In our analysis, we found that the previously significant strength of association between quadriceps strength and T1rho LSI in the regions of MFC 3, MFC2, MFC1 became statistically non-significant when controlling for patient-reported pain. Our hypothesis for this change in the association is that due to the levels of patient reported pain (KOOS 84.18 ±8.16) that our subjects were experiencing, their selection of ADLs could have been self-modified in order to improve their quality of life[156]. Muller et al., found that a score of 88.9 in the KOOS pain subscale was a relevant threshold to find those who identified as being satisfied with the health of their knee at 3 years post ACLR[157]. It is important to note a large limitation in this post hoc analysis where the already small sample size of the study (n=24) was decreased even more through lack of patient reporting, with only 18 subjects having completed the KOOS survey at time of post hoc analysis. The smaller sample size increases the possibility of a type two error and reduces the statistical power of the analysis. This suggests that additional analysis with larger sample sizes would serve to better illustrate the effect of pain on the strength of association between normalized quadriceps strength and T1rho LSI.

This study was, to our knowledge, the first to evaluate isometric quadriceps strength and mean T1rho relaxation times values at 6 months post-ACLR. Our findings of a correlation between weak quadriceps post-ACLR and elevated T1rho relaxation times for weight-bearing cartilage illustrate the role of quadriceps strength in early changes to cartilage composition post-ACLR. A study has been completed

using healthy subjects and using T2 quantitative MRI[126] for the measurement and evaluation of the collagen constituent of cartilage[158]. The study found that there was a significant negative correlation between the muscle strength of the quadriceps and T2 relaxation times for both women and men in the medial compartments of the femur and tibia[126]. This corroborates very well with the results of the current study, suggesting that there is a role that quadriceps strength plays in the early stages of cartilage compositional change.

Limitations of Study - Further Development

While the current study provides valuable preliminary information regarding the interaction between quadriceps strength and proteoglycan density, there are limitations to what this study can deduce. The cross-sectional nature of the design limits the ability to quantify the changes to cartilage over time. While there were significant associations present with quadriceps strength and T1rho values, the small sample size limits generalizability and serves to indicate the usefulness of continued research. Because this study focused on the association between MVIC and T1rho values, the presence and role of bone marrow lesions and the location and severity of meniscal tears were not included as part of the analysis. Additionally, the use of a different measure of quadriceps strength and activation, such as RTD or CAR, could provide a more sensitive picture of the functional capability of the quadriceps group to affect proteoglycan density. Finally, while pain was evaluated through use of the KOOS subscale, the presence and severity of knee pain experienced was not evaluated in the course of the actual isometric strength testing

protocol, which could have contributed to the decreased strength values presented in the injured knees.

Conclusion

In conclusion, we found preliminary evidence that isometric quadriceps strength, normalized to body weight, is associated with the LSI for T1rho relaxation times in the weight-bearing regions of the medial femoral condyle at 6 months post-ACLR and could potentially be affected by pain. This data demonstrates that added emphasis should be placed on improving quadriceps strength post-ACLR in order to improve long-term knee health outcomes by mitigating proteoglycan depletion. Further analysis should determine the impact of pain on the association between strength and tibiofemoral proteoglycan density.

Figures and Tables

Table 1. Subject Demographics

Demographics	
N=24, (14 Males, 10 Females)	
	Mean (±Std. Deviation)
Injured Right Knee	16
Injured Left Knee	8
Presence of Medial Meniscal Tear in injured Knee	2
Presence of Lateral Meniscal Tear in injured knee	17
Age (Years)	21.88 (±3.55)
Height (m)	1.76 (±0.12)
Mass (kg)	74.63 (±12.88)
Body Mass Index	23.97 (±2.18)
Time from Injury to Surgery (d)	31.74 (±15.83)
Time from Surgery to Testing (d)	197.09 (±23.75)
MVIC LSI	0.64 (±0.19)
MVIC Inj Normalized (Nm/kg)	1.91 (±0.51)
MVIC Uninj Normalized (Nm/kg)	3.09 (±0.63)
KOOS Pain Scale	84.18 (±8.16)

Table 2. Inter-Rater Reliability

Inter Rater Reliability- Cartilage Volume, T1rho Relaxation Times					
Compartments	*ROI*	*Cartilage Volume ICC*	*Standard Error of the Measure (Voxel)*	*Mean T1rho Relaxation Time ICC*	*Standard Error of the Measure (ms)*
Lateral Femoral Condyle	*LFC 3*	0.862	185.19	0.983	0.78
	LFC 2	0.625	242.84	0.937	0.85
	LFC 1	0.755	206.65	0.895	1.02
Medial Femoral Condyle	*MFC 3*	0.934	124.69	0.872	1.47
	MFC 2	0.723	296.54	0.887	1.11
	MFC 1	0.202	230.65	0.846	2.22
Lateral Tibial Condyle	*LTC 3*	0.927	193.91	0.895	1.43
	LTC 2	0.895	227.01	0.837	1.42
	LTC 1	0.546	266.93	0.809	2.35
Medial Tibial Condyle	*MTC 3*	0.85	180.99	0.888	0.86
	MTC 2	0.84	252.86	0.875	0.95
	MTC 1	0.653	84.08	0.894	1.35

Table 3. Intra-Rater Reliability

Intra Rater Reliability- Cartilage Volume, T1rho Relaxation Times					
Compartments	ROI	Cartilage Volume ICC	Standard Error of the Measure (Voxel)	Mean T1rho Relaxation Time ICC	Standard Error of the Measure (ms)
Lateral Femoral Condyle	LFC 3	0.802	106.82	0.982	0.79
	LFC 2	0.933	117.04	0.851	0.53
	LFC 1	0.973	71.73	0.709	2.14
Medial Femoral Condyle	MFC 3	0.927	134.56	0.939	1.15
	MFC 2	0.898	155.70	0.934	1.02
	MFC 1	0.825	88.12	0.986	0.89
Lateral Tibial Condyle	LTC 3	0.901	181.62	0.958	0.83
	LTC 2	0.954	142.67	0.957	0.88
	LTC 1	0.883	127.01	0.72	2.55
Medial Tibial Condyle	MTC 3	0.881	183.77	0.935	0.79
	MTC 2	0.825	179.68	0.943	0.68
	MTC 1	0.897	64.25	0.782	2.09

Table 4. Mean T1rho Values

	Anterior ROI			Central ROI			Posterior ROI		
Mean T1rho Relaxation Times (±Std. Dev)									
	Injured	Uninjured	LSI	Injured	Uninjured	LSI	Injured	Uninjured	LSI
Lateral Femoral Condyle	50.97(±5.27)	45.87(±3.69)	1.12(±0.14)	53.9(±8.45)	49.16(±5.65)	1.10(±0.17)	60.01(±8.26)	53.04(±8.36)	1.13 (±0.21)
Medial Femoral Condyle	54.9(±6.24)	51.1(±3.86)	1.08(±0.1)	54.06(±6.5)	49.76(±5.45)	1.09(±0.13)	55.39 (±5.61)	53.93(±6.51)	1.03 (±0.09)
Lateral Tibial Condyle	54.75 (±7.83)	51.81(±7.49)	1.07(±0.19)	43.47(±3.5)	43.71(±8.31)	1.02(±0.15)	52.10 (±8.01)	46.66(±5.09)	1.13 (±0.23)
Medial Tibial Condyle	53.04 (±8.36)	45.99(±4.21)	1.083(±0.21)	48.24(±7.19)	45.99(±4.21)	1.06(±0.2)	48.54(±4.71)	47.58(±5.11)	1.03 (±0.14)
* LSI=Limb Symmetry Index (Injured/Uninjured)									

Table 5. Results of Paired Samples T-Test for T1rho Relaxation Times

Compartments	ROI	Mean T1rho Relaxation times (ACLR)	Mean T1rho Relaxation times (Contralateral)	T Statistic	p value
Paired samples T-Tests comparing T1rho signal relaxation times at 6 months post-ACLR between injured and uninjured knees.					
Lateral Femoral Condyle	Posterior	60.01(±8.26)	53.04 (±8.36)	2.87	0.009*
	Central	53.9(±8.45)	49.16 (±5.65)	2.97	0.01*
	Anterior	50.97(±5.27)	45.87(±3.69)	4.36	<0.001*
Medial Femoral Condyle	Posterior	55.39 (±5.61)	53.93 (±6.51)	1.39	0.179
	Central	54.06 (±6.5)	49.76 (±5.45)	3.16	0.004*
	Anterior	54.9 (±6.24)	51.1 (±3.86)	3.67	0.001*
Lateral Tibial Condyle	Posterior	52.10 (±8.01)	46.66 (±5.09)	2.51	0.019*
	Central	43.47(±3.5)	43.71 (±8.31)	-0.12	0.904
	Anterior	54.75 (±7.83)	51.81 (±7.49)	1.39	0.175
Medial Tibial Condyle	Posterior	48.54 (±4.71)	47.58 (±5.11)	0.693	0.495
	Central	48.24 (±7.19)	45.99 (±4.21)	1.219	0.235
	Anterior	53.04 (±8.36)	45.99 (±4.21)	1.664	0.11
*denotes significant associations (p≤ 0.05)					
**Degrees of Freedom= 23					

Table 6. Results of Paired Samples T-Test for Cartilage Volume

Paired samples T-Tests comparing cartilage volume at 6 months post-ACLR between injured and uninjured knees.					
Compartments	ROI	Mean Cartilage Volume (ACLR)	Mean Cartilage Volume (Contralateral)	T Statistic	P value
Lateral Femoral Condyle	Posterior	1049.64(±558.98)	997.93 (±363.65)	0.70	0.49
	Central	1201.4(±456.98)	1138.45 (±300.85)	0.770	0.448
	Anterior	930.96(±445.91)	863.10(±300.74)	0.781	0.442
Medial Femoral Condyle	Posterior	1283.48 (±469.61)	1277.24 (±462.73)	0.081	0.936
	Central	1588.97 (±585.97)	1458.72 (±524.73)	1.033	0.311
	Anterior	795.92 (±266.02)	729.32 (±216.3)	1.377	0.180
Lateral Tibial Condyle	Posterior	1652.05 (±765.25)	1608.63 (±654.45)	0.417	0.68
	Central	1783.8 (±663.5)	1691.98 (±565.36)	0.609	0.547
	Anterior	743.57 (±440.26)	613.37 (±323.87)	1.694	0.102
Medial Tibial Condyle	Posterior	1255.4 (±455.15)	1452.89 (±532.56)	-2.428	0.022*
	Central	1584 (±654.78)	1598.58 (±495.69)	-0.133	0.895
	Anterior	516.63 (±256.17)	548.58 (±261.93)	-0.538	0.595
*denotes significant associations (p≤ 0.05) **Degrees of Freedom= 23					

Table 7. Correlations between Quadriceps Strength and T1rho LSI

	Correlations Between Quadriceps Strength and T1rho LSI		
	ROI	MVIC Injured (Nm/kg)	MVIC LSI
Lateral Femoral Condyle	Posterior	*-0.089 (0.679)*	*-0.2 (9.26)*
	Central	**-0.211 (0.322)**	**-0.190 (0.373)**
	Anterior	*0.066 (0.758)*	**-0.176 (0.412)**
Medial Femoral Condyle	Posterior	*-0.427 (.037)*￼*	*-0.348 (0.96)*
	Central	*-0.451 (.027) *￼*	*-0.266 (.209)*
	Anterior	*-0.480 (0.018) *￼*	*-0.90 (6.77)*
Lateral Tibial Condyle	Posterior	**0.275 (0.194)**	**0.003 (0.987)**
	Central	**0.348 (0.096)**	**0.171 (0.424)**
	Anterior	*0.273 (0.196)*	*0.126 (0.559)*
Medial Tibial Condyle	Posterior	*0.192 (0.369)*	*-0.059 (0.785)*
	Central	*-0.021 (0.922)*	*-0.138 (0.519)*
	Anterior	**0.026 (0.904)**	**-0.068 (0.753)**
*denotes significant associations (p≤ 0.05) ** LSI=Limb Symmetry Index (Injured/Uninjured) **Bold=Spearman Rho** *Italics=Pearson Product Correlation*			

Injured Quadriceps MVIC (Nm/kg) and T1rho LSI for Medial Anterior Femoral Cartilage

r =-0.427
p=0.037

Injured Knee Quadriceps Strength (Nm/kg)

T1rho Medial Anterior Femoral Cartilage LSI (Injured/Uninjured)

Figure 2. Scatterplot of association between Injured MVIC and T1rho LSI for MFC 2

Injured Quadriceps MVIC (Nm/kg) and T1rho LSI for Medial Central Femoral Cartilage

r=-0.451
p=0.027

Injured Knee Quadriceps Strength (Nm/kg)

T1rho Medial Central Femoral Cartilage LSI (Injured/Uninjured)

Injured Quadriceps MVIC (Nm/kg) and T1rho LSI for Medial Posterior Femoral Cartilage

r =-0.480
p=0.018

Injured Knee Quadriceps Strength (Nm/kg)

T1rho Medial Posterior Femoral Cartilage LSI (Injured/Uninjured)

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